THE CANCER LETTER

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Vol. 37 No. 12
March 25, 2011

Clinical Research

Why Four? Official Challenged To Explain Rationale for Proposed Number of Groups

By Paul Goldberg and Conor Hale

What's so special about the number four?

Since last fall, everyone in oncology has accepted that NCI would fund no more than four clinical trials cooperative groups focused on adult cancer.

There has been some grumbling, but no one has challenged NCI officials who shaped the plan to state their rationale for mandating mergers that would shrink the number for groups from nine to four.

Why not three? Why not five?

On March 21, at a workshop conducted by the Institute of Medicine National Cancer Policy Forum, IOM scholar in residence Sharon Murphy took the microphone and asked James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis and the official who has shaped the institute's

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Professional Societies:

McCormick to Serve as President-Elect of AACR; Garber to Begin Term as Association President

FRANK McCORMICK was chosen president-elect by the **American Association of Cancer Research.** McCormick will take the position April 4 in Orlando, at the AACR's 102nd annual meeting.

Judy Garber will be sworn in as president of the AACR. Garber is director of the Center for Cancer Genetics and Prevention at the Dana-Farber Cancer Institute, associate professor of medicine at Harvard Medical School, and an associate physician of medicine and attending physician of medical service at Brigham and Women's Hospital in Boston.

Garber succeeds **Elizabeth Blackburn**, Nobel laureate and the Morris Herzstein professor of biology and physiology at UCSF. Blackburn served as AACR president for the 2010 to 2011 term and will assume the role of past-president.

McCormick is the director of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco. He holds the E. Dixon Heise distinguished professorship in oncology and the David A. Wood distinguished professorship of tumor biology and cancer research. He is the associate dean of the UCSF School of Medicine and a distinguished professor in residence in the departments of microbiology, immunology, biochemistry and biophysics.

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Why Four? See IOM Report, p.148, NCI Official Doroshow Explains

(Continued from page 1)

plan, to justify it.

"I'm really curious, why four?" asked Murphy, a former group chair, who was a staff member on both last week's workshop and the committee that provided the impetus for the current reorganization of the groups.

Does NCI have flexibility on that number? Is there any chance that five groups may be allowed to go forward?

"We understand you don't want one [cooperative group]; that's clear," continued Murphy, a former member of the NCI Board of Scientific Advisors who served as chair of the Pediatric Oncology Group before it merged into the Children's Oncology Group nine years ago.

"And you don't want ten, but can there be some latitude still?"

NCI officials have said that they would formulate their final plan sometime in July. However, the interim version has caused a radical realignment among cooperative groups (The Cancer Letter, March 11, March 18). In recent weeks, the groups announced a series of mergers—which some observers described as shotgun weddings mandated by NCI. Currently, the number of groups stands at five.

"I think what we've seen is a rather hasty rush to the altar in some arranged marriages, and this was not what the IOM suggested," Murphy continued, standing at the microphone at the IOM meeting. "The train has left the station, the horse is out of the barn."

The institute's effort to reform the groups was rooted in last year's report titled "A National Cancer Clinical Trials System for the 21st Century" (The Cancer Letter, April 16, 2010).

Generally, government agencies have considerable latitude in interpreting recommendations from IOM.

Murphy wasn't alone in wondering about the origin of the number four. In interviews with The Cancer Letter, several members of the IOM committee and its staff said that the group deliberately refrained from mandating the number of groups. For example, the report's Recommendation 1 urges NCI to "facilitate *some consolidation* of cooperative group front office operations by reviewing and ranking the groups with defined metrics on a similar timetable and by linking funding to review scores."

"You have the book?" asked Doroshow, responding to Murphy's question.

"I have the book," replied Murphy.

"Would you go to page 148? I can show you the sentence..."

"Actually it's from page 16," said Murphy, referring to Recommendation 1, which stops short of recommending the number of groups.

"No, it's in the back of the book, specifically between pages 147 and 149 in the final published version, where it recommends four multidisciplinary adult groups," Doroshow said.

Indeed, the passage containing the number "four" appears in the middle of page 148 of the report. It is, however, presented as a hypothetical. The passage reads:

"One possible way to reorganize the group front offices would be by disease type. For example, there could be four multidisciplinary groups dedicated to adult cancers, with the task of performing trials for different diseases and with true cooperation occurring among all the groups. Each group could perhaps have four disease-specific committees to ensure broad coverage and some overlap for each disease. In other words, two groups would undertake trials for lung cancer, two for colon cancer, two for breast cancer, two for head and neck cancer, two for hematology, and so on. One way to achieve consolidation would be to alter the peer review process for the cooperative groups to focus on the accomplishments of disease committees."

The number four has also been questioned in two white papers, one issued by the Gynecologic Oncology Group, the other by directors of cancer centers. The latter

THE CANCER LETTER

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Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $395 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Founded Dec. 21, 1973, by Jerry D. Boyd.

document, obtained by The Cancer Letter, presents a reorganization plan very different from NCI's, which includes alternative scenarios for the number of groups (See story on page 5).

Earlier this month, the NCI Board of Scientific Advisors threw out two key elements of the NCI plan—the informatics structure and tissue banks.

The informatics debacle involves the institute's caBIG program, which spent $350 million without the benefit of peer review.

Sources in cooperative groups said to The Cancer Letter that plans to deploy a single data capture system appear to be on track. However, the NCI contract covering the system is facing a legal challenge.

The tissue banks problems are equally profound. The institute planned to drop the number of grants funding tissue banks from the current number of nine to just three. These three banks would have served the four adult groups and the pediatric groups. Since many group chairs also serve as the principal investigators on the tissue bank grants, this reorganization would have placed the tissue banks outside the groups' control. Bouncing the concept back to the NCI staff, the BSA said that a reorganization of biospecimens banks before completion of reorganization of the groups would be premature.

The workshop, which was co-sponsored by IOM and the American Society of Clinical Oncology, was intended to provide a public discussion of implementation of the IOM report. Another workshop is expected to take place next year. Audio files and slides from the presentations are posted at http://www.iom.edu/Activities/Disease/NCPF/2011-MAR-21.aspx.

"Maybe John Would Want to Comment on This"

In another question to Doroshow at the March 21 workshop, Murphy focused on an oversight structure for the network of groups.

Would that new extramural group oversee the entire clinical trials system?

The proposed oversight board was a part of Doroshow's slides since November (The Cancer Letter, Dec. 17, 2010). However, in the past, no one focused on its role.

"We have by no means figured out exactly what this is going to do or be, except to tell you that I have, in my position for the past seven years, absolutely needed an extramural group to provide input, with respect to what the strategic priorities across diseases might be," Doroshow said. "We've really had no clear way to do that."

The new board may help NCI prioritize resources, Doroshow said.

"Given what we face in terms of resources, one job of such a group—which will involve membership of many constituencies, I'm sure—will be to help advise," Doroshow said. "It hopefully can be constructed as a subcommittee of the Clinical and Translational Research Advisory Committee, so that it will have real status.

"But what's so important is having a place for a lot of different constituencies to actually look when we have to make these difficult decisions strategically. What is our portfolio like, to provide national perspective on that. We don't really have such a group."

After posing her two questions to Doroshow, Murphy suggested that John Mendelsohn, chair of the committee that produced last year's IOM report and president of MD Anderson Cancer Center, might want to comment on both the issue of the number of groups and the overarching review board.

"Maybe John would want to comment on this," Murphy said. "I was engaged a bit with this committee report, though not a member of the committee and we clearly sort of wanted peer review to play a role, but maybe Dr. Mendelsohn… What was that page again? I was on page 16 where it's in bold type."

"Read through bottom of page 147, 148, 149," Doroshow replied.

Mendelsohn didn't challenge NCI on the number of groups, and instead focused on the role of steering committees in the groups.

"My constitutional law degree; I've forgotten all I've learned," Mendelsohn said. "The report here may not be totally consistent, but the question of who does the review of whether there's one group or four groups or ten groups.

"I don't remember a strong feeling one way or the other. In fact, I think the way it's bubbling up is very excellent.

"As long as I have the microphone, I just wanted say that there's one interesting area of tension—and this has been a terrific discussion incidentally, and what's happened in six months is amazing to me and everyone should be proud of the cooperativity and the collegiality that we've all seen.

"The area of tension is in the area of centralization. And one of the main things I remember from these many committee meetings is the importance of the scientific steering committees that are going to be disease-site oriented, and they are the single empowered group to say yes or no. It's not the NCI and it's not nine different groups, it's the scientific steering committees.

"Now why did we put such an emphasis on that?

"Because, in spite of what I've heard—all the great things that have been done by the cooperative groups—there was redundancy. There were trials being done that were not asking the most cutting-edge questions, and the fact that 40 percent of the trials never got finished sort of emphasizes that. And we had hoped the scientific steering committees could add that extra patina—and it could be frustrating to people in a particular group if they proposed something and it didn't get approved, but today, it's only about 10 percent of grants that get approved. So we're sort of used to that.

"I think the other reason it was important to have the scientific steering committees, that Jim alluded to, and there was a sentence in the report that sort of said: we hate to say this, but if there isn't more money, the expense of doing the kind targeted, therapeutic trial that we want to do in the future is even greater—we'll have to do fewer trials. That's not what we recommend, but that would be the fallback position.

"We are in a tough budget area. And the scientific steering committees will add that extra power of expertise to help us prioritize, so that we can afford to do the trials where it may cost $8,000 or $10,000 a patient to do the detailed study we need, in order to screen 200 patients to find the 12 that are relevant for the new drug.

"So I haven't heard much discussion of the scientific steering committees, and I hope they're not neglected. They were an important thing—I think Rich will agree, because he was at all these meetings too—there were very important part of the planning process that we tried to put on paper in the report."

Richard Schilsky, chair of the workshop planning committee and section chief of hematology and oncology at the University of Chicago Medical Center, urged Doroshow to provide more detail on the purpose of the new oversight board.

"Just to be clear, I think most people are aware that the scientific steering committees have been going on for some time already, even before our report," Schilsky said "I think some of the issues that have come out—at least in my observation, certainly the current group chairs are more involved with this than I am—number one is, again, the speed of the process.

"Do they encumber the process in some way? Many of the steering committees now have subcommittees that are often referred to as task forces—where there's a lot of pre-review and back and forth with the groups before the concept even gets to the steering committee for formal review. And now there's going to be an overarching oversight committee that's going to do final prioritization, is that going to add yet another layer of review to the whole process?"

