THE CANCER LETTER

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NCI Proposes Consolidation of Nine Cooperative Groups to Four, In Two Years

By Kirsten Boyd Goldberg

NCI officials have proposed a reorganization of the nation's cancer clinical trials program that would drastically change the program's structure and peer review.

Among the changes institute officials proposed, in a presentation released on NCI's website Dec. 10 and discussed with the NCI Clinical Trials and Translational Research Advisory Committee on Dec. 15:

• Consolidating the current nine groups studying adult cancers into four multidisciplinary, multi-disease site groups, including the operations and data management centers.

• Consolidating nine grants for human tissue banks to three.

• Changing peer review to reward the scientific importance of trials

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FDA News:

FDA Moves To Revoke Avastin's Breast Cancer Accelerated Approval, Genentech Vows To Fight

By Paul Goldberg

The Genentech drug Avastin is now officially on track to become the first drug to lose an accelerated approval.

FDA officials said Dec. 16 that they have started the process of removing the drug's indication as a first-line treatment for metastatic HER2-negative breast cancer because the drug has not been shown to be safe and effective for that use, the agency said.

When FDA asks to remove a drug from the market, companies capitulate, sometimes with perfunctory protestations.

Genentech seems to have adopted a different strategy for Avastin (bevacizumab). It has vowed to fight.

"The U.S. Food and Drug Administration is proposing to withdraw the approval for Avastin for breast cancer, potentially taking away a choice for the thousands of women facing the disease," Sandra Horning, senior vice president, global head, Clinical Development Hematology/Oncology at Genentech, said in a webcast.

"Our goal is to cure cancer," Horning said. "The reality is, many people in the U.S. are diagnosed each year with an advanced cancer that is not curable. For these individuals, there is clearly a need for multiple treatment choices. That is why we will ask the FDA for a hearing and continue to work to maintain the ability of doctors and patients to make an informed choice, to

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Final Issue For 2010:
This is the final issue of The Cancer Letter for 2010. The next issue is scheduled for publication on Jan. 7, 2011.

Cancer Clinical Trials Network Would Replace Group Model

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and a group's collaboration with other groups in the network, rather than crediting individual groups for leading trials.

• Competitive review of all four adult groups and one pediatrics group in the same year, every five years, so that funding can be allocated based on merit.

• "Harmonized" operations, remote data entry, and statistical centers, requiring a move to a common IT infrastructure.

Under the plan, the existing Children's Oncology Group would remain the single pediatrics cooperative group. COG was formed 10 years ago in the voluntary consolidation of four different pediatric cooperative groups.

The proposed reorganization is NCI's response to the Institute of Medicine report earlier this year recommending wide-ranging changes in the cooperative groups and NCI's interaction with the groups (The Cancer Letter, April 16, 2010).

"We are interested in supporting a system that will rapidly complete large, randomized, multi-site phase II and phase III clinical trials of very high scientific priority," James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis, said in presenting the plan to CTAC. "This will require the kind of change that will justify the additional investment that the system clearly needs."

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The proposal represents a major conceptual change for the Cooperative Group Program, moving from a fragmented collection of groups working mostly independently, to an integrated clinical trials network, Doroshow said. The reconfigured program, to be called the National Clinical Trials Network, would serve as the institute's primary platform for large phase II and phase III trials. The NCI-designated cancer centers and the Specialized Programs of Research Excellence would be encouraged to work with the groups to move ideas into cooperative group trials. Separately from the cooperative group reconfiguration, changes would be required to NCI's guidelines for the cancer center and SPORE grants to provide incentives for those interactions.

"The critical thing is that, at the end of the day, we have a system that not only provides the essential infrastructure for cooperative group trials, but is the enabler across all of the NCI's clinical research programs for cutting edge translational research," Doroshow said to the CTAC.

Over the next year and a half, NCI officials will develop a new Request for Applications for the program. The concept for the RFA will be reviewed by the NCI Board of Scientific Advisors. NCI has stopped accepting applications for the grants that support the cooperative groups, Doroshow said. The institute will provide the existing groups with supplemental funding until awards are made under the reconfigured program in the fall of 2013, with fiscal 2014 appropriations.

NCI provides about $145 million a year for the Cooperative Group Program. The groups also receive substantial resources through philanthropy, industry, and pro bono volunteer time from their member institutions and investigators.

Doroshow presented the plan as a starting point for discussions with the groups and NCI advisors, and said he is seeking comment from all involved in the program. Nevertheless, if the proposal he described goes forward as planned, the nine cooperative groups would have until about November 2012, when the new grant applications would be due, to decide whether or how to merge.

The cooperative groups have anticipated some changes for the past 15 years, but the NCI proposal, first presented at a Nov. 29 meeting of the cooperative group chairs, is the first explicit move by the institute toward mandating a consolidation.

"This represents a real transition point from having the group program that we've had for the last 55 years, to having a national network of sites that conducts publicly funded clinical trials that can originate from

anyone investigator in the country, and where the data is collected and managed by any one of a number of NCI-funded operations offices," CTAC member Richard Schilsky, professor of medicine and associate dean for clinical research, University of Chicago, and a former cooperative group chairman, said to The Cancer Letter. "That's where this is going to end up. Whether that is ultimately going to be good or bad remains to be seen."

Schilsky served on the IOM committee that wrote the April 2010 report on the clinical trials program. "[The report's] recommendations called for steps along these lines," he said. "The system we have been working in for last 55 years is a highly inefficient system. Change is clearly necessary. I haven't heard anyone suggest that there shouldn't be change. Even the group chairs themselves put out a response to the IOM report praising it and saying that it raised many important points and helps facilitate change."

NCI began the Cooperative Group Program in 1955 to organize national clinical trials of new therapies. The program enabled doctors at different hospitals to share patient data and methodically develop standard terminology, cancer staging, and treatment methods. In its first decade, the system led to the first longer-term remissions in childhood leukemia and Hodgkin's disease. Advocates for a national "war on cancer" pointed to these successes as evidence that a better-funded and more directed cancer research program could turn cancer into a curable disease.

However, in recent years, the Cooperative Group Program has been criticized as too slow, unwieldy, and fragmented, and unable to deal with the increasingly complex molecularly-driven therapeutics research. Also, the existing groups are each too small and not rewarded under the current system to launch trials within their groups in some less common cancers such as head and neck cancer and sarcomas, Doroshow said.

At least five reports over the last 15 years have recommended changes to the program, said Schilsky. "None of them have recommended eliminating the cooperative group program," he said. "Most of the reports leading up to the IOM report recommended tinkering with it in various ways to try to improve its efficiency. The IOM report went the furthest in recommending various ways in which the functions of the cooperative groups could be consolidated, if not the groups themselves.

"As soon as you start down the road to consolidating the operations, then it's a short skip to actually consolidating the groups," Schilsky said.

Three groups already are merging their statistical centers and are in discussions about merging completely. Cancer and Leukemia Group B, the North Central Cancer Treatment Group, and the American College of Surgeons Oncology Group began more than a year ago to merge their statistical operations. Leaders of the three groups are beginning to work with their disease committees and membership to discuss a full consolidation.

Another group, the Radiation Therapy Oncology Group, has also begun discussions with other groups on merging, said Walter Curran, RTOG chair. "We are talking with other groups to see whether we have sufficient commonality in our goals and in our culture that there is an advantage of us aligning with one group versus another," Curran said to The Cancer Letter.

"Since IOM report came out, I have been saying to my brothers and sisters that they ought to be having these conversations, because it was very clear to me what the IOM was saying," Laurence Baker, Southwest Oncology Group chair, said to The Cancer Letter. "Now there is full recognition of that. There are certain groups—SWOG would like to believe it's one of them—that are large and multidisciplinary, and study several cancers, and I think that is the most efficient mechanism."

Earlier this week, the cooperative group chairs and NCI jointly issued the following statement:

"A joint message from the Cancer Cooperative Group Chairs and NCI Leadership: In response to the Institute of Medicine recommendations for reinvigorating the national cancer clinical trials infrastructure, the National Cancer Institute is recommending integrating existing cooperative groups by providing up to four grants for adult multidisciplinary groups plus one grant for a pediatric multidisciplinary group.

"There are two primary goals for increased integration of the groups. The first is to promote scientific collaboration among laboratory and clinical investigators for the purpose of translating the science of cancer biology into improved therapeutic outcomes for patients. The second goal is to improve efficiency by integrating operational support for the groups, including protocol development, statistics and data management, and biobanking.

"NCI and Cooperative Group leadership are working collaboratively to determine the most effective and flexible organizational structure to support the recommendations from the Institute of Medicine."

NCI's transition plans and the presentation to the cooperative group chairs are posted at http://transformingtrials.cancer.gov/.

Varmus: Giving Trials A Strong Science Base

NCI Director Harold Varmus mentioned the proposal at the Dec. 7 meeting of the National Cancer Advisory Board. "We think that the group functions are going to be enhanced dramatically," he said. "We are creating three biorepositories to be sure that we are making adequate use of clinical samples from patients who are enrolled in trials. An IT system is being developed for a national trial management system. The Central IRB is being strengthened.

"Most important from my perspective, in this era of molecularly informed therapeutics, the trials are hopefully going to be more amenable to a strong science base," Varmus said. "The genomic data and ancillary data on gene expression are becoming increasingly important in the design of clinical trials and even in the choice of therapies. The nation's confidence in this development I think is strong, based on the performance of Gleevec and a number of other new drugs being used in the treatment of diseases. But there is also a dark side of this, which is that we haven't yet fully figured out how to credential molecular findings to allow assignment of patients to arms of clinical trials of therapeutic strategies.

"That was dramatically revealed recently by an episode at Duke University, in which it was discovered that there was what appeared to be a combination of scientific misconduct and inadequately validated algorithms for assignment of patients to various therapies, and led to the abrupt closure of several trials," Varmus said.

"The NCI was not funding those studies, but because we had been involved in supporting the work that led to them, I've asked the Institute of Medicine, National Cancer Policy Board, to do a study, which they are currently undertaking, of how we regulate and certify and establish the validity of molecular signatures that will be used in both clinical trials and clinical practice in the future," Varmus said. "I expect that study to be done sometime in the next several months. The intention is not to investigate certain aspects of the situation at Duke, but to learn from that situation with respect to how we go about validating the criteria for making assignment of patients to various therapies.

"I don't want to link it too forcefully to the cooperative groups, but I do want to recognize that the design of clinical trials, the kind of science that employs genomic methodologies, will be heavily used, and we need to feel confident that those methodologies are telling us important things before we assign patients to the arms of trials of therapeutic regimens."

Unlikely to Save Money

The consolidation will not save NCI money in the short term, Doroshow and several cooperative group chairs said.

"I have and I will continue to beg, borrow, and steal resources to make this happen, because it's not something that in the short run—I hope in the long run, but not in the short run—is going to save any money," Doroshow said to CTAC. "It costs more money to do these kinds of things, and we need to be able to provide resources for this transition."

Also, NCI will need to invest in the IT infrastructure on an ongoing basis, Doroshow said. "We need to appropriately resource these infrastructures so we can preserve what is a 55-year investment in this current system that has a remarkable level of achievement," he said.

While there would be fewer groups, the number of investigators and study sites should remain at least the same, particularly so that training of new clinical investigators continues to take place, Doroshow said. The idea would be to combine the disease committees of the groups "rather than to disenfranchise investigators," he said.

The CALGB-NCCTG-ACOSOG merger of statistical centers wouldn't have been possible without a substantial supplemental grant from NCI, said Monica Bertagnolli, CALGB chair.

"It will cost a lot to do this right," Bertagnolli said to The Cancer Letter. "It's crazy to think that all the consolidation that needs to happen can be done without a substantial infusion. And then, we are still left with the issue of the per capita payments $4,000 per patient below the break-even mark.

"If we are spectacularly successful and bring up all these really great studies and get them going and get them accruing like crazy, which is what we are hoping to do—if we do that, we'd break the bank," Bertagnolli said. "It has happened to all of us. 'You'd better stop accruing, because we don't have enough money.' That's just the nature of the beast.

"The NCI really has not put a substantial portion of its budget toward clinical trials," Bertagnolli said. "I wish that would change. Nothing will change for the patients without clinical trials."

Among the IOM report's recommendations: "NCI should allocate a larger portion of its research portfolio to the Clinical Trial Cooperative Group Program to ensure that the program has sufficient resources to achieve its unique mission."

When the IOM report was released, the American

Society of Clinical Oncology called for NCI to triple the per-case reimbursement from $2,000 per patient to "a more realistic rate of $6,000 per patient," which the society said would require an infusion of $120 million into the cooperative group program.

"Everyone understands that the system is grossly underfunded, that the last two NCI directors have really turned down the oxygen," said Robert Comis, chairman of the Eastern Cooperative Oncology Group and president of the Coalition of Cancer Cooperative Groups. "The key thing in the IOM report is that they say, on page 9, 'It is imperative to preserve and strengthen the unique capabilities of the cooperative group program as a vital component in the NCI's translational continuum.' It would be nice to have Dr. Varmus or someone agree to that statement.

"We are acting on good faith that, in fact, they are going to agree with that."

CTAC Discussion

Members of the CTAC generally praised the NCI proposal for its attempt to broaden involvement in cooperative group trials, but pressed Doroshow on the number of groups, scientific priorities, and issues of peer review.

"I think this reorganization and restructuring is a great opportunity not only to change the organization itself, but also the mindset," said Olivera Finn, professor and chair of immunology, University of Pittsburgh School of Medicine. "There have been some large groups that are interested in different types of trials that have not found a welcoming environment in the current structure. There is a lot of opportunity to target the tumor microenvironment. Those types of clinical trials do not get the enthusiastic response they could otherwise, so those groups have had to go outside the existing structure. If we reassemble, then those outsiders might become more insiders, so I welcome this opportunity. It's an opportunity for new research and new types of clinical trials to be done."

"This is looking very good," said Edith Perez, deputy director, Mayo Comprehensive Cancer Center, Jacksonville, Fla. "It has been a long process, but it's good to take the time to do it right. The timeline doesn't look outrageous to me, to be able to get input from people and come up with the right system. What are the types of trials the groups will do versus the trials done by the centers, SPOREs or the phase II consortium? Because now they totally overlap, but the cooperative group trials are viewed as less scientifically valid than trials done by the phase II consortium or the SPOREs."

"This is the best presentation we've had in three years," said James Wade III, director of Medical Oncology, Decatur Memorial Hospital Cancer Care Institute. "It is certainly a change from when we were hearing there might not be any cooperative groups, so this is a great improvement."

Wade asked whether NCI had any data on trials at centers and SPOREs. "Are trials at SPOREs and centers being done that much better, and is there reason to believe that these studies are going to easily flow into the cooperative groups if they are successful?"

Doroshow said NCI is working on gathering accrual data on trials at centers and SPOREs, but the process will take two to three years.

"Everyone applauds efficiency, but I would like to think we would start with: These are the scientific priorities, and then these are the number of groups to meet those priorities," said Deborah Bruner, director of clinical trials recruitment, retention, and outreach at Abramson Cancer Center. "The first question is, 'How many groups?' I'm just still not clear on how the number four came up. If I were a company and I was consolidating, I would say, 'What are the projections that show me that four is the number, that four gives us the savings?' Because unless I had a delusional moment, I recall you saying you didn't see the savings in the consolidation, given all of the volunteer work, etc. So, where are the projections?"

"I think that's an excellent question," Doroshow said. "You look at the costs. The issue really is, how many patients are you going to accrue? If you are you going to accrue x number of patients, you need y number of statisticians and z number of data managers, and so on. Whether it is four or three [groups] or whatever, that's a matter of what is the size that's efficient, I don't think there is an a priori number. One is probably inefficient. Nine is clearly inefficient and probably underpowered. If most of the money goes to accrual costs, then it is the number of patients. What is the total accrual for the number of trials the government wants to support?

"In no way would I sit here and say that we will initially save money to do the integration," Doroshow said. "It will cost money to do the integration. Also, we have a little bit of data that we might save a little bit of money in administrative costs. Ultimately, we need advice from the extramural community, and that's why we need a high level group to look at what is the accrual number that is appropriate. That really is the driver."

Schilsky said he agreed with the proposal to review the all of the groups on the same cycle. "It raises the question whether you would expect there would be some

natural relationship between success in peer review and budget, because up until now, there has been basically no relationship," he said. "If the groups are competing on the same cycle, it offers the opportunity to compete against each other with the same review criteria. One hypothetical outcome of several cycles of peer review, over some decades, could be that one or two of the four groups emerge as the most successful and the other two go away. If funds are actually allocated based upon success in review, there could be substantial shifting of funds across groups. It raises the question as to, if the four groups are going to be essential to the maintenance of the system, it's a little bit unclear to me how the system is going to be maintained, with what presumably would be a flat budget, reallocating funds based on peer review outcome. It seems like there would be an opportunity to link budget with outcome in review, and have you thought about that as one desirable goal?"

DOROSHOW: "Is it OK if I tell everybody that you did well on your last review?"

SCHILSKY: "We had the same budget for 15 years."

DOROSHOW: "The CALGB did particularly well in its last review and just as Dr. Schilsky said, got rewarded with a flat budget. I think it makes sense that if groups do better and they accrue better and they help the whole system get studies done faster, then they should be rewarded for it. Having review done at same time will allow review to evaluate contributions one to another and for us to adjust budgets in a way we have not been able to do. Longer term, it's impossible to argue that we are paying people on a per case basis an appropriate sum. What other boards have suggested is that show us you can change things and make it more efficient, and then we can consider, economic conditions notwithstanding, putting additional money, clearly we are going to need if we are going to continue to accrue as many patients as we need to."

SUSAN ARBUCK, R&D consultant: "I'm wondering about having more ability to be flexible and responsive as the science changes. I liked the idea of the simpler review that didn't take months and months of preparation and many pages of documents. Perhaps a more directed, straightforward review could be done more often than every five years?"

SCHILSKY: "The last competing renewal and I led for CALGB, a couple of years ago, we had probably 40 people from CALGB present and 40 reviewers in the room," Schilsky said. "We went through a long day of presentations. If I remember correctly, I think I could count on no more than the fingers of both hands and maybe the fingers of one hand, the number of questions we actually got from the review panel. Almost all of those questions, I was prepared to answer on behalf of the group. I completely agree that the review process could be greatly streamlined. I think a well-written application that focuses on major accomplishments, not trivia of how many protocols did you activate, but what did you actually learn from doing those, having the group leadership present with others members of the scientific leadership available on the phone, could make for a very streamlined review process. I wouldn't necessarily advocate that it be done more frequently, but it could be done more easily and much less expensively."

Returning to the number of groups, Joel Tepper, professor and chair of radiation onocology, University of North Carolina School of Medicine, said four is a reasonable number. "There are a number of factors that control it and it's not necessarily true efficiency, but it does relate to getting different ideas bubbling up in different ways, having different orientations of the groups, and very much the issue of mentorship, being able to bring people up in the organization and giving more people a chance to participate, and not have a single group that can get ossified easily. I think having a number of groups is good and four sounds like a reasonable number.

"The second issue I have is the review process and potential problems that could come up," Tepper said. "If the groups are structured in such a way so that some disease sites or some approaches are represented by one group, and that group does badly in review, if that doesn't get funded, what happens to that disease site? How does the system respond and still go forward in those areas, and make sure the expertise in those areas doesn't die away? I think these are issues that can be handled, but they need to be thought about very carefully so that we don't lose some of the benefits we have because of the redundancy of the present system."

Peter Adamson, chief, clinical pharmacology and therapeutics, Children's Hospital of Philadelphia, said the system needs flexibility. "I think that the more structure that is imposed, the less innovation there will be. We have an opportunity, with competition, to foster innovation. We put up a structure there, and we honestly don't know if it's effective. There may be much more effective, efficient ways to do studies if you allow much more flexibility of the resources. The question comes back to the steering committees. When they emerged out of the [Clinical Trials Working Group], if I recall correctly, the overarching rationale for the

steering committees were two-fold: One to bring peer review to the process, and two, as a work-around for the dysfunctional network of adult cooperative groups. Now that you are addressing the fundamental issue with the reorganization of the cooperative groups, are the steering committees going to play the same role? Where will priorities be set?"

"We need peer review, and having that go out to a standard grant review would be impossible," Doroshow said. "Everybody needs to realize that even a relatively small trial is millions of dollars. A standard SPORE grant is $2 million. We need review. We need a way to get the groups to work together as they develop ideas. I don't know what the best way is. At the other extreme, you could say that with a new structure, people will a priori be working together, and I would hope that would be true. We have to have the goal in mind that we want competition of ideas, but after that competition is done, there has to be buy-in that this is the study that we are going to go forward with. Whatever the best way to do that is the structure we need. We don't want NCI to be reviewing concepts, making the decisions about what the best science is. We can help facilitate, but the best science should be decided by the experts."

Doroshow said the Cancer Therapy Evaluation Program "isn't doing full review of protocols separate from the steering committees."

Mitchell Schnall, chair of the American College of Radiology Imaging Network, said that if the types of diagnostic studies that his group does aren't given enough credit in peer review, "they will slowly be squeezed out. Groups will do what they need to do to get a good score."

"The parallel work to create a common infrastructure allows for a lot of organizational models," said David Parkinson, president and CEO, Nodality Inc. "There obviously is value to having standing cooperative groups. It's communities, associations, relationships. So there is a fixed element to what we are thinking about here. But then, it's very hard to predict what technological, biological, therapeutics development will occur. You might want to have a variable aspect. Something that cuts across. You want to have the machinery and infrastructure, so that these groups exist as communities that are in place to answer questions that we can't anticipate right now. What you don't want to do is have that fixed infrastructure end up, as is so often the case, to be running a lot of things through the machinery to justify the existence of the machinery. You might want to consider fixed infrastructure costs and then competition for the variable element, for emerging science and opportunities."

"I think what David suggested is outstanding," Doroshow said. "I think we need to be as nondirective as possible, but on the other hand, if we have a new system three years from now and we still can't do trials in sarcoma or head and neck cancer, we haven't really done much. So we have to build this in a way that, maybe you can't get renewed unless you contribute to a national head and neck effort—I'm just making that up. There are many examples of things that are emerging scientific opportunities that because we're not submitting, or because it has been disadvantageous in the review process, have been de-emphasized. If you have to keep in your mind how is this different that big pharma? How can we address things are not very commercial?"

"And things that are not just disease sites," said Bruner. "Wouldn't if be wonderful for the national cooperative groups to address accruing patients over 75, where we have 0.5 percent accrual of incidence cases?"

Kenneth Cowan said he liked the idea of centers being more actively encouraged to participate with the groups. "Cancer centers have always been involved in cooperative groups. I like the idea of engaging more cancer center investigators to be part of this mechanism. I like the idea of having some sort of way of having people from SPOREs, phase I, phase II, involved," he said. "I like the idea of having some cancer center criteria review process that might encourage cancer centers to participate more actively in this network, getting credit and getting some support for it as well." He noted that NCI support for cancer centers generally is used for core resources and little is left for clinical trials. He suggested that the new clinical trials network offer a pool of money for clinical trials that center investigators could compete for.

"I understand the reason for targeting a specific number of cooperative groups to consolidate to, but from the discussion around the table, I think there may be some advantage to setting out some basic principles of what you want to accomplish from a scientific standpoint, even accrual goals, and let the existing groups compete or consolidate and not set a specific target number," said James Abbruzzese, chairman of gastrointestinal medicine, MD Anderson Cancer Center.

"When we go up on the Hill and ask for money for NCI, we need to be able to tell a good story," said Nancy Roach, of the Colorectal Cancer Coalition. "This work will make it easier to tell a good story. It's very hard to tell a good story when a lot of this stuff is done

pre-clinically. If we can start highlighting some of the clinical work and some of the advances that are coming because of the reorganization and the speed at which things will be done, it's much easier."

Videocasts of the CTAC meetings can be viewed on the NIH videocast website: http://videocast.nih.gov/PastEvents.asp?c=115.

Comments by Schilsky, Group Chairs

Following are comments that Schilsky and several cooperative group chairs made to The Cancer Letter in interviews earlier this week.

Richard Schilsky, panel member for IOM report on cooperative groups: NCI's reaction to the IOM report is to conclude that there should be four adult groups and one pediatric group, which represents about a 50 percent downsizing of the number of cooperative groups. The way they intend to accomplish this is to issue an new RFA for the cooperative group program, to which any group that wishes to apply could apply, but only four would be funded. It will ultimately be up to the cooperative groups to decide in what configuration do they wish to apply for the new RFA. Theoretically, all nine of the existing adult groups could decide to apply individually, which I think would be foolish, because clearly only four would be funded. Or, they could decide to reorganize themselves in some way and come in with fewer number of applications, representing new, consolidated structures.

My guess is that now all the groups are going to be thinking about what their options are, and jockeying for position, and figuring out what would make for the strongest application going forward.

Then there are the related issues about NCI wanting the new cooperative group structure to be the primary vehicle for doing studies that are developed out of cancer centers and SPOREs, primarily larger randomized phase II studies. This reconfigured cooperative group program would essentially become a national network of sites that conduct clinical trials that are reviewed and approved by the steering committees and available throughout the network.

It is very much a move from the somewhat fragmented system we have had of having multiple cooperative groups that collaborate in various protocols, to essentially having a national network of qualified sites—qualified by virtue of meeting criteria to allow them to be a member of a cooperative group—that then runs clinical trials that can either originate from the scientific committees of a cooperative group, or could originate from an individual investigator working in a cancer center or a SPORE. As long as they get approved by the relevant steering committee, they could access this network and enroll patients.

This represents a real transition point from having the group program that we've had for the last 55 years, to having a national network of sites that conducts publicly funded clinical trials that can originate from anyone investigator in the country, and where the data is collected and managed by anyone of a number of NCI-funded operations offices. That's where this is going to end up. Whether that is ultimately going to be good or bad remains to be seen. That's the $64,000 question.

I was on the IOM committee and I support what its recommendations were. Its recommendations called for steps along these lines. The things that to me are clear and that I strongly support are that, No. 1, we must preserve a highly functional and efficient publicly-funded cancer clinical trials system in this country, for a whole host of reasons, but basically because such a system is the only mechanism of doing important clinical trials that are not of interest to industry. Secondly, the system we have been working in for the last 55 years is a highly inefficient system, for a variety of reasons, many of which were pointed out in the IOM report. They relate to the basic structure of the system, the interaction between the cooperative group system and the NCI, and the level of funding that has been available in the system.

Change is clearly necessary. I think everybody recognized that. I haven't heard anyone suggest that there shouldn't be change. Even the group chairs themselves put out a response to the IOM report praising it and saying that it raised many important points and helps facilitate change.

There have been at least five reports over the last 15 years or so recommending modifications of the cooperative group program. We had the Armitage report, then the implementation committee, then the Clinical Trials Working Group, then the Operational Efficiency Working Group, and now we have the IOM report. That's five reports. None of them have recommended eliminating the cooperative group program. Most of the ones leading up to the IOM report recommended tinkering with it in various ways to try to improve its efficiency. I think the IOM report went the furthest in recommending various ways in which the functions of the cooperative groups could be consolidated, if not the groups themselves. As soon as you start down the road to consolidating the operations, then its a short skip to actually consolidating the groups.

Now that I am no longer in the parochial position of being a cooperative group chair, I don't have quite

as much of a stake in this as I did for the 15 years leading up to this. I think that this is not necessarily a bad direction to go in.

There are two areas that concern me a lot. One is, will the general community of oncologists who participate in clinical trials be interested in bringing forward ideas for clinical trials to this national network? Will they conclude that the network has sufficient efficiency and sufficient capacity to make it worth the effort for them to bring forward an idea? If people start bringing forward a lot of proposals for studies and get turned down a lot, it's going to be discouraging.

Secondly, will the oncologists who are out there in the trenches seeing patients put patients on those trials, as opposed to the variety of other trials, mostly industry-sponsored, that they would have access to? I think the answer to that is likely to be yes if the reimbursement is adequate. If the NCI can't fix the per-case reimbursement for the sites, then I think it doesn't matter what the configuration is. People are going to start walking away from these trials.

The other area I have a lot of concern about, related to the issue of funding, is the notion that least 50 percent of funding that supports the whole cooperative group program up until now comes from non-NCI sources. Much of that comes from the goodwill and contributions of the institutions that participate in the cooperative groups. The reason they are willing to do that is because the doctors or the faculty who are the cooperative group participants find a lot of personal value and satisfaction in their participation in the group. It's good for professional advancement, it's good for networking, it's good for collegiality, it's good for a lot of things. If that goes away, if the groups transform into a national network that has some scientific committees and some operations offices, many institutions may find it's not worth it to them to financially support these kinds of clinical trials, which would be damaging to the system overall.

I think it is greatly underappreciated how valuable the groups have been in developing the careers of clinical researchers. We have many people who are national leaders in clinical oncology who made their careers by coming up through the cooperative group system. If the structures that enable that are not preserved in the new system, then it does not serve the country well. There is really no other venue where clinical researchers can get the kind of exposure to leaders and experts that can be found in a cooperative group program.

It's clear that the NCI has given a lot of thought to this. From what I heard from people who attended the [group chairs] meeting, there was not a great deal of pushback from the cooperative group chairs. There seemed to be a high level of acceptance on most of these points.

There are some important details that need to be worked out. Apparently NCI is proposing that funding be divided between two PIs, a scientific leader like the group chair currently and someone who is an operations leader. That, I think, is probably not a good idea. If the group chair doesn't have control of the operations, then they don't have control of the group. It's not clear why they would be proposing that. It would be better to have everything consolidated under a single PI who is also the group chair, and hold that person accountable for the work of the group.

The other thing will be how to ensure that ideas that come out of other places, coming from a SPORE, for example, how does it get adequately prioritized into the work of the national system, as opposed to an idea coming out of a cooperative group scientific committee.

It's also important to point out that the IOM report includes many recommendations for how the NCI should conduct its business differently. There is an explicit recommendation that NCI staff should not participate in review of concepts that come to steering committees. The only job of the NCI staff should be to organize the steering committees, but not to serve as scientific reviewers. That would be a 100 percent turnaround from where it is now, where the NCI does participate as scientific reviewers, and by hearsay at least, often dominates the discussion.

Apparently Jim Doroshow didn't say anything in his remarks to the group chairs about changing the way the steering committees work. There are recommendations about NCI not even reviewing concepts if the group holds the IND on the drug being studied, and in such cases, the NCI's only role should be facilitating getting the protocol up and running as soon as possible. Apparently, they are not addressing that either.

The NCI is addressing the recommendations regarding how the groups should change their operations. It's not clear yet that they are addressing any of the recommendations about how the NCI should change their own operations in response to the IOM report.

Robert Comis, chair, Eastern Cooperative Oncology group and president of the Coalition of Cancer Cooperative Groups: Whatever time and money spent on this restructuring, the emphasis should

be on what makes the system better and more capable of performing cutting edge trials. I think people are focusing too much on the numbers, whether it's nine and should be four, or should be three. The question is whether the government is going to provide what's required to make the program more efficient and more effective.

At that meeting, it was clear from their discussion that their initial thought was to maintain the three multidisciplinary groups, that is, ECOG, CALGB—which is now in the process of combining with ACOSOG and NCCTG—and SWOG, and establish some reconfiguration of the remaining modality and disease-oriented groups, including ACRIN.

I think all of us felt that rather than a priori saying there would be the remaining groups structured in some way that might or might not be natural, that however the system is reconfigured, it ought to address the strengths of the existing multimodality groups and the strengths of the other groups, so that as we come together, we get real synergy. I think that is the intent and the hope of the group chairs. We know that from the CALGB experience that this is a huge endeavor. It is going to be a huge, huge effort. It can't become a distraction from doing the research. We just completed the largest biomarker-driven study ever done in the country, the TAILORx study. We did genetic typing on 10,000 women and randomized 4,000 to 5,000. We can do this stuff, we know how to do it. This can't be a huge distraction for the next five years.

The terminology they use is "up to four" multidisciplinary adult groups. It could be three or it could be four, but no one wants one or two. However that works, it's going to take a lot of effort on the part of groups that are involved in somehow coming together. However we decide to come together, it ought to be for some synergistic gain rather than for the number.

Everyone knows the whole system is underfunded. It's clear from the report presented at the [Sept. 21] CTAC meeting, how much the groups bring to the table independent of NCI funding. Depending on how you cut it, it's anywhere from $57 million to $170 million. NCI puts in about $189 million. Its important that it's recognized that the groups bring to the government a considerable amount of cost sharing, pro bono investigator time, and funds from private and philanthropic sources. It's not as if the groups are somehow disinterested parties. We are partners in this.

I think one of the things that is clear in the IOM report is that there is a clear direction for the NCI to change as well as for the groups to change and to take on a more facilitating role as opposed to an overseeing role. That wasn't discussed at all. That has to be on everyone's table, and it isn't on the table yet. That relates to how studies move forward, how much review there is, what the relationships are between the groups and the steering committees. We have to figure out a more effective and efficient way to work together.

Another area is the discussion in the IOM report about back-end functions, IT functions. The government is going to have to facilitate the development of these back-end functions and pay for them. We can't afford to pay for the infrastructure it will take to get a remote data entry system, to get the tissue banking system, to develop some sort of technology that will link the cancer centers, the SPOREs and the groups and the contractors. The NCI has to come to the plate and do that. Looking for efficiencies in the back-end functions, when you have a system that is so underfunded, is naive. I think clearly the government has to come forward with that. That have that to some extent with the CTSU.

Five years ago, we presented a plan for them to develop a group-wide remote data entry system or clinical trials data management system, and it's still not up. There has to be a strong commitment to facilitate us working as a functioning unit.

NCI has to, and they say they are in the process of doing this, somehow bring the functions of the cancer centers, SPOREs, contractors, and groups more closely aligned. The groups are the national infrastructure. The cancer centers don't do phase III trials and they never will, because they don't have that infrastructure. The groups have to be nerve center for these programs. In spite of the fact that there are discussions and people are working on harmonization, it's not there yet. It can't just be the groups this and the groups that, it has to be the whole system. It's very disparate now.

On the one hand, the centers are the scientific lifeblood. Most of the studies and most of the committees are run by cancer center people. The commitment of the centers above and beyond those people varies tremendously from center to center. As move into the molecularly-driven study era, we are going to have to bring those things together.

Everyone understands that the system is grossly underfunded, that the last two NCI directors have really turned down the oxygen. The key thing in the IOM report is that they say, on page 9, 'It is imperative to preserve and strengthen the unique capabilities of the cooperative group program as a vital component in the NCI's translational continuum.' It would be nice to have Dr. Varmus or someone agree to that statement. We are

acting on good faith that, in fact, they are going to agree with that. It's implicit, but it's not explicit.

The tissue bank consolidation is complicated. There are nine grants which support 17 different banks, and they want to consolidate that down into three. There are certain banks that have already come together, the Children's Oncology Group and the Gynecologic Oncology Group, are based in Ohio at the Children's Hospital, and CALGB is based at Ohio State. There is some consolidation there. ECOG has our bank, which is the largest consolidated bank, at the Laurie Cancer Center at Northwestern, which supports all the solid tumor work. We also have a leukemia bank and an immunology bank as well. Within ECOG, we have hundreds of thousands of specimens.

It's clear from discussion with the NCI that they don't have the money, and it wouldn't be a good idea necessarily, to do a physical consolidation. They want some sort of administrative consolidation of the grants, with multiple PIs.

What the country really needs is a virtual bank that brings all these banks together so that investigators within the groups and outside the groups can find out what's in the banks and how to get access to them in an equitable fashion. I think we are all in agreement with that. But once again, is nine better than three? That's not the point.

NCI's commitment to an IT solution is a real essential thing here. The issue can't be cutting down the NCI's administrative costs for banking and for groups. It's got to be how to make the system better.

Jan Buckner, **chair, North Central Cancer Treatment Group**: [The NCI proposal] is extremely responsive to the IOM recommendations. It is going down the line of what the IOM recommended. It is certainly going to be challenging for the groups to do this. I do think that at the end of the day, we will still have a very strong cooperative group system.

The pieces that are particularly strong are the plans to integrate the informatics support so that it will be more standardized and harmonized, and it will make it much easier to complete national trials. The system has been selected and is in the first phases of being implemented. These are huge IT projects. Imagine all the insurance companies in the U.S. deciding they are going to use the exactly the same language and define every term exactly the same, and they are going to use the same system to collect all the information. The standards have been set, the user requirements have been identified, the tools to collect the information have been identified, and system to make it happen. The statistics and data center that is supporting North Central, ACOSOG and CALGB is already being implemented. We will have trials starting to roll out with this new system in 2011, so it's real. The other groups also will be using the same system. It will roll out. It will take some years to implement it all. Its all electronic data capture, all compliant with FDA standards for submitting data to support indications. It's a very robust system. It is quite a labor intensive and expensive enterprise, but when you get there, it's worth the effort. I think that's a real plus.

I think that the efficiency piece that's recommended will be good in setting timelines that both the groups and NCI must abide by in order to get trials up more quickly. Hopefully, that will spur third parties such as industry and FDA to come along and help us meet those timelines. There are some concrete steps toward efficiency that really will improve the overall function of the groups. I think the plans are clearly to increase the collaboration among the groups so we can do the important trials and we can do them quickly and we can provide the tissue resources to understand why treatments work when they do or why they don't when they don't, to integrate with the scientific community more effectively. That's all a plus.

Nobody said this was going to be easy. Clearly, this change favors the larger groups in terms of being multi-disease, multidisciplinary groups. Having said that, there is going to be a lot of change for existing groups. Proposing change on this scale is never going to be easy, even when it's voluntary. It's going to require both the groups and NCI to try to be flexible and still aim toward the goals that the IOM recommendations hoped to accomplish.

Along with the IOM report that said basically, we support the groups, we think this is an important national resource for publicly-funded trials, the report also called for increasing the funding, and ASCO has called for doubling the funding. It's only fair if we are successful in making the changes proposed, that we be rewarded with sufficient funding to get the job done.

It is going to be difficult to maintain the momentum of the science at the same time we are remodeling the fundamental infrastructure. It's like trying to remodel the foundation of your house without disrupting the day-to-day household activities. If there is not some additional funding to help do that, then the science, at least in the short term, will suffer.

As our groups, NCCTG, CALGB and ACOSOG, are merging right now the statistics and data center, we have received some supplemental funding to help do

that. As we go forward to integrate the scientific agenda, the operations of the groups, then it is going to take time and money to pull it all together.

Two years is a very short timeline for this kind of change, from our perspective. But, when there is a tight timeline, people figure out ways to meet it.

I think it's going to be key for NCI and the groups to work together so that we can promote investigator-initiated science that is facilitated by the NCI staff as recommended in the IOM report. Our risk is that if it becomes too large and too bureaucratic, then investigators will become so discouraged that we will not have the input and buy-in from the scientific investigators and from the community members. All along, we have to remember that this is still largely a volunteer effort. People are willing to do it, because of the goals. The goals are worthy goals. But if there is too much central control and there is insufficient funding, then that will not create the environment that will engage the academic and community investigators to continue to participate, and that's really key.

If we really want this national collaboration to take place, we have got to figure out a way to provide incentives for cancer centers to partner with their clinical and translational scientists to make this work. If you you incentivize collaboration, you get collaboration. If you incentivize individual effort, then you never get collaboration. This could really be the infrastructure that can support broad NCI translational initiatives, but it's got to engage the national investigator community in a very broad and appealing way.

The funding mechanisms of the past really rewarded individual laboratories or individual investigators, and as science has gotten bigger, the questions have gotten bigger in terms of what is required both from the number of patients and the complexity of the science. We need to provide financial incentives that reward people working together. I would think NCI would accomplish its goals more effectively by rewarding cancer center investigators to participate in these broader initiatives. If there are rewards to collaborate, people will collaborate.

This is a big change for the cooperative group program, and we sure hope that the outcomes are more successful than in the past.

Laurence Baker, chair, Southwest Oncology Group: SWOG is very pleased with it. What we've heard thus far is very positive and we are quite supportive of it. I was reading earlier today about the need for team science, in reference to the cancer centers. The cooperative groups invented the idea of team science 40 years ago when several of the groups started doing multidisciplinary research. It's not an accident that the word "cooperative" is in the name of the group. What I think Jim Doroshow is proposing and what we certainly endorse is now it's time for cooperative groups to have reasons to cooperate with each other. That's one of the key things we think is important going forward. I can't say that we have always behaved that way. I think Doroshow recognized that we didn't have the incentives in terms of review to collaborate as we should. I think that's the most important thing we've heard so far.

Currently, the presumption is that your score [i peer review] is a function of how creative the disease committees are in proposing and carrying out new studies. While there have been people speaking about getting credit for participating in some other group's study, that doesn't always translate to recognition of its importance. I know that at the last SWOG site visit, we pointed out how many patients our sites put on the studies of other groups, and we're very proud of that. But we didn't get much credit for that. That's the kind of thing that needs to be changed.

There are two keys to going forward. One is that the groups that do survive, they have to, clearly, be interested in collaborating with the other groups. Second, if you do that, then the group should be rewarded for that kind of behavior. Some of the cooperative groups have been doing that for 40 years, they just haven't explicitly agreed to supporting each other's trials with the same enthusiasm.

Since the IOM report came out, I have been saying to my brothers and sisters that they ought to be having these conversations [regarding mergers], because it was very clear to me what the IOM was saying. Now there is full recognition of that. There are certain groups—SWOG would like to believe it's one of them—that are large and multidisciplinary and study several cancers, and I think that is the most efficient mechanism.

The timeline that Jim showed is ambitious. He has to get buy-in from lots of people along the way. We only had one meeting with him. There are other things that need to be discussed and agreed upon. I don't see why there is an advantage in stalling. I think we should be moving forward, and we welcome that. I presented to the NCAB in July to their task force and told them that we think the IOM recommendations are correct and should be followed, but SWOG has been engaged in making many of those changes for the past several years, so there weren't surprises for us. We have been engaged in trying to do the things that make us efficient and more effective,

make decisions about the kinds of trials we want to be doing, trying to make the studies we do always aimed at changing the practice of medicine. So any phase III trial we do has to pass that test, that it would change the practice of medicine in a significant way. Not in the way that pharmaceutical studies seemed to be focused, which is what's the lowest hurdle I can pass to get FDA approval. That's the kind of thing we have been talking about openly for the past several years.

I think that money is going to be important. Obviously, it's a function of our country's economy. We have to remember that the economy is not so terrific, so to be clamoring for more money doesn't seem like it's likely to be successful, nor it is very good strategy. I think if we show the kind of things that we need to be doing to improve, I think the money will follow. But I also think it's important that when the NCI says it wants to comply with the IOM, that it's very important that all of the recommendations be followed, and we've only heard about some of them.

We haven't heard any details about [NCI internal changes] and that's as important as the groups changing.

It's not easy to change. These things are not easy to do, but we were quite pleased with what Jim said. We are not threatened by it. We think we are going to be one of the survivors.

For past couple of years, I have been talking about the need for a redefinition of the cancer centers and cooperative groups working in a collaborative fashion. I was very pleased to see Jim Doroshow talking about that. I was pleased to see the NCAB task force recommending that the centers do that. For SWOG, the single most important category of membership are the cancer centers. They are the people who provide the faculty, who write the studies. They are the people in our system, each U10 holder must have from their own institution, at least 50 patients. This is the most encouraging news that I've seen in that regard. The cooperative groups will only be successful if the cancer centers are convinced that it's in their interest to be collaborating.

Just like the cooperative group guidelines need to be amended, the cancer center guidelines also need to be amended to include that you are going to get rewarded as a cancer center for participating in the national cooperative group system. That deserves some emphasis.

I was a cancer center director, and when you talked about what clinical trials you participated in, it was sort of discounted when you said you put patients on national cooperative group studies. It was absolutely discounted. If I am a faculty member at a cancer center and I have a great new idea that comes out of my laboratory and it goes into the clinic, and I can see in phase I and phase II that it has promise, shouldn't you think that I should also be willing to put my patients into the phase III study that proves that the idea is really important? Absolutely. But that has never been explicitly stated.

SWOG requires that if you want to be [an institutional member] and be funded, you have to put 50 of your own patients onto the trial. We did that six years ago, we made that expectation known, and people thought we were a little bit nuts, but all of our grant holders have met that requirement. It demonstrates the kind of leadership that can come from a cancer center, putting your own patients onto the trials of your own ideas. That's not incompatible with what a cancer center ought to be doing. There ought to be rewards for cancer cancers that do that well, and perhaps punishments for those that don't do it at all.

The single best thing you can do to improve cooperative groups is to incentivize the cancer centers, provide them U10 grants so they can participate. That program needs to be expanded. One of the requirements to be a U10 site is to have an active training program. It's not surprising to see Doroshow talk about the importance of training in the cooperative groups. The training largely takes place in the cancer centers. There are many places we can be working better together, but because of the way the cancer centers were organized and the cooperative groups were organized and the way the CCOPs were organized, they all need to be working in a collaborative fashion for this to work.

The cooperative groups are the lynchpin of that effort, because they are the ones that provide the definitive evidence that some things work well. I also think we should be studying the cost of one treatment versus another, because we have the ability to do that.

Monica Bertagnolli, chair, Cancer and Leukemia Group B: I really feel that this is a great opportunity. The spirit so far is that everybody is working really hard and sincerely wanting to have the spirit of the IOM report followed and to really transform the system into a system that works really well for everyone.

Everybody wants to do the right thing. Everybody wants to do good cancer trials. Nobody wants anything other than that. The NCI has been acting in good faith, and groups have been acting in good faith. There have been these multiple different aspects of the system that have been making it harder and harder. Finally, we see an opportunity where everybody has to make this

happen. It's not just one group pointing their finger at another group, saying you have to change. It's everybody realizing that everybody had something to contribute to slowing the system down, and now everybody has something to contribute to transforming it. That's what the IOM report did very well. It took a step back, looked at every single component of the system, looked critically at the problems and then asked for changes across all the different parties. So far, we are very optimistic.

The groups are doing their part to take the suggestions very seriously, to really implement them. So far, we see evidence that the NCI is also taking this seriously in trying to work with the groups. We hope the other components that are really essential will also be there. The one that we are not sure about is funding. This is an environment where funding is just so hard to come by. That has people nervous. After all this change, there really isn't any way to make this any cheaper. We are concerned that that piece, which is pretty critical, is not going to be there. But all we can do is do the best we possibly can.

I think there was a very broad acceptance of the IOM report as being a very good roadmap. It took a group that could step away from the whole situation and ask for global changes, as opposed to the participants who are mired in the system. It's much harder to make realistic change when you are down in the trenches. It takes a group to go beyond it and take a large view and analyze the situation, and come up with recommendations that really address the issues on all sides. That's what the IOM report did so well. People read that and at the end of it said, if everybody did what this says, things would really work well. They could see the potential if everybody did their part. I really think that is the theme here. Everybody needs to do their part.

Our interactions with NCCTG pre-existed the IOM report by eight or 10 months. It made sense to us way back that consolidating our statistical operations would be a good thing. That was completely independent of my knowledge that the IOM committee was meeting. Your statistical center is the heart of the entire group almost, because it's the data operations, information technology, it's the communication network of the whole group. The NCI supported that financially, which really made it possible. I have to really give them a lot of credit for that support. We dealt with so many of the issues that it takes to bring two different groups together that it made it easier for us to get started doing more consolidation as time went on.

The three groups have formal governance structures, and each have a board of directors we answer to. Our board of directors need to approve any merger plan or formal consolidation of the group. There are many different directions we could go. It's got to be approved by our different boards. We have not completed that process. We are clearly very much discussing how we can integrate the groups fully, both scientifically and operationally, but the exact plan and our boards approving that plan, that's still underway. It will take some time.

The real value of the groups is that the investigators themselves have an identity with the group, have loyalty to the group, and literally sacrifice for the groups. The last thing we would want to do is to force some kind of situation that our members would not support. That would damage the groups. So we are trying to proceed with the very clear involvement of our members. That takes time.

What we are seeing now is our scientific groups are getting together, our different boards of directors are getting together to talk about what is the vision of the organization, what we want to achieve. Really doing the groundwork, so that at the end of this, if we are successful, will have a very vital group where every one of the members is invested and has a real part. Frankly, we can't afford to lose the loyalty of our members. They really are the group. If we are going to do this and we are going to do it right, we are going to do it in a way where these very dedicated members feel that this is the right thing to do. That's how we are proceeding. That's not something the group chairs can decide.

It's clear that a group is really more than the NCI grant. A group is [made up of] institutions that are willing to do this work for such a reduced cost. It includes the teams that can partner with industry to help augment the federal support. The process of getting a good cohesive group together is not just an application for a grant, it's all those other things. Fortunately we have been partnering with NCCTG and ACOSOG over the statistical center, so a lot of the groundwork has been done for us. The key now is not to focus on our statistical center, but to focus on our members. I think we are going to be able to do it and have a good cohesive group by the time of the next grant application.

It will cost a lot to do this right. It has been done on such a shoestring for so long. It's crazy to think that all the consolidation that needs to happen can be done without a substantial infusion. And then, we are still left with the issue of the per capita payments $4,000 per patient below the break-even mark. If we are spectacularly successful and bring up all these really

great studies and get them going and get them accruing like crazy, which is what we are hoping to do—if we do that, we'd break the bank. It has happened to all of us. 'You'd better stop accruing, because we don't have enough money.' That's just the nature of the beast.

Our NCI resources have not been placed in clinical trials to a significant degree. It takes a lot of money to do clinical trials. The NCI really has not put a substantial portion of its budget toward clinical trials. I would wish that would change. Nothing will change for the patients without clinical trials.

We are now gearing up the system to be very responsive, very well-vetted, and very cutting edge, and getting exciting new research into the system, it's a great time, people are very enthusiastic and excited and ready to go, but without additional funding it will come crashing in on us. That will be a big shame for our patients.

I know that Jim Doroshow is 100 percent supporting us in this, but he's not Congress. All we can do is make the case and get our ship in order as quickly as we possibly can, which I think we're doing, and do everything we know we should be doing, and hope for the best when it comes to the actually funding to allow us to do our work.

Walter Curran, chair, Radiation Therapy Oncology Group: If you think big picture, the actual number shouldn't matter as much as making sure they are adequately funded and that they provide sufficient diversity in the emphasis and research. If by reconfiguring, we are more successfully able to get enthusiastic support from NCI, then it's a good thing. I don't have a strong opinion as to what the idea number is. It will require a good bit of work to realign a few groups or to merge a few groups, but we're prepared to do that if, in the end result, we have a more vigorous system. I don't think it's a good idea to have a smaller number of groups and not have diversity of focus among the groups. Right now, one of the strengths of the cooperative group system is that you have just one group focusing on children's cancers, another on gynecologic cancer, RTOG looks at those diseases where radiation treatment in conjunction with other approaches could make a meaningful difference. What we don't want to see is just duplication of infrastructure and emphasis among the groups. I think having diversity is critical and I'm hopeful that we will be able to work with a new structure to be able to do that.

It's hard to know exactly how it's going to be played out, when there are mergers and consolidations. We are talking with other groups to see whether we have sufficient commonality in our goals and in our culture that there is an advantage of us aligning with one group versus another.

The key concern that I have is that there is so much volunteerism among physicians and other people in the current structure that we in no way want that to be harmed by this process. You have people whose identity professionally is so strongly associated with the group to which they belong, we just don't want mergers to get people to lose that positive spirit of volunteerism.

At the last CTAC meeting, there was a presentation of the amount of volunteerism, and it's substantial. It was a nice analysis, but I actually think it's an underestimate. So it's really critical that the surgeons involved with ACOSOG or NSABP, or the gynecologic oncologists in GOG, or the radiation oncologists in RTOG feel like, in a consolidated model, they still have a home to which they will dedicate their precious time and energy. That's really a critical issue. I'm hoping that NCI really understands that there is probably not going to be a huge savings in this financially, but the hope would be that there can be sufficient resources to make processes more efficient.

We don't have a formal agreement with any group, but we certainly are talking. With the expectation that we are going to have the five groups as of January 2014, this is a pretty tight timeline. The submission of new revised grants will be taking place within the next two years. We are having conference calls this week and next week with RTOG leadership to get some broader feedback on some of the options to consider. We knew something like this was going to come out.

If it's two groups coming together, it can't be one swallowing the other, it has to be a partnership where the membership of both groups and the leadership of both groups really feel they have a stake in the new entity. If that's done wisely, then hopefully, we could have a stronger model moving forward.

Any merger in the business world and elsewhere is challenging. When I talked to a business leader about this, his response was, "I'm assuming you don't have a mergers and acquisitions department." I said, "I don't think so."

FDA News:

Avastin Battle To Be Fought At FDA—And On Capitol Hill

(Continued from page 1)

decide if Avastin is the right medicine for them."

If this battle is indeed fought, it will be the first of its kind.

The authority to withdraw accelerated approval indications is included in the 1992 legislation that created the approval mechanism that allows contingent approval of drugs based on evidence that a surrogate endpoint is reasonably likely to predict clinical benefit.

However, the withdrawal mechanisms have never been used by the agency. The agency has taken other routes to yank accelerated approval drugs from the market. For example, AstraZeneca's lung cancer Iressa (gefitinib) was placed in a restricted access program in 2005. The same year, MedImmune voluntarily withdrew one of the indications for Ethyol (amifostine). And earlier this year, Pfizer withdrew its leukemia drug Mylotarg (gemtuzumab ozogamicin) after three studies failed to demonstrate its efficacy.

If Genentech indeed fights to keep Avastin's billion-dollar breast cancer indication, the battle will involve Congress, advocacy groups, and breast cancer experts. The drug, which costs about $8,000 a month, seems to have enthusiastic supporters among conservatives, who state repeatedly that FDA is basing its decision on cost.

The agency denies these accusations, stating that the decision to pull the drug is based solely on clinical data. The agency has no authority to consider cost when it makes decisions on drug approval.

In July, the FDA Oncologic Drugs Advisory Committee voted 12 to 1 in favor of revocation of the accelerated approval Avastin received in 2008 (The Cancer Letter, July 23). However, drug compendia continue to list the drug's breast cancer indication.

FDA was originally expected to make a decision on Sept. 17, but said it would delay for 90 days in order to consider new data submitted by the sponsor. There were no known new phase III data to consider, and the decision to delay was made on request from the administration, sources said.

Indeed, some conservative politicians were portraying the drug's availability as an example of "Obamacare" and the administration was apparently trying to contain losses in the midterm election (The Cancer Letter, Oct. 22).

At a press conference Dec. 16, FDA officials said that they have informed Genentech about their intent to eliminate Avastin's breast cancer indication. "Genentech has not agreed to remove the breast cancer indication voluntarily, so the agency has issued a Notice of Opportunity for a Hearing," the agency said.

Reaction on Capitol Hill was immediate. Incoming chairmen of House committees that have authority over FDA responded with a joint statement.

"Allowing the FDA to factor in the cost of a drug when determining whether that drug should be approved is the first big step towards government rationing," said a statement signed by Fred Upton (R-Mich.), incoming chairman of the House Energy and Commerce Committee, Committee Vice Chair Sue Myrick (R-N.C.), incoming Health Subcommittee Chairman Rep. Joe Pitts (R-Penn.), and senior Health Subcommittee Member Phil Gingrey (R-Ga.).

"The FDA should only look at the safety and efficacy of a drug. Allowing the FDA to inject cost into the approval process jeopardizes the care of those nearly 18,000 women who rely on this drug. At a time when Europe is moving away from restricting access to life-saving medications, the FDA appears to be moving in the opposite direction.

"Last year, the U.S. Preventive Services Task Force recommended that women under 50 forgo routine mammography screenings. Today, the FDA is withdrawing its approval of a drug that helps prolong the lives of thousands of women living with aggressive breast cancer. Unfortunately, this is only just the beginning. The new health reform law—the so-called Patient Protection and Affordable Care Act—creates 159 new boards, commissions, and agencies that will destroy the doctor-patient relationship and replace it with federal bureaucrats deciding who gets care and what treatments they can receive."

Avastin has not been shown to produce a survival advantage. The drug was approved based on progression-free survival, and is now being withdrawn because the magnitude of PFS wasn't large enough to justify approval.

FDA officials said the Centers for Medicare and Medicaid Services will continue to cover the drug's use in breast cancer while the accelerated approval proceedings run their course.

FDA's Nine Reasons to Withdraw Indication

"After careful review of the clinical data, we are recommending that the breast cancer indication for Avastin be removed based on evidence from four independent studies," Janet Woodcock, director of the

FDA's Center for Drug Evaluation and Research, said in a statement announcing the decision.

"Subsequent studies failed to confirm the benefit observed in the original trial. None of the studies demonstrated that patients receiving Avastin lived longer and patients receiving Avastin experienced a significant increase in serious side effects," Woodcock said. "The limited effects of Avastin combined with the significant risks led us to this difficult decision. The results of these studies are disappointing. We encourage the company to conduct additional research to identify if there may be select groups of patients who might benefit from this drug."

The FDA decision memorandum, written by Richard Pazdur, director of the FDA Office of Oncology Drug Products, said Avastin is being pulled for nine reasons.

An excerpt from Pazdur's memo follows:

• Presently, Avastin has been studied in four large randomized trials in breast cancer. No trial to date has demonstrated an improvement in OS. Based on consultation with ODAC in 1999, FDA has recommended that an improvement in OS be the regulatory endpoint for applications evaluating drugs and biological agents in the first-line setting in metastatic breast cancer. An improvement in OS is considered direct clinical benefit. None of the trials for initial treatment of metastatic disease (E2100, AVADO, RIBBON1) were reviewed by the Agency under a special protocol assessment and the Agency did not agree with the primary endpoint (PFS) prior to trial initiation. Recent approvals in the first-line setting of metastatic breast cancer, including trastuzumab plus chemotherapy (1998) and gemcitabine plus paclitaxel (2004), were supported by data indicating both OS and PFS improvements.

FDA has considered PFS as a surrogate endpoint of clinical benefit rather than a direct measure of clinical benefit. In granting accelerated approval for Avastin as a first-line treatment in metastatic breast cancer in the absence of an OS improvement, FDA demonstrated regulatory flexibility in its desire to make available promising drugs to patients with serious and life-threatening disease. As noted above, several ODAC consultants believed that the magnitude of improvement in this disease setting could be considered clinical benefit. The continued marketing of Avastin for the metastatic breast cancer indication was contingent upon either an improvement in PFS of a similar magnitude as noted in E2100 or an improvement in OS in the AVADO and RIBBON1 trials.

• FDA considers additional measures of direct clinical benefit to include amelioration of disease-related symptoms, a delay in symptoms or improvement in patient-reported outcomes, including health-related quality of life measures. No evidence has been provided by Genentech that Avastin improves patient symptoms or patient-related outcomes. Genentech has not provided evidence that the addition of Avastin delays progression of disease-related symptoms in breast cancer.

• FDA has received numerous testimonials from patients and families attesting to the benefit of Avastin in the treatment of individual patients with breast cancer. For the indication under consideration, Avastin is added to conventional chemotherapy, which makes it very difficult to isolate the effect of Avastin outside of a controlled setting. While it is possible that some patients may receive clinical benefit from Avastin for treatment of breast cancer, the available data are not sufficient to demonstrate that such a subgroup exists and, if so, how to identify the patients in advance.

• FDA has accepted regulatory endpoints using radiographic measures to approve drugs in other disease settings, including refractory (second and third-line) metastatic breast cancer. These endpoints include PFS and ORR. Approximately 80% of events used in the determination of progression in the first-line breast cancer trials (E2100, RIBBON1, AVADO) were on the basis of measurable disease determined primarily by radiographic examinations. Since these changes in radiographic endpoints are indirect measures of clinical benefit, an improvement in PFS must be robust, and be of sufficient magnitude to demonstrate a favorable risk/benefit analysis in relation to the observed adverse event profile, disease setting, and available therapies.

• Due to the indirect relationship of an improvement in PFS to clinical benefit and the subjectivity in evaluating radiographs, FDA informed Genentech that the magnitude of improvement noted in the E2100 trial would need to be confirmed in additional trials. FDA had previously evaluated the AVF2119g trial in second and third-line metastatic breast cancer and was aware that this trial did not demonstrate an improvement in PFS or OS.

