**National Cancer Advisory Board (NCAB)**
**Subcommittee on Clinical Investigations**

Hyatt Regency Bethesda, One Metro Center
Old Georgetown Road, Bethesda, MD
Monday, June 27, 2011
6:00 p.m. – 7:30 p.m.

**SUMMARY**

Participants:

*Subcommittee Members*
Dr. Waun Ki Hong (Subcommittee Chair)
Dr. Anthony Atala
Dr. Judith Kaur
Dr. Jeff Abrams (Executive Secretary)

*Other Participants*
Dr. Margaret (Meg) Mooney
Dr. Olufuńmilayo Olopade
Dr. Jennifer Pietenpol
Dr. Marcia R. Cruz-Correa
Dr. Jon Samet
Dr. Bruce Chabner
Deborah Jaffe (NCI)
Darrell Anderson (The Scientific Consulting Group, Inc., rapporteur)

**Cooperative Group Re-organization & Other Related Initiatives—**Dr. Meg Mooney

Dr. Jeff Abrams, Executive Secretary of the Subcommittee, introduced the topic by explaining that it is hoped that the Cooperative Group re-organization could move forward so the first concepts would be presented to the Board of Scientific Advisors (BSA) by the fall of 2011.

Dr. Meg Mooney, Chief of the Clinical Investigations Branch, CTEP, DCTD, NCI, provided an overview of the re-organization, which began with the review of the Institute of Medicine (IOM) 2010 report that emphasized the need for public clinical trials, but also recommended changes in the organization of clinical trials at the NIH. The IOM set forth 4 goals and 12 recommendations. The goals were to:

- Improve speed/efficiency of development and conduct of clinical trials.
- Incorporate innovative science and trial design.
- Improve trial prioritization, support, and completion.
- Incentivize participation of patients and physicians.

In July 2010, the NCI began to meet with the Cooperative Group Chairs and others to discuss a response to the IOM Report. NCI is implementing a comprehensive approach to transforming its clinical trials system to create a highly integrated network to address rapid advances in cancer biology based on the recommendations from the IOM Report, previous reports (e.g., the Clinical Trials Working Group and the Operational Efficiency Working Group), and current stakeholder input.

IOM Goal #1 (Improve Speed and Efficiency of the Design, Launch, and Conduct of Clinical Trials) encompassed two recommendations:

- NCI should facilitate some consolidation of Cooperative Group "front-office" operations by reviewing/ranking the Groups with defined metrics on a similar timetable and by linking funding to review scores.

- NCI should require/facilitate consolidation of Cooperative Group "back-office" operations and working with the extramural community, make process improvement in operations and organizational management a priority.

The IOM's scientific rationale for the re-organization was to encourage the ability to prioritize molecular characterization resources and develop molecularly-driven trial designs, which are critical for success of multisite clinical trials. The re-organization also should meet the need to improve prioritization of the phase 3 portfolio across disease entities as trial costs (because of size and/or complexity) increase with limited resources; remove disincentives to study less common diseases because of accrual risks; allow the sharing of the IT infrastructure with a common front end for clinical data management and for tissue resource management; harmonize procedures for scientific/administrative oversight for therapeutic trials and quality of life/cancer control studies; and enhance molecular screening of large patient populations. In addition, scientific interactions around imaging may be facilitated by integrating ACRIN, with optimal use of tissue specimens, and open access to a National Clinical Trials Network for clinical/translational investigators not currently involved in the Cooperative Group platform, which will assure the best competition of ideas and toward movement high priority science into trials.

The NCI response to Goal #1 of the IOM Report was integration into not more than 4 Adult Groups and 1 Pediatric Group with multi-modality capacity in a broad range of diseases, all fully committed to a national clinical trials system. Potential strategies to assist integration include the following:

- Utilize multiple PIs now permitted through NIH grants, which may help with leadership transition

- Incentivize the transition with provision of additional resources.

- Allow distributed data management and operations to avoid disruptions of ongoing trials

- Combine (rather than disband) overlapping disease committees to include all current participants

The final response was to re-configure NCI review of the clinical trials program with an emphasis on incentives for a national system. In practice, the recommendations are meant to change the clinical trial culture of the Cooperative Groups to foment more collaboration and networking. Incentive transition is critical to the re-organization.

Dr. Mooney reviewed the current organization of the Cooperative Group system, which was composed of 10 groups, each with their own Disease Committees, operation components, data and analyses components, and tumor/specimen banks. Attempts were made to streamline the clinical trial process throughout the years. For example, the CTSU was created a decade ago to try to centralize regulatory functions, and 5 years ago the Disease Steering Committees were formed to look at all phase 3 trials in a centralized fashion across Cooperative Groups, and attempts were made to create a central IRB (one each for adult and pediatric).

The proposed re-organization will consolidate the Cooperative Groups into four adult groups and one pediatric group. They will share common Disease Committees, consolidate tumor/tissue banks, create five statistical data centers with common functionality, and synchronize the review process. This will help allocate resources, and the Groups will have the CTSU for administrative oversight. The vision of the transformed network will:

- Allow the system to not only provide the essential infrastructure for Group trials in treatment, control, screening, diagnosis, and prevention, but will be a major enabler of cutting-edge translational investigation across all of NCI's clinical research programs.

- Allow trials to open rapidly once approved by the Steering Committees and complete accrual according to defined guidelines by leveraging an integrated national network of performance sites.

- Provide unified clinical and translational infrastructure for the extramural cancer community: investigators, patients, advocates, and industry.

- Create a forward-looking system for translational oncologic discovery and efficiently functions to answer critical questions not well supported in a commercial environment.

Dr. Mooney provided evidence that progress is being made on IOM Goal #1. Specifically, the first step toward consolidation is occurring, with Cooperative Groups forming collaborations. Examples are RTOG and NSABP; ACOSOG, CALGB, and NCCTG; and ECOG and ACRIN. GOG recently announced that they are in negotiations to join the RTOG-NSABP collaboration. In addition, the CTSU will be incorporating COG in all trials in the near future.

Dr. Chabner asked if SWOG is included in any of the collaborations. Dr. Mooney indicated that SWOG has not been included at this point. Dr. Abrams said that SWOG has not found a partner, but they have said they are re-organizing within SWOG. Dr. Chabner responded that it seemed as if SWOG should have some natural partners, such as ACRIN and ECOG. Dr. Abrams

explained that the NCI left it to the Cooperative Groups to form their own collaborations, and SWOG certainly has an opportunity to become involved. If they meet the criteria of multi-disease and multi-modal trials, they should be able to take that to the reviewers. When the NCI developed the re-organization plans it was thought that four Groups would be able to meet the goals of the IOM Report. Dr. Chabner asked how the collaborations compared size-wise to the existing Groups. Dr. Mooney responded that they vary, but most would be bigger than SWOG. Dr. Chabner asked if the perceived lack of production by some existing groups, such as SWOG, would have anything to do with who chooses to form a collaboration. Dr. Abrams said that was up to the reviewers to decide what collaborations are likely to be productive.

Dr. Samet asked about the rationale for proposing four Groups. Dr. Abrams said that there was nothing magic about proposing four Groups in the re-organization; the reviewers may only choose three Groups or add another if there are qualified collaborations. One reason for the re-organization was to be able to have groups focus on molecular-based studies with imaging and it was felt that having collaborations with all aspects to conduct those trials (e.g., basic science, clinical trial experience, molecular and biomarker expertise, and imaging) was the best way to proceed. A smaller organization with incentives for collaborators would allow a quicker scientific response to emerging findings and discoveries. The basic concept is that the NCI wants studies but they must be conducted within a collaborative infrastructure.

Dr. Hong noted that according to the IOM Report, the NCI budget has been flat since 2002, and reductions may occur. Given this reality and the need to be more efficient, re-organization seems practical. However, molecular and imaging studies are very expensive. He asked how this fit into the paradigm. Dr. Abrams responded that molecular and imaging studies are expensive, but if fewer and smaller trials are conducted efficiently, the re-organization can help weather the economic realities. There is a question of whether four Groups can support as many trials as in the past. Also, in the past, reimbursement given to the Cancer Centers was not enough to incentivize the Cooperative Groups. NCI believes that their response to the IOM Report has met the criteria of having a public clinical trial system that is responsive to the science, especially in areas where pharmaceutical companies are unlikely to compete, such as in cancer prevention and pediatric cancers. The Cancer Centers still will have a role in these areas but they need to change with the science. Publicly-funded clinical trials must be conducted in those areas that need attention but where few other organizations will step forward.

Dr. Kaur said that another question that comes to mind as they look at a new system is whether they are still looking at the paradigm of disease site. She asked what would happen if trials are opened up to molecular-based studies that are not specific for melanoma, breast or lung cancers; if there could be cross translation as an option and whether the new system could accommodate different tumors. Dr. Abrams thought it could be cross-translational. There already is a study on patients with different lymphomas that is investigating the same target. There are other examples, but the overriding theme should be to pursue the science wherever it leads.

Dr. Mooney returned to her presentation and discussed the components of the new review process for the transformed clinical trial system. One important change is that the NCI external peer-review process will be re-configured with emphasis on incentives for a national system, all trials on the CTSU will be open to all sites, and sites can credit any Group to which they belong.

The review criteria will concentrate on collaboration and evaluation and allow them to use the multiple-PI construct. NCI also may modify the U10 program so that the higher accruing sites or Cancer Centers could apply independently. Accrual across the network would count. Dr. Olopade asked where the Cancer Centers are in the new system. Dr. Mooney said that they are trying to harmonize the system across all the existing centers. In talks with the Cancer Center Directors, they felt they had their own grants but that they could develop collaborations by including Center leadership in the networks. Dr. Abrams added that this was one of the positive outcomes of the meeting between the Cancer Center Directors and Dr. Harold Varmus, NCI Director, because they said they would collaborate and participate in the network. The Directors understood that they could participate in strategic thinking and they have leaders on many of the Disease Committees. They understand that they can compete for funds but they must be part of the network and share resources and ideas. This reiterates the theme of the re-organization.

Dr. Olopade asked how the central data center will work. Dr. Mooney said that they are consolidating and will be using common systems, such as Metadatarray. All trials will use the same system and harmonize their procedures. At the present time, there are many systems across the Cooperative Groups, but this has to change in the name of efficiency, although the NCI will help affect this change. The new system will not be that different from current systems, but the new data system will be synchronized. However, each group still will use its own analyses tools as it chooses. Much of the system will be Internet-based. Dr. Hong commented that this is a very important aspect of the new system, and it should improve the time to trial.

Dr. Mooney returned to her presentation and stated that review will no longer focus on trials put forward by specific disease committees; emphasis will shift to assessing the role of the Group as part of an integrated clinical trial network system. Tenets of the new review criteria include the following:

- Accrual to trials of any Group in the relevant disease areas across the system
- Timely implementation and completion of trials, as well as analysis and dissemination of trial results
- Collaboration with other Groups & other NCI-funded investigators, including combining trial concepts to design the most effective trials
- Leadership & participation in Steering Committees & Task Forces as well as Clinical Trials Planning Meetings
- Number and quality of concepts proposed & trials approved over the full award cycle
- Mentoring of young investigators to provide opportunities for them to develop concepts and lead trials

Dr. Chabner asked where the incentives for innovation are in the new system, because it appears that the only rewards are for the process. Dr. Mooney indicated that there will be a separate pool of money reserved for Groups who innovate. Those that score well in this area will get

additional funds. Dr. Chabner said that this is an important issue. Dr. Abrams commented that there will be some weight placed on innovation but more weight always will be on the science. Dr. Mooney quantified the weight in the scoring system: 50 percent for the science, 25 percent for operational efficiencies, and 25 percent for collaboration.

Dr. Olopade said that she was concerned about young investigators and how they can progress in the new system. It appears there is nowhere for them to excel. Dr. Mooney responded that they are unlikely to be experienced enough to be a PI on a phase 3 trial, but there may be a place for them in phase 1 or 2. There needs to be a high degree of expertise and experience for phase 3 trials, but it is expected that PIs will mentor young investigators. One thing that is expected is that the leadership of the Disease Committees needs to have transition plans that include bringing along younger investigators. Dr. Abrams added that there are incentives for turnover in the leadership within the organizational criteria. Dr. Kaur agreed on the importance of encouraging young investigators. Dr. Hong commented that bringing up the next generation of investigators is critical. However, the young do not have the intellectual maturity for large trials; this does not mean that they do not have a role, especially in phase 1 trials.

Dr. Mooney presented information on operational efficiency for the new system, but deferred in-depth discussion because this would be covered by Dr. Abrams in a presentation following this. In general, there will be the implementation and maintenance of an integrated and efficient operational framework for all aspects of the trials within each Group. There will be system-wide and Group-specific IT infrastructure and tools to enhance coordination and productivity. Operational timelines will be set for each step in trial activation with the expectation of achievement of target accrual goals, the implementation of processes for effective trial oversight and response to safety issues, and data quality as evidenced by audit results.

The new system will include active participation with NCI in collaborative management of the overall Group Program, with identification of system-wide issues, management and operational best practices applicable across the system, and the development of new cross-Group initiatives and/or policy/procedural changes. There will be the implementation of agreed upon improvements in operational and management policies and procedures, provision of clinical trial infrastructure resources for prioritized multicenter phase 3 and 2 trials originated outside the Group, and effective management of cross-Group committees for rare diseases and implementation of prioritized trials in rare diseases.

Dr. Mooney reviewed IOM Goal #2 (Incorporate Innovative Science and Trial Design Into Cancer Clinical Trials) and progress made on Recommendation #6 (Cooperative Groups should lead the development and assessment of innovative designs for clinical trials that evaluate cancer therapeutics and biomarkers (including combinations of therapies). NCI has initiated the Biomarker, Imaging, and Quality of Life Studies Funding Program to ensure that critical correlative studies could be incorporated in a timely manner into phase 3 and large, multi-institutional phase 2 trials during the process of concept development. From mid-2008 through 2010, 14 of 40 concepts have been approved incorporating biomarkers, a commitment of $22 million. An example is the COG AAML0531 trial investigating the FLT3/ITD biomarker, which was part of the high allelic ratio. Other integrated biomarker studies and imaging tests have been

approved. Other studies through BIQSFP applications for Group phase 3 treatment trials that have been approved include the following:

- CALGB-30801: Phase 3 Double Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced NSCLC *(Integral & Integrated Markers)*

- RTOG-1010: Phase 3 Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma *(Integral Marker)*

- COG - AAML1031: A Phase 3 Randomized Trial for Patients with *de novo* AML using Bortezomib and Sorafenib for patients with FLT3 ITD *(Integral & Integrated Markers)*

- S1007: A Phase 3 Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone-responsive and HER2-negative Breast Cancer According to Recurrence Score *(Integral Marker)*

Dr. Mooney briefly reviewed IOM Goal #3 (Improve Prioritization, Selection, Support, and Completion of Cancer Clinical Trials) and progress on Recommendation #8 (NCI should re-evaluate its role in the clinical trials system). NCI has initiated the Clinical Trials and Translational Research Advisory Committee, which is the first federally-chartered NCI advisory group in a decade. It has been in operation for approximately 3 years with specific responsibilities for NCI's clinical trials programs; it currently is engaged in the evaluation of implementation of CTWG recommendations. NCI also revamped the prioritization process for large phase 2 and phase 3 treatment and control trials by creating disease- and modality-specific Steering Committees to ensure that the most important trials are given the highest priority. While NCI has a voice on the Steering Committees, its role is to facilitate trial implementation, rather than to direct primary review. The Steering Committees convene clinical trials planning meetings to identify critical clinical trial issues for future studies.

Dr. Mooney presented a list of current disease-specific and non-disease Steering Committees. All adult and pediatric cancers are covered by these committees. They are considering seating melanoma and sarcoma steering committees in the future. Dr. Chabner noted that the Chairs of the Steering Committees appear to be older investigators. Dr. Abrams responded that the committees have many younger investigators, but the experienced investigators are Chairs.

Dr. Mooney presented the timeline for the re-organization. It included the following dates:

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| Dec 2010 – Jul 2011: | Gather information/input from stakeholders and community for New FOA & Guidelines; develop Concept |
| Aug 2011: | NCI Divisional/CTROC Concept Review |
| Sept 2011: | NCI Scientific Program Leadership Concept Review |
| Nov 2011: | BSA Concept Review |
| Nov 2011 – July 2012: | NCI DEA & NIH Review of FOA & Guidelines |
| July 2012 | New FOA Released/Published |
| Nov 2012 | Receipt of Competing Applications for New FOA |
| Feb 2013 | Review of Competing Applications by DEA |

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| May 2013 | NCAB Review |
| After Oct 2013 | Rollout of Awards in FY2014 |

**General Discussion**

Dr. Hong commented that this is an ambitious timeline. One of the disconcerting facts in the IOM Report is that approximately 40 percent of trials are never completed. He asked for the role of the Steering Committee. Dr. Abrams responded that its role is two-fold: (1) to review concepts from the community, including those not involved in the Cooperative Groups, and (2) to strategize with their groups to develop concepts that meet scientific needs and questions. An example would be for pancreatic cancer, where there are no questions ready to be answered for phase 3 trials but there are questions ready for investigation in phase 2 trials. The Steering Committees across all NCI Groups could develop good ideas. The same is true for HPV and head and neck cancer, where a good idea was developed in a brainstorming session.

Dr. Chabner commented that something that happened spontaneously is that the Cancer Centers got together and came up with ideas about trials of EGFR. How can that happen within the new system? Dr. Abrams said that he hopes that someone from the Cancer Centers with a good idea will come to the Steering Committees or go to an outside group. There are funds to conduct this type of trial even if the Group is not a part of the Cooperative Groups. Dr. Chabner added that it will not work unless the ones with the idea believe that the system will react quickly and that they will get credit for the idea.

Dr. Kaur asked if health disparities research is included in this new system. Dr. Abrams responded that the Minority-based CCOPs have done a wonderful job conducting trials for health disparities and this is likely to continue. There still need to be incentives for this type of research. At present, there is not a minority-based Steering Committee in the new structure. There is a review of a program in the NCCCT.

Dr. Hong noted that there does not appear to be representation among the Steering Committee Chairs for translational research. Dr. Abrams said that there are basic science members on each committee, but none are Chairs, but that this is a good idea. Some members belong to SPOREs, which are productive regarding translation.

Dr. Olopade asked what impact the impending end to the genetic mapping for humans will have on personalized medicine. The information coming from the genetic mapping should be considered for any future trials, and should be included in new RFAs. This will create a need for more pathway-based translational researchers. Dr. Abrams affirmed this need but added that there are pathway-based researchers in each of the Cooperative Groups that are working on this.

Dr. Chabner reiterated that he does not see cutting-edge individuals on the Steering Committees. He asked how the NCI expects to conduct cutting edge research without molecular-based researchers. Dr. Abrams responded that there are representatives on most of the Steering Committees, although they are not Chairs. He said that he would make available the complete list of Steering Committee members through Debbie Jaffe at NCI. Dr. Pietenpol commented that the Cooperative Groups are only one part of the larger NCI cancer portfolio. Most Groups have

mixed research and work with many markers. Even so, there are so few patients to work with because the criteria for trials of markers are narrowing. Some marker trials in her institution can only find 2-3 patients with the appropriate marker (example was specific ALK mutation). A network could allow broader access to patients with specific markers. Dr. Abrams agreed and said that this is one reason the NCI does not believe an individual institution is incapable of conducing molecular-based trials.

Dr. Olopade thought that there may need to be a committee on integrated biology that examined a cross-tumor platform. Having it nationally, with support from the NCI, could accrue enough patients with molecular characteristics. Dr. Chabner noted that institutions would have to molecularly characterize (e.g., for ALK) each patient up front, which they are unlikely to do because of the cost. The Cooperative Groups could do this, but the challenge still is finding enough patients. Rare mutations will not appear in very many people. This is basic discovery, but before the trial. Dr. Abrams used HER2 as an example of a mutation that is being tested for by almost all oncologists because it is known and impacts treatment.

Dr. Chabner commented that for the newer molecular-based studies the NCI should be involving the M.D./Ph.D. students; these are the investigators that understand the technologies and are innovators. Dr. Kaur said that the NCI has a role in this. Dr. Chabner stated that for each of the large histological diseases (lung, colon, and breast cancers), it is likely that a least one biomarker for every subset of patients will be available to inform therapeutic decisions. Dr. Olopade added that in the future, everyone will be performing broad genetic tests for as little as $1,000.

Dr. Abrams asked Dr. Chabner if there is anything that could be offered that would encourage investigators to work with the Cooperative Groups. Dr. Chabner said that the promise of a quick approval and start of a trial is a big incentive.

This led to a discussion of the R21 Quick Trials RFA, which appears to have been an ideal funding mechanism for incentivizing new trial ideas. Dr. Abrams said that for the treatment R21, a decision was made to discontinue it. After discussion, the Subcommittee members recommended that NCI should consider re-instituting a global treatment R21 as part of the new system, and that this should be presented to the NCAB on June 28.

Dr. Hong thanked members of the Subcommittee and asked that the presentation by Dr. Abrams scheduled for this meeting be placed on the agenda for the next Subcommittee meeting.

The Subcommittee meeting adjourned at 7:35 p.m.

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| Dr. Waun Ki Hong | Date | Dr. Jeff Abrams | Date |
| Chair | | Executive Secretary | |