DOROSHOW: "Let me make it very clear, the idea behind that is not to do another scientific review, at all—but to take a look several years down the line to say: where are there scientific opportunities, and provide input to the NCI about where the priorities ought to be.

SCHILSKY: "So, just so we're clear, if I understand you, Jim, you're saying that you view this overarching committee as a committee that actually might assist more in planning, than in review or evaluation of things that are bubbling up through the steering committees?"

DOROSHOW: "It's not a review of trials in any way. Because we have more than enough of those layers, I would only say with respect to speed, that, as you saw on my slides, we have now data that we never had before to understand the impact of every stage. So I think that we are clearly able to address what is the impact of every piece of the puzzle."

SCHILSKY: "Hopefully we'll be able to manage that going forward. Great."

As Long as They Are Happy

First Norm Met Wally, Then Norm & Wally Met Phil

Discussion of the NCI-influenced mergers of cooperative groups continued to inspire allusions to love, marriage and sexual exotica.

"I'm the only one without an engagement ring," Philip DiSaia, chair of the Gynecologic Oncology Group and an oncologist at the University of California, Irvine, said at the March 21 workshop focused on realignment of the clinical trials system.

The only remaining small cooperative group, GOG is an obvious target for a merger. However, the group doesn't see obvious synergies with other groups and would prefer to remain single.

"Gynecologic Oncology Group is thriving," DiSaia said at the workshop co-sponsored by the Institute of Medicine Cancer Policy Forum and the American Society of Clinical Oncology. "We accrued to protocol almost 5,000 patients last year. We have, in the last 12 years I think, been the major participant in the only two NCI alerts. The backbone of the Gynecologic Oncology Group are the gynecological oncologists. There are only about 1,000 of us in this country, most of whom participate in the Gynecologic Oncology Group. I might say a lot of it is on a volunteer basis.

"We enjoy answering questions that come up scientifically. We had the best turnaround time of any

group. So it's hard for my executive committee to figure out how we're going to merge. Could you cut us up into five pieces or four pieces and put us in each group? Other groups have tried to create gynecologic oncology committees and failed. And I think that will fail.

Now, recently I have talked with Dr. Wally Curran [chair of the Radiation Therapy Oncology Group] and Norman Wolmark [chair of National Surgical Adjuvant Breast and Bowel Project] about joining their alliance.

And maybe the secret is in an alliance. I'm not sure what that means yet. But I just think that we don't fit very well—and maybe we should be a fifth group.

WOLMARK: So, Phil, in front of all these people, and this is being broadcast, so in front that audience as well—and there must be dozens of people watching!—I ask you, in an unabashed and straightforward manner, will you marry me?

Now full disclosure, it will be a threesome. But you know, we have to sacrifice in these times.

DiSAIA: I think open marriage could work.

WOLMARK: All right, we've solved another problem.

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Centers Propose Another Way To Revamp Cooperative Groups

Directors of cancer centers submitted a white paper that suggests a plan for reorganization of NCI-sponsored clinical research.

The paper, titled "Building an Integrated National Cancer Clinical Trials Program; A Proposal for Re-Organization from NCI Cancer Center Directors," is significant because centers are a politically influential constituency both at NCI and on Capitol Hill.

The paper argues that cancer centers are entitled to be represented in discussions of the future of cooperative groups because they provide support for group activities, from payment of salaries of group investigators to shouldering costs associated with enrolling patients in group trials.

The paper is co authored by six center directors, William Dalton, of H. Lee Moffitt Comprehensive Cancer Center and Research Institute, Steve Rosen, of Northwestern University Robert H. Lurie Comprehensive Cancer Center, Craig Thompson, of Memorial Sloan Kettering Comprehensive Cancer Center, Donald Trump, of Roswell Park Cancer Institute, George Wilding, of University of Wisconsin Carbone Cancer Center, and Cheryl Willman, of the University of New Mexico Cancer Center.

"While we recognize that the NCI cooperative groups have particular strengths and capabilities, particularly the infrastructure and expertise to conduct large randomized phase III trials, a final model that does not incorporate the NCI cancer centers or make use of their regional capabilities and networks, and, which does not find a way to effectively integrate community practices and health systems, will not be successful," the paper states.

The report urges NCI to focus on science, as opposed to organizational structures.

"We believe that the effort to reorganize our national clinical trials system is best done by first focusing on the development of multi-institutional, multi-disciplinary (medical oncology, radiation oncology, surgical oncology, gynecologic oncology, pediatric oncology, imaging, prevention, survivorship, etc.) disease-specific scientific working groups or 'teams,' who together focus on the design and development of large national phase III and possibly large randomized phase IIb clinical trials," the document states.

The white paper presents three approaches for structuring the teams.

Finally, the center directors call for creating a single "common national infrastructure to drive national phase III and randomized IIb clinical trials."

"This common infrastructure could be in an extramural setting, or in an institutional or industry setting, or partially at NCI, and would provide fully integrated IT support; tissue banking; finance and administration; interfacing and negotiating with pharmaceutical companies and institutions; contracting and legal services; statistical support for clinical trial design and analysis, etc.," the report states.

