June 30, 2011

Harold Varmus, M.D., Director
National Cancer Institute
James H. Doroshow, M.D, Division Director
NCI Division of Cancer Treatment and Diagnosis

Dear Drs. Varmus and Doroshow,

We are writing to you as advocates working in the US Cancer Cooperative Groups to express our thoughts and concerns about the IOM/NCI clinical trials implementation. The NCI-funded Cooperative Group system is a national treasure. We need to be both bold and careful as we move forward to make it better, because breaking it would be a tragedy for all cancer patients, current and future.

As advocates, cancer survivors and people touched by cancer, we share with you nine recommendations concerning this transformation initiative and respectfully request that NCI respond to these with an action plan:

1. Incorporate into the implementation plan tangible patient and scientific outcomes as primary endpoints
2. Integrate instrumentation, transparency, and accountability (i.e., clear metrics with targets, timeframes and responsible parties) into the management of this implementation
3. Define what constitutes success in terms of concrete endpoints and timeframes and decide how these will be managed
4. Avoid allowing the pace of change to get ahead of rational design and planning for the implementation. If the design is not vetted or the metrics are not in place, move the implementation date(s) back until there is a solid design and clear metrics to guide the implementation
5. Be quicker to course-correct/adapt and more transparent and flexible, reflecting the lessons learned in prior implementations
6. Incorporate milestones with go/no-go decision points and pilot programs for the more challenging elements of the new operating model
7. Clarify plans to address IOM recommendations relative to NCI's role in the clinical trials enterprise
8. Incorporate enforcement of NIH Policy and Guidelines on the Inclusion of Women and Minorities in Clinical Research as prescribed in the NIH Revitalization Act of 1993, PL 103-43 into the change program
9. Meaningfully involve the cooperative group advocates as full partners in the implementation and beyond

The remainder of this letter provides the background and rationale for these recommendations.

There are lessons learned from prior initiatives that should be applied to this transformation

As many of us have been involved in clinical trials for many years, we are also cognizant that this is not the first effort to restructure and reengineer the system. There are clear lessons learned that we all need to keep in mind as we approach this critical, game-changing transformation.

Previous efforts have been fraught with false starts, unintended consequences and stillborn constructs. Protocol development pipelines, patient accruals and, consequently, the pace of science and improvement of patient outcomes were all impacted as some changes were fine-tuned and others were aborted. The current change program is far more aggressive than prior efforts and has incredible potential. Many of the same people who were involved in prior restructuring initiatives are involved in the present effort—at NCI, within the groups, at contractors supporting on-going operations and change management. Much has been learned from the prior initiatives. However, we expect that there will be challenges as this effort moves forward and we all need to keep a close eye on key metrics and be ready to fine tune the strategy and implementation.

Recent events bode well for the success of this effort

We note the success in initiating rigorous deadlines for various stages of protocol development and their positive impact on lead times. We also note the initiation of a parallel process for protocol activation for sites not using the NCI Central IRB (CIRB) and the positive impact on activation times at sites not using the CIRB. Remarkably, there has also been a concomitant, dramatic reduction in CIRB throughput times. These successes demonstrate the power of good metrics and clear targets in driving tangible results, as well as the importance of addressing these issues early in the change process (these metrics and targets were not introduced until over eight years after the CIRB was instituted.) Also encouraging are public statements by NCI openly acknowledging that, in order to fund an orderly transition, costs will likely rise before they fall.

Recent events also suggest that the effort is resulting in potentially precipitous actions

The pace of change is getting ahead of design of the new model and plans to manage the transition and measure its effects. We cite two examples here to illustrate this concern:

- Declaration of the intent to move from ten adult groups to four has resulted in the existing groups deciding to consolidate ahead of the implementation (anticipatory consolidations.) There is some merit to allowing marketplace forces to build the appropriate alliances. However, there has been no analysis to determine which of the existing groups would most appropriately be consolidated to best leverage existing resources and position the system to meet the challenges of the future. And, there is still much uncertainty about whether the result will preserve the most valuable elements of the existing groups, especially the focus of some of the groups on specific cancers and populations (e.g., the Gynecological Oncology Group, GOG) and therapies not directly related to drug therapy (e.g., radiation and surgery.) This uncertainty stems largely from ambiguity about how the funding opportunities will be structured and the constraints being put into place by anticipatory consolidations
- National Disease Site Steering Committees appear to have been deployed without explicit metrics or evaluation programs in place to measure their effectiveness.

There is much discussion about negative impacts on the protocol development pipeline. Unfortunately, the data is largely anecdotal and there is little or no objective data available to confirm or refute the concerns that have been raised

This transition should be viewed as one would view a prospective clinical trial

In our view, an undertaking of this magnitude and complexity on such a critical resource is best viewed as analogous to conducting a clinical trial on patients with a terminal disease (e.g., cancer.) There is no one "right answer" and, while there is great potential, there is also the potential for disastrous impacts on the science and patient outcomes. When initiating a transformation of an organism as massive, complex and precious as the NCI-funded clinical trials enterprise, one should ask many of the same questions that an IRB would ask in reviewing a cancer clinical trial. Unfortunately, the answers to those questions for this effort are cause for concern:

- The transformation is essentially a single-armed trial with an ambiguous schema – If scientists identify a new molecule with an exciting mechanism of action in vitro, the molecule would be taken through Phase I and Phase II trials to establish dose and efficacy in vivo. The investigators would then be required to show that the new treatment is superior to the standard of care in a randomized Phase III trial. Large-scale business transformations with far less at stake and similar issues about the feasibility of rigorous multi-phase trials substitute financial and operations modelling to choose among available alternatives and develop clear implementation plans. This effort appears to be going straight to implementation without adequate solution design, business case (cost/benefit) analysis, or migration planning

- There is no dose modification plan—Clinical trial protocols make explicit provisions for adapting the treatment plan in response to adverse events (e.g., reducing doses in the event of dangerous cytopenias.) There does not appear to be any explicit criteria for what would constitute a dangerous or unanticipated consequence that would require adaptation of the implementation program. This, coupled with the lack of metrics and clear endpoints is deeply concerning

- The data monitoring plan is weak-- While there is a stated intent to manage performance to reach a higