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June 7, 2011

Harold E. Varmus, MD
Director
National Cancer Institute
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Dear Harold:

Thank you, again, for taking the time to come to ASCO's meeting and to talk with our Board of Directors and attendees. We have many exciting opportunities to work together in this time of unprecedented opportunity for cancer advances. I am writing on behalf of the American Society of Clinical Oncology (ASCO) to highlight one of the issues that is very important to our membership – the transformation of the Cooperative Group Program. On behalf of ASCO's 30,000 members, I appreciate the opportunity to comment on NCI's role in reorganization of the system. We have a keen interest in ensuring the long-term viability of a federally funded, national clinical trials network.

We appreciate the priority you are placing on making needed improvements to the Cooperative Group Program. The NCI and the Groups have begun to make important changes to address some of the major issues raised in the IOM report. NCI is soliciting feedback on these revisions. ASCO believes—overall—that the proposed revisions are headed in the right direction, but we are concerned that they do not appear to be based on a rationale that is derived from a strategic, scientific, or budgetary plan for the cooperative groups.

Because the NCI proposal represents significant changes, we believe it is essential that NCI articulate in advance a clear vision of what a successful reorganization will bring about and specific metrics for determining success. Achieving consolidation and reduction in the number of cooperative groups to an arbitrary number should not be viewed as a desirable or successful outcome. Pre-specified metrics of success should guide an analysis in the initial stages of implementation to ensure that the process is on track and that the outcomes can be adjusted as necessary. Furthermore, a thorough evaluation should be performed after complete implementation to determine if the outcomes were met. This has not been done consistently in the past, and such an evaluation is even more important because of the large scale changes that are envisioned and the risk posed if the changes diminish the impact of the national system.

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Toward that end, ASCO suggests the following goals for reorganization that could also serve as the basis for development and adherence to metrics, which should be transparent, and indicators of success:

1. **Enhance Inclusion of Innovative and Clinically Meaningful Science and Decrease Duplication Across all NCI-Supported Clinical Trials** – As you have noted in numerous presentations, we are just beginning to realize the potential of genomic-based cancer therapeutics. We must ensure that the revised Cooperative Group Program or National Clinical Trials Network (NCTN) is poised to capitalize on this innovative science. We can accomplish this, in part, by enhancing the connections between successful concepts that come out of NCI-supported translational and early-phase clinical trial mechanisms into innovative and efficient trials in the NCTN. The network should also be open to receipt of scientific concepts from outside of the NCI-supported system.

   It is important that the NCTN devote high priority and sufficient resources to trials that incorporate innovative science and hold the most promise for addressing practice-changing questions that have meaningful clinical benefit. The network should also focus on trials that a federally-funded system is uniquely poised to conduct or partner with industry to conduct. As the IOM report notes, federally-funded trials are particularly well suited to evaluate multi-modality treatments, adjuvant therapy, combinations of novel agents, screening and prevention strategies, and therapies for rare diseases.

   NCI should continue to assess the scientific merit of the concepts each applicant Group proposes and advances, as well as each Group's contributions to the NCTN. A revised system ought to incorporate a peer review process that enables comparisons of the scientific merit of all proposals applicant organizations submit within a disease area. The review criteria for the Groups should focus on 1) scientific merit of developmental studies (i.e., randomized phase 2 concepts with novel hypotheses that lead to phase 3 trials and correlative science concepts that incorporate biomarker discovery and validation) and 2) support for and recruitment to high priority trials across the entire network (including efficiency and completion metrics). Funding to the Groups should reflect both scientific merit of the application and support for trials across the network.

2. **Improve Timeliness of Concept Development and Scientific Review** – Numerous analyses have demonstrated that successful accrual of a Cooperative Group trial depends on the relevancy of the scientific question. In order to ensure that our trials are poised to answer the timeliest questions, we have to improve the speed with which we accomplish scientific review – from when a concept is first proposed within the Groups through to protocol approval. NCI and the Groups have made tremendous strides in improving the efficiency of the trial initiation process from the time of concept approval to trial launch. This same intense focus should be directed to the concept development portion of the timeline. The scientific review process should focus on value-added review, not minor changes. It should also enable reviewers to understand the thought process that occurred during concept development, so that reviewers can understand ideas already incorporated and benefit from the rich discussion that occurs within the Groups. In addition, NCI and the Groups should clarify the purposes and roles of steering committees and task forces to streamline the system as much as possible.

3. **Promote Efficiency Across the Network** – NCI has developed important tools and devoted increased resources to provide greater transparency and accountability and modernize the protocol development and trial launch process. In a national network, the emphasis should be on standardization across the system. Any deviation from the standards (e.g., protocols, case report forms, informed consent documents, auditing, etc.) should be minimal and justified. As part of this, we urge the NCI to expedite its plans to transform its central institutional review boards (CIRBs) into freestanding IRBs and **require** that institutions participating in the NCTN use the CIRBs as the IRB of record. In addition, NCTN should be the chief vehicle for conducting NCI-funded phase 2 and 3 trials, and all NCI-funded mechanisms should support and be held accountable for their participation and enrollment on NCTN trials. The NCI has started this process by aligning all the review guidelines across major NCI-funded mechanisms for clinical trials. This process should be expedited and review criteria should incorporate credit and the expectation for enrollment and participation in NCTN trials.

4. **Increase Funding for NCI-Supported Clinical Trials** – For trials that are prioritized in the NCTN, NCI funding should be sufficient to cover actual research costs and take into account trial complexity. The Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP) is an important component of the NCI portfolio and should be expanded to support development and validation of biomarkers. In addition, BIQSFP funding review should be simultaneous with clinical trial concept review and protocol development to ensure that a trial can launch as quickly as possible. ASCO continues to advocate for federal funding for NCI and hopes that the Institute will prioritize funding for NCTN trials and the overall infrastructure for NCI-supported clinical trials.

5. **Ensure Continuation of a National Infrastructure to Enable Physician Participation** – ASCO members consistently value and prioritize their participation in Cooperative Group trials. NCI has rightly recognized the tremendous volunteer hours and institutional and practice resources that are key to making the program a success. The review criteria for NCTN Groups should recognize the key role that the Groups play in training and career development. In addition, review criteria for other NCI mechanisms (e.g., SPOREs, designated cancer centers, U01 networks, etc.) should provide credit and recognition for the scientific leadership that researchers/faculty provide in the NCTN Groups.

Thank you again for the priority that you have placed on ensuring a robust national clinical trials system. Ensuring implementation of all of the IOM report recommendations is one of ASCO's highest priorities. I am including an attachment that goes into more detail about ASCO's recommendations on the specifics of the NCI proposal.

We look forward to continuing to work with NCI to ensure that all stakeholders heed the call to make needed changes to preserve and improve our federally-funded system. We stand ready to assist you and the NCI in any way that we can.

Sincerely,

George W. Sledge, Jr., MD
ASCO President

cc: James H. Doroshow, MD
Jeffrey S. Abrams, MD

ASCO Detailed Comments Regarding Reorganization of the Cooperative Group Program

- Important concepts that NCI has included in its proposal:
  - Multi-modality and multi-disease groups
  - Simultaneous competition of the groups
  - Emphasis on collaboration in a national clinical trials network
  - Incentives to study less common diseases
  - Focus on critical questions not well supported in a commercial environment

- Funding Opportunity Announcement should:
  - Include review criteria for the Groups that focus on 1) scientific merit of developmental studies (i.e., randomized phase 2 concepts with novel hypotheses that lead to phase 3 trials and correlative science concepts that incorporate biomarker discovery and validation) and 2) support for and recruitment to high priority trials across the entire network (including efficiency and completion metrics). Specify process for promoting and integrating rare disease trials across system.
  - Require that applicants demonstrate how they will collaborate with all components of the NCI-funded research system to promote promising scientific proposals (e.g., SPOREs, designated cancer centers, U01 networks, etc.)
  - Require consolidation of audit functions to avoid duplication and provide credit if a site participates in multiple groups, except in cases where a protocol has unique activities/requirements
  - Specify that groups collaborate to provide investigator and CRA training
  - Require that applicants implement a system that continuously provides leadership opportunities for early career investigators, including through term limits on leadership positions in the Groups

- NCI should:
  - Decrease NCI staff roles in scientific review. The concepts should come from and be reviewed by the extramural community with the NCI playing primarily a facilitative role during the process.
  - Align the number of biospecimen network awards with the number of Group awards
  - Urge OHRP to issue more definitive guidance in support of institutions using NCI CIRB
  - Harmonize review criteria across all NCI mechanisms to reflect the importance that society places on involvement in the federally-funded trials system
  - Work with CMS to resolve coverage of phase I cancer trials and promote Medicare beneficiaries' enrollment in NCTN high priority trials (similar to 2005 CMS National Coverage Decision (CAG-00179N) for trials investigating anticancer chemotherapy for colorectal cancer)
  - Conduct distribution of all drugs provided in cooperative group trials, regardless of IND holder

- Evaluation criteria for new system should focus on the ability to:
  - Foster innovative trials
  - Advance scientific concepts across all NCI-funded mechanisms
  - Focus on trials that the NCI-funded system is uniquely qualified to conduct
  - Maintain and enhance broad access to studies
  - Reduce redundancy across the trials portfolio
  - Promote scientifically promising trials in less common diseases
  - Reduce time from submission of concept to completion of trial
  - Promote successful strategies for accrual, particularly among under-represented populations