The system would be run by a single governing body at the NCI. This structure could include NCI leaders, center directors, advocates, and the industry.

The document is dated March 3. Its text follows:

Background

At the recent NCI cancer center directors' meeting held on the NIH campus on Feb. 17-18, 2011, following a status report by Dr. Jim Doroshow on the ongoing effort to reorganize the NCI cooperative groups in response to the IOM report, the NCI cancer center directors engaged in discussions with Dr. Doroshow, Dr. Harold Varmus, and other NIH/NCI retreat attendees on the topic of how to best re-organize our nation's cancer clinical trials effort to build a more integrated, efficient, and successful program. Like all entities engaged in these critical discussions, the NCI cancer centers wish

to be fully involved in this process for the following reasons:

1. The scientific discoveries and scientific foundation underlying the design of the majority of clinical trials conducted within the NCI cooperative groups emanates from the NCI cancer centers and their associated investigators.

2. The vast majority of the investigators who drive NCI cooperative group trials, disease committees, and correlative science studies through a "minimally funded, volunteer" effort under the auspices of the NCI cooperative groups are NCI cancer center investigators, whose permanent faculty support, research programs, and career development are primarily supported by the NCI Centers and their institutions.

3. Many of the NCI cancer centers have developed extensive statewide or regional networks for the conduct of cancer research and clinical trials (both therapeutic, prevention, and survivorship), and prospective and retrospective population-based cohorts, in collaboration with community-based oncologists and health systems, and as such, are poised to help build this national program by extending access and participation in clinical trials to larger number of Americans.

4. Many of the NCI cancer centers have built excellent infrastructures (CLIA-approved molecular diagnostic laboratories, tissue banking expertise, genomics/next generation sequencing core facilities, innovative functional imaging platforms, statistics, and bioinformatics) and hold the scientific capability to conduct the comprehensive genomic characterization of patients using next generation technologies which will be required for the prospective identification and targeting of patients to innovative trials and for monitoring therapeutic response.

5. Given the insufficient and comparatively low rates of reimbursement for participation in NCI-sponsored trials conducted by the NCI cooperative groups, the NCI cancer centers heavily subsidize the NCI cooperative group program by providing significant support for the faculty and staff effort and the infrastructure required to conduct NCI-sponsored trials in their institutions and communities using their cancer center, institutional, state, and/or private philanthropic sources. This "funding gap" is quite large.

A recent AACI survey demonstrated that in many cancer centers, while accruals to NCI-sponsored clinical trials may account for 40-60 percent of all accruals, the current NCI/NCI cooperative group reimbursement rate and funding mechanism provides only 8-15 percent of the actual cost of a cancer center's clinical trials staff and operation, not inclusive of faculty time and effort.

Our proposal focuses on the problem that together, we are all trying to solve: how can we best and most rapidly drive science forward into the design and conduct of innovative, practice-changing, national clinical trials to not only improve outcomes in cancer patients, but also prevent the disease or its recurrence, and, assure a high quality of life for survivors? We want to assure that all Americans benefit from the fruits of cancer research and have access to and can participate in a national cancer clinical trials system.

While we recognize that the NCI cooperative groups have particular strengths and capabilities, particularly the infrastructure and expertise to conduct large randomized phase III trials, a final model that does not incorporate the NCI cancer centers or make use of their regional capabilities and networks, and, which does not find a way to effectively integrate community practices and health systems, will not be successful. The ultimate redesign must be facile—able to move rapidly from scientific discovery to the design, implementation, conduct, completion, analysis, and reporting of a national clinical trial.

Thus, we are all invested in a new solution.

Given the state of the nation's cancer clinical trials program today, with a highly fragmented and competitive system spread among multiple NCI Cooperative groups with similar or overlapping disease-focused committees; with significant duplication of resources and investments to build multiple parallel infrastructures (among the NCI cooperative group program and also among community-focused efforts such as the CCOP/MB-CCOP and NCCCP programs); with unacceptably slow rates of implementation and completion of clinical trials; with an "engine" and evaluation metric that has required trials to be in place even if there is not a compelling question or critical hypothesis; and with exceedingly poor rates of patient participation and accrual across the nation, we believe that a far more radical re-structuring of this program is in order and we want to be part of the solution.

Proposed Models and Solutions

Part I: Multi-Disciplinary Disease-Focused Teams

The primary driver to reorganization should be a focus on science and the disease itself—not the infrastructure.

Fighting cancer comes first, not who controls the fight. The infrastructure should serve and facilitate the science, not control it.

We believe that the effort to reorganize our national

clinical trials system is best done by first focusing on the development of multi-institutional, multi-disciplinary (medical oncology, radiation oncology, surgical oncology, gynecologic oncology, pediatric oncology, imaging, prevention, survivorship, etc.) disease-specific scientific working groups or "teams" who together focus on the design and development of large national phase III and possibly large randomized phase IIb clinical trials, as we proposed at the NCI cancer center director's meeting.

This model has already proven highly successful in Europe and other countries and we could benefit from a thorough investigation of the opportunities, strengths, and weaknesses of these existing programs.

These disease-oriented multidisciplinary working groups would be national teams of translational and clinical scientists which are nimble and which can move quickly with the science, not heavily funded infrastructures which become entrenched or which create top-heavy, costly administrative structures.

A single team would focus on a single disease or group of related diseases.

Individual disease-focused teams should be heavily multi-disciplinary and multi-institutional, but their individual operational infrastructures and administrative support and coordination could be housed at a specific institution, ideally an NCI designated cancer center, for a single term contract (possibly 5-7 years), using a similar model for contract support that many national organizations use to manage the content and management of their scientific journals.

Proposed teams would be competitively reviewed. In a process we are continuing to discuss, and, as part of the competitive team-building process and application, a national working group chair would be identified by each disease-focused group and the Chair's institution would hold the funding support for the contract period. This individual would be charged with leading the team and would interface with the NCI and supporting infrastructures (see part II below). These multi-disciplinary working groups would be "scientific think tanks" that drive clinical trial concepts and design, develop correlative science studies, and set prioritization of trials for targeted accrual.

A major strength of this approach to reorganization is that the formation of disease-focused multidisciplinary national clinical trials teams would greatly facilitate alignment, communication, collaboration, and synergy between our nation's cancer clinical trials activities and many other disease-focused basic and translational research efforts funded by NIH, NCI, and other federal and private agencies (including SPORES, PO1s, various U and P series center grants, and R01-funded individual investigators).

Each disease-specific working group would work closely with NCI to assure that tissue banking and appropriate scientific infrastructure was in place (at NCI, at a specific institution, within industry) to conduct a specific trial and was appropriately centralized and coordinated. Statistical support for trial design would have to be integral to the function of each group.

Given their nature and potential footing in academic institutions or potentially NCI cancer centers, it would be critical for these multi-disciplinary, multi-institutional working groups to be familiar with the science and early phase (phase I, phase I/II, phase II) clinical trials ongoing in the NCI cancer centers and other academic entities (where we believe these early phase trials should be based), and across the world, and to select the most important concepts to be tested in national phase III or late stage randomized IIb trials.

While the NCI should be lauded for attempting to move in this direction with the formation of steering committees, the success of these committees is reportedly uneven.

Not all committees have been fully empowered, and, efforts have periodically broken down with the need of each steering committee to interface with multiple different groups (each with their own disease committee and committee chairs) to actually complete the design and implementation of a clinical trial.

Furthermore, appointment to critical national committees or working groups that drive national phase III/randomized phase II clinical trial design needs to be a more open, competitive process. To date, the NCI cancer centers, academic centers, and community oncology networks which actually drive the science and/or have access to the majority of cancer patients have not been as invested or as engaged in this re-design and system as is appropriate.

Understanding the need for efficiency, what is the right number of national multi-disciplinary scientific working groups to be formed, building off natural collaborations and areas of disease focus, again remembering that these are not heavily funded infrastructures?

Certainly, one could envision a disease-focused working group for every type of cancer, but this is likely too unwieldy. We have considered multiple options, ranging from four multi-disciplinary working groups with various subcommittees (which may be too few) to six or seven (as proposed see below). This will require

further discussion and consideration.

Three options are presented below:

Four Group Model

1. Hematologic Malignancies (with leukemia/MDS and lymphoma/myeloma subcommittees).

2. Women's Cancers (with breast and GYN (ovarian, cervix, endometrium) subcommittees).

3. Solid Tumors (all other cancers, exclusive of 1 and 2; would require multiple subcommittees).

4. Pediatric Cancers

Seven Group Model

1. Hematologic Malignancies (with leukemia/MDS and lymphoma/myeloma subcommittees).

2. Genitourinary Cancers (with renal, bladder, prostate subcommittees).

3. GI/Hepatobiliary Cancers (with potential subcommittees).

4. Lung and Aero-digestive Cancers (with lung, esophageal; head and neck cancer subcommittees).

5. Women's Cancers (with breast and GYN (ovarian, cervix, endometrium) subcommittees).

6. Neuro-Oncology/Bone and Soft Tissue Cancers/Sarcomas/Skin Cancers.

7. Pediatric Oncology (while this could be its own working group and COG has been successful, there could/should be significant intermingling of the members of the pediatric working group with groups #1, and 6 in particular).

Six Group Model

1. Hematologic Malignancies (with leukemia/MDS and lymphoma/myeloma subcommittee).

2. Genitourinary Cancers and GI/Hepatobiliary Cancers (with subcommittees).

3. Lung and Aero-digestive Cancers (with lung, esophageal; head and neck cancer subcommittees).

4. Women's Cancers (with breast and GYN (ovarian, cervix, endometrium) subcommittees).

5. Skin and Rarer Cancers (Neuro-Oncology, Bone and Soft Tissue, Sarcomas, Endocrine).

6. Pediatric Oncology (while this could be its own working group and COG has been successful, there could/should be significant intermingling of the members of the pediatric working group with groups #1, and 5 in particular).

Part II: An Integrated Infrastructure to Support the Multidisciplinary Disease-Focused Working Groups

To support these working groups, we believe that there should ideally be ONE common national infrastructure to drive national phase III and randomized IIb clinical trials.

This common infrastructure could be in an extramural setting, or in an institutional or industry setting, or partially at NCI, and would provide fully integrated IT support (standard consents; harmonized data elements; tailored data elements for specific working groups; web-based remote patient data entry; web-based clinical trials data management, monitoring, and reporting); tissue banking; finance and administration; interfacing and negotiating with pharmaceutical companies and institutions; contracting and legal services; statistical support for clinical trial design and analysis, etc.

While this single integrated support model is ideal, it may not be initially or ultimately achievable.

Thus, it may be more realistic to have two (and perhaps three) cooperative infrastructures develop that could contract to NCI to provide these services for different disease-focused working groups.

However, should it be determined that more than one infrastructure is required, all groups should be required to use identical data elements, IT systems, and reporting systems. Such infrastructures could be reorganized or realigned components of the current NCI cooperative groups.

Depending on the ultimate design and number of multi-disciplinary disease-focused scientific working groups, an infrastructure could support more than one disease-focused working group. Significant consideration should be given to which of the components of these infrastructure needs (such as tissue banking) could be or should be centrally housed at NCI and supported through the intramural programs.

Part III: A National Clinical Trials Network

To actually provide access and accrual of patients to clinical trials, it is essential to build a single, integrated national cancer clinical trials network that takes advantage of, harmonizes, and integrates networks that are already in place or are being built within the NCI cooperative groups, NCI cancer centers, CCOP/MB-CCOPs and other community-based cancer programs and healthcare systems.

One such model could be designed by treating NCI cancer centers and aligned community practices, or, large free-standing community practices, as regional nodes in a network that can reach out to patients to provide access and participation in clinical trials.

A critical question that we have been discussing

is how reimbursement would be managed for patient accrual and how funds would flow in a newly structured and integrated system. It would be ideal to create a direct reimbursement system with little administrative overhead.

It is our significant hope that with integration and consolidation of current programs and networks, that over time, reimbursement for individual patient participation in NCI-sponsored clinical trials could be significantly increased.

Part IV: Oversight and Governance

Given the critical importance of cancer research and its translation to clinical interventions and clinical trials in the overall NCI mission, creating a single governing body at the NCI focused on the development and oversight of this national cancer clinical trials effort would seem essential.

This governing body could include NCI leaders, NCI cancer center directors, community representatives, industry representatives, and leaders of the infrastructure groups (discussed in Part II above).

The chairs of the disease-focused multidisciplinary scientific working groups would report to this oversight group on a regular basis.

Clinical Research

Pazdur: Trials Need Same Rigor Whether Conducted by Groups Or Commercial Sponsors

Clinical trials intended to support registration should meet the same standards, regardless of whether they are conducted by cooperative groups or drug companies, said Richard Pazdur, director of the FDA Office of Oncology Drug Products.

Speaking at the IOM workshop March 21, Pazdur said criteria are needed to determine which trials warrant being funded with taxpayers' money.

"What needs to come the forefront is: Which trials are unique, which trials are so interesting that the cooperative groups should spend taxpayer money on them to advance the field of oncology? What are those areas that position themselves in a unique focus, that is not outside of the field of the commercial sponsors?" Pazdur said.

Pazdur said the role of cooperative groups in registration studies is shaped by four factors:

• The interactions throughout the approval process are almost exclusively limited to FDA and the commercial sponsor. The range of interactions is extensive and "might not be known to the cooperative groups," Pazdur said.

• The sponsor and the cooperative group need to have clear communication at the initiation of the collaborative relationship. This should define the scope of work and set targets for accrual and completion of studies. "As far as these communications, we really emphasize that there should be joint meetings between the FDA, CTEP, the cooperative group and the commercial sponsor at every stage of the game," Pazdur said.

• The company and the group must decide prospectively whether the trial would support registration. Pazdur said groups and sponsors should seek to avoid the following scenario: "A company is doing a trial with a cooperative group, and then after the trial is done, somebody decides that this is going to be a registration trial."

• Drug companies should consider assuming selective financial and regulatory responsibilities for group trials intended for registration. Funding—whether public or commercial—should be sufficient to support a filing.

The text of Pazdur's remarks follows:

Several years ago we started working and having a dialogue with PhRMA about cooperative group studies, which resulted in a PhRMA white paper.

The white paper never saw the light of day, for some reason. And what I thought I would do is go over some of the general principles that were listed in the white paper.

We have to take a look over the past 20 years at what has really happened both with the cooperative groups and also with pharma. I'm not going to comment on the cooperative groups, since there are people here who are much more expert in discussing that aspect than I.

But if one really takes a look at pharma over the past 20 years, one sees a major commitment in oncology—with added resources going to oncology.

When I was starting my career in medical oncology in the seventies, I was told very few companies in the pharmaceutical industry—sponsors—would be interested in pursuing drug development in oncology.

I was told that oncology is a "terminal disease field." Companies would not want to be associated with this stigma. There would be low prices and short market lives for oncology drugs, so there would be very little interest. Well, obviously these statements have been a gross misconception and a misstatement—history has proven those people wrong.

The other area we should take a look at is the increase in international studies over the past 20 years. We, in the United States, are not the sole players.

The FDA is not the sole regulatory authority. Sponsors answer to multiple regulatory agencies—including the EMA, Swiss Medica, Health Canada, Health Australia—there are other players who want participation in the clinical trials process, as well as having their specific regulatory requirements met.