• The evaluation of PFS in E2100 was based on an interim analysis. E2100 was stopped early when 65% (357/546 of the planned events had occurred). Stopping a trial early for efficacy based on an event-driven, pre-planned analysis with pre-specified allocation of type I error ensures that a valid statistically significant result has been obtained. However, the estimate of the treatment effect based on an interim analysis is more variable than

at the study completion and may represent a "random high" estimate of the true effect size of Avastin in that trial. In contrast, nearly all the planned events were observed in the AVADO and RIBBON1 trials and the trials were not stopped early. Although all three trials demonstrate a statistically significant result for PFS, it is possible that the magnitude of effect observed in the E2100 based on the interim analysis represents a random high and that the true effect is more consistent with the smaller effect seen in the other trials.

• The randomized "add on" design of the four trials in breast cancer allowed the evaluation (isolation) of Avastin effect from the chemotherapy regimens. These chemotherapy regimens included anthracycline or taxane-based chemotherapy, gemcitabine, vinorelbine, and capecitabine. In 2008, Genentech proposed the AVADO and RIBBON1 be used to confirm the observed 5.5-month improvement in PFS noted in E2100 with the expectation that the observed effect of Avastin on PFS would be consistent irrespective of the chemotherapy regimen. Assertions that there is a unique interaction between Avastin and paclitaxel providing a rationale for the magnitude of PFS change observed only in E2100 has not been substantiated by either clinical or non-clinical evidence.

• Genentech is encouraged to further develop Avastin in breast cancer to identify patient subsets who are likely to benefit in a risk/benefit evaluation. No current subgroup analyses have demonstrated this evidence. We strongly urge Genentech to submit future trials under special protocol assessments to ensure agreement with the Agency.

• A comprehensive understanding of Avastin's effect on PFS, ORR, OS, toxicity, and risk/benefit analysis in breast cancer has become evident since the accelerated approval in 2008. Excluding the PFS results of E2100, the results of the remaining three trials of Avastin (first and second-third line breast cancer populations) are consistent and indicate that when Avastin is used with chemotherapy in breast cancer there is a modest effect on PFS and ORR with substantial increases in toxicity without a demonstrated improvement in OS or symptom benefits.

FDA documents related to the Avastin decision are posted at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm193900.htm

Oncologists treating patients with Avastin for metastatic breast cancer should use their medical judgment when deciding whether a patient should continue treatment with the drug or consider other therapeutic options, the agency said.

FDA officials said they are open to working with Genentech on any proposals to conduct additional studies of Avastin in patients with metastatic breast cancer designed to identify a population of patients in which the drug's benefits exceed the risks.

The Mechanism of Losing Approval

The process of stripping an accelerated approval requires a separate public hearing before an expert panel. It's likely that in the case of an oncology drug, this panel would be comprised of ODAC members, sources said.

Considering complexity of bureaucratic procedures that will come into play, this means that Avastin could retain its accelerated approval for months to come, as oncologists, patient groups and politicians continue to wrangle over the future of the billion-dollar indication.

Withdrawal procedures are spelled out in 21 CFR Subpart H 314.530. Here is how the process works:

• The director of the FDA Center for Drug Evaluation and Research writes a letter containing a "notice of an opportunity for a hearing" on the center's proposal to withdraw the approval of an application. The letter contains the reasons for the action. This is what has happened with the Proamatine application last month.

• The sponsor then has 15 days of receipt of the notice, the applicant waives the opportunity for a hearing. If the sponsor requests a hearing, the agency announces the hearing in the Federal Register. The sponsor then has 30 days of receipt of the notice of opportunity for a hearing to submit the data and information which would form the basis of the hearing.

• "An advisory committee" would be present at the hearing, the regulations state. However, it's not clear whether this would be the same committee that would have been consulted on approval. The committee will be asked to review the issues involved and to provide advice and recommendations to the FDA commissioner.

• The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the center may question any person during presentations. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

• The commissioner's decision would constitute

final agency action from which the applicant may petition for judicial review.

European Authorities Act on New Data

After obtaining approvals for the Avastin-paclitaxel combination based on the E2100 trial, Roche, Genentech's parent company, decided to broaden the indication to include docetaxel and capecitabine.

This strategy instead led to regulatory moves to eliminate the indication in the U.S. and to narrow it in Europe.

On the day the U.S. regulators said they would seek to withdraw the Avastin-paclitaxel combination, the Europeans announced that are setting in motion the machinery to remove the Avastin-docetaxel combination. That combination was approved in Europe in September 2009. The U.S. never approved the docetaxel combination.

In a statement dated Dec. 16, the European Medicines Agency said also that the Avastin-capecitabine combination wouldn't be approved.

In Europe, Avastin had regular approvals for breast cancer. Though Europe has an approval category equivalent to accelerated approval, such approvals—called conditional approvals—are granted only to new molecular entities, as opposed to supplemental indications.

No new data for using Avastin in conjunction with paclitaxel were presented to either the U.S. or European authorities.

The text of the EMA announcement on Avastin follows:

The European Medicines Agency has confirmed that the benefits of Avastin in combination with paclitaxel outweigh its risks and that this combination remains a valuable treatment option for patients suffering from metastatic breast cancer.

The agency's Committee for Medicinal Products for Human Use (CHMP) also concluded that the balance of benefits and risks of Avastin in combination with docetaxel is negative and that this combination should no longer be used in the treatment of breast cancer.

Patients who are currently being treated with this combination should discuss their ongoing treatment with their doctor.

Avastin is an anticancer medicine which contains the active substance bevacizumab. It is used in combination with other anticancer treatments to treat cancers of the colon, rectum, lung, kidney or breast. The CHMP's review was restricted to the use of Avastin in breast cancer and does not affect its use in the other indications.

The CHMP started a review of the use of Avastin in the treatment of metastatic breast cancer because new data from a study suggested that Avastin in combination with docetaxel may have a negative impact on the overall survival (how long patients lived after treatment was initiated).

The study was submitted to the agency to support an application to extend Avastin's breast cancer indication to include combination therapy with capecitabine.

Combination therapy of Avastin and docetaxel for metastatic breast cancer was approved in September 2009 on the basis of data that showed a small but significant increase in progression-free survival (how long the patients lived without their disease getting worse), and no detrimental effect on overall survival.

The new data submitted to the agency add uncertainty about the effect on overall survival and a detrimental effect on overall survival cannot be excluded. The new data also question the size of the effect on progression-free survival, which appears to be smaller than previously observed.

Because the increase of progression-free survival remains very small, the CHMP concluded that the benefits of Avastin in combination with docetaxel no longer outweigh its risks.

For Avastin in combination with capecitabine, the committee found that although the data showed a modest increase in progression-free survival, no clinically relevant effects were observed on other endpoints such as overall survival or health-related quality of life.

The relatively modest benefits were considered not to outweigh the high toxicity of the combination of Avastin and capecitabine, given that the new indication was aimed at patients for whom a relatively mild treatment would be appropriate. Therefore the committee concluded that the new indication should not be approved.

For Avastin in combination with paclitaxel, the committee concluded that the benefits continue to outweigh the risks, because the available data have convincingly shown to prolong progression-free survival of breast cancer patients without a negative effect on the overall survival.

The committee therefore recommended that for the treatment of breast cancer Avastin should only be used in combination with paclitaxel.

The committee's recommendations have been sent to the European Commission for the adoption of a decision. The review of Avastin was carried out under Article 20 of Regulation (EC) 726/2004.

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DEPUTY DIRECTOR POSITION AVAILABLE

The University of California, Irvine is recruiting a physician scientist for a tenured position at the associate or full professor level who will also be the Deputy Director of the Cancer Center. We are seeking an experienced translational scientist with an established research program focused on either basic/translational investigations or clinical/translational science. This is a senior leadership position within a National Cancer Institute designated Comprehensive Cancer Center. Responsibilities of the selected individual would include:

(1) Conducting a translational research program with external peer-reviewed funding.
(2) Bridging basic, clinical and cancer control research among the 6 research programs with the goal of facilitating translational programs, P0-1s, SPOREs and similar multi-investigator grants and contracts.
(3) Providing senior leadership for the physician-scientists and clinical investigators in the Center.
(4) Managing the clinical research infrastructure within the center.
(5) Representing the Cancer Center throughout the campus and greater community.

As the current long-term Director has announced his departure from this role following the next CCSG review, responsibilities of the Deputy Director will expand in the near future to include transitioning the Center with new leadership.

Applicants must hold an MD or equivalent degree, be board certified in their cancer related sub-specialty, and be eligible to obtain an active license to practice medicine in the state of California.

For more information, contact Krista Hollinger, MPH at kholling@uci.edu.

Application Procedure: Interested candidates must submit a cover letter, curriculum vitae, statement of research, statement of teaching, and contact information for 3-5 references via the University of California's Academic Personnel RECRUIT system at http://recruit.ap.uci.edu. Please reference OEOD# 5012.

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