From a regulatory perspective, when a trial is being done—whether it's being done by a cooperative group or whether it's been done by industry—it has to serve multiple masters.

The other question that I'll leave for you—and I hope our esteemed panel will try to answer it, but I think it's also something that you all should ponder— is what specific trials should cooperative groups do?

You could answer that question with "innovative and interesting trials," but exactly what does that mean? In defining the cooperative group's role one has to question, "What trials would industry be better at doing? What trials would the cooperative groups be better at doing?"

Several years ago it was said, "Well, cooperative groups should do adjuvant studies, because the industry simply can't do those studies." Well, that's wrong now.

Several years ago it was said, "Well, cooperative groups should do small, interesting and rare diseases." We've had many supplements submitted to the FDA by commercial sponsors, looking at very small groups of patients and orphan diseases. Very small populations have gotten indications approved.

What needs to come the forefront is: Which trials are unique, which trials are so interesting that the cooperative groups should spend taxpayer money on them to advance the field of oncology? What are those areas that cooperative groups can position themselves in that are a unique focus outside of the field of the commercial sponsors?

Let's go to those guiding principles from the PhRMA white paper.This presentation is going to be much more "where the rubber meets the road," and more granular than the other talks in this session. It's going to really deal with the specifics of the cooperation and the interaction between the FDA or other regulatory bodies, cooperative groups, NCI and commercial sponsors.

In this white paper, there were several guiding principles—I'm only going to talk about four of them that are much more germane to today's discussion.

The first guiding principle annunciated is that "the accountability of the delivery of quality data to FDA belongs exclusively to the sponsor." In other words, the interactions that we have when an NDA, or a new drug application comes in; or a when a BLA, a biological licensing application comes in, is pretty much with the commercial sponsor.

We have ongoing relationships with commercial sponsors that go over many products for many years. There are ongoing issues that have to be addressed even when a new supplement comes in, such as, have post marketing requirements for a previous supplement been addressed? Have manufacturing issues been addressed? Have clinical pharmacology issues been addressed.

It's not just plopping a clinical trial and saying "approve" it. There are many more issues that need to be addressed. And the complexity of these issues for a given drug—whether it's a supplement or a new molecular agent—might be quite extensive—and that might not be known to the cooperative groups.

The other point, and this is the second guiding principle, is that there "needs to be a clear communication between cooperative group and sponsor and that should be defined at the initiation of the collaborative relationship."

This is obvious. A discussion of who is going to do what needs to occur. What is the responsibility and who is assuming it? What are timelines that are to be met as far as activation of the protocol, as far as completion of the protocol, as far as milestones in the enrollment of patients—particularly if this is going to be a post-marketing requirement, such as a fulfillment of an accelerated approval commitment or a post-marketing requirement that involves safety issues.

Remember post-marketing requirements are now under FDAAA [the Food and Drug Administration Amendments Act] and failure to meet these requirements carry financial penalties.

We emphasize that there should be joint meetings between the FDA, CTEP, the cooperative group and the commercial sponsor at every stage of the game.

It's very confusing to all parties when we're only talking to one of the three or one of the four members of this entire development team. There should be a clear delineation of what regulatory document goes to each partner. Which regulatory documents go to CTEP? Which regulatory documents go to the cooperative group? To the industry? These need to be very firmly and clearly spelled out.

The third goal in this white paper was that there should be a "definition of the goals of the study a priori as a registration or non-registration"

And this might seem obvious to everybody, but this

is really one of the major bugaboos here. A company is doing a trial with a cooperative group, and then after the trial is done, somebody decides that this is going to be a registration trial.

There is a lot that goes into what composes a regulation submission, and as we previously stated, we would like to have early communications regarding the design of the trial.

What are the requirements for regulatory submission? Who is going to submit it? It is a suboptimal situation when somebody has to clean up the data for a year, or six months, or eight months, because it has not been thought out and discussed that the trial will be used for registration.

If a clinical trial is isolating the effect of the drug in its design, and if it is a new indication, we assume that these trials are going to be registration trials—irrespective of how large the population is. We usually discuss these with CTEP. We would encourage sponsors to look at this quite closely, and be quite truthful of where they are going with a development plan when they discuss a trial with a cooperative group.

The fourth and final recommendation that I'd like to talk about is that "consideration should be taken in delegating elements of cooperative group conduct to the pharmaceutical sponsor." Perhaps by using the word "consideration" points to some "waffling" or uneasiness.

This needs discussion. For example, should part of the monitoring of the trial be done by the cooperative group, if it is going to be submitted to a regulatory authority? Should increased emphasis or some increased financial resources be allocated upfront to these monitoring activities, irrespective of whether or not this is done by the pharmaceutical sponsor?

I realize that there is some tension here, because the cooperative groups are independent entities and want to maintain their independence.

Here again, this is not an FDA issue. It is really a dialogue that has to continue, and should continue, between the cooperative group and the pharmaceutical firm.

Professional Societies:

AACR Announces Board, Committee Members

(Continued from page 1)

McCormick's research has focused on the molecular basis of cancer, and how genes turn normal cells into oncogenes. His current research focuses on the Ras pathway and methods of targeting this pathway for cancer therapy.

McCormick served as program chair for the 2010 annual meeting, as member of the board of directors from 2002 to 2005 and as co-chair of the annual meeting program committee in 2001. He chairs the Task Force on Co-development of Investigational Drugs, and has chaired the Award for Lifetime Achievement in Cancer Research committee and the Team Science Award committee.

McCormick is a scientific editor of Cancer Discovery, and was a senior editor of Molecular Cancer Research from 2002 to 2006. He was the recipient of the 2002 AACR G.H.A. Clowes Memorial Award for outstanding recent accomplishments in basic cancer research.

The scientists elected to the AACR board of directors for the 2011 to 2014 term are:

• **Joan Brugge** is chair and professor of the department of cell biology at Harvard Medical School. She is a member of the Council of Scientific Advisors and the Kirk A. Landon-AACR Prize for Basic Cancer Research Selection Committee.

• **Arul Chinnaiyan** is the S.P. Hicks endowed professor of pathology, professor of pathology and urology, director of the pathology microarray laboratory, director of cancer bioinformatics at the comprehensive cancer center, director of pathology research informatics, and director of the Michigan Center for Translational Pathology, all at the University of Michigan Medical School.

• **Thomas Sellers** is executive vice president of population sciences, associate center director of cancer prevention and control, CEO of the Lifetime Cancer Screening and Prevention Center at the H. Lee Moffitt Cancer Center & Research Institute. He is also the director of the Moffitt Research Institute.

• **Laura van 't Veer** is professor and HS clinical instructor in the department of laboratory medicine, leader of the Breast Oncology Program and director of applied genomics at UCSF. She is head molecular biologist and group leader of molecular pathology at The Netherlands Cancer Institute, and chief research

officer at Agendia BV in Amsterdam.

• **Kristiina Vuori** is president, professor, Pauline & Stanley Foster presidential chair and cancer center director of the Sanford-Burnham Medical Research Institute. She is also co-director of the Conrad Prebys Center for Chemical Genomics at the Sanford-Burnham Medical Research Institute.

The scientists elected to the nominating committee for the 2011 to 2013 term are:

• **Tom Curran** is the deputy scientific director of the Children's Hospital of Philadelphia, CHOP Research Institute; a member of the division of cancer pathobiology at CHOP; professor of pathology and laboratory medicine at the University of Pennsylvania School of Medicine; and associate director of translational genomics at Penn Genome Frontiers Institute at the University of Pennsylvania School of Medicine. Curran was AACR president from 2000 to 2001.

• **Raymond DuBois** is the provost and executive vice president of The University of Texas MD Anderson Cancer Center, where he is also professor of cancer medicine and cancer biology. DuBois was AACR president from 2008 to 2009 and served as a member of the board of directors. He chairs the clinical and translational cancer research committee and the AACR Margaret Foti Award for Leadership and Extraordinary Achievement in Cancer Research selection committee.

• **Lynn Matrisian** is professor and chair of the department of cancer biology at Vanderbilt University School of Medicine, and the Ingram distinguished professor of cancer research at the Vanderbilt-Ingram Cancer Center. Matrisian has served as AACR president from 2004 to 2005, as a member of the board of directors and as chairperson of the publications committee.

• **Helen Piwnica-Worms** is the co-director of the BRIGHT Institute, associate director of basic science at Siteman Cancer Center, and an investigator with the Howard Hughes Medical Institute. She is the Gerty T. Cori professor of cell biology and physiology, professor of internal medicine, and professor of cell biology and physiology at Washington University School of Medicine.

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FDA News:

BMS Agent Yervoy Approved For Metastatic Melanoma

FDA approved Yervoy (ipilimumab) for late-stage melanoma. The drug is sponsored by Bristol-Myers Squibb.

Yervoy is a monoclonal antibody that blocks a molecule known as cytotoxic T-lymphocyte antigen or CTLA-4. CTLA-4 may play a role in slowing down or turning off the body's immune system, affecting its ability to fight off cancerous cells. Yervoy may work by allowing the body's immune system to recognize, target and attack cells in melanoma tumors. The drug is administered intravenously.

"Yervoy is the first therapy approved by the FDA to clearly demonstrate that patients with metastatic melanoma live longer by taking this treatment," said Richard Pazdur, director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research.

The agent was approved based on a single international study of 676 patients with melanoma. All patients in the study had stopped responding to other FDA-approved or commonly used treatments for melanoma. In addition, participants had disease that had spread or that could not be surgically removed.

The study was designed to measure overall survival, the length of time from when this treatment started until a patient's death.

The randomly assigned patients received Yervoy plus an experimental tumor vaccine called gp100, Yervoy alone, or the vaccine alone.

Those who received the combination of Yervoy plus the vaccine or Yervoy alone lived an average of about 10 months, while those who received only the experimental vaccine lived an average of 6.5 months.

Common side effects that can result from autoimmune reactions associated with Yervoy use include fatigue, diarrhea, skin rash, endocrine deficiencies (gland or hormone), and inflammation of the intestines (colitis).

Severe to fatal autoimmune reactions were seen in 12.9 percent of patients treated with Yervoy.

When severe side effects occurred, Yervoy was stopped and corticosteroid treatment was started.

Due to the unusual and severe side effects, the therapy is approved with a Risk Evaluation and Mitigation Strategy to inform health care professionals about these serious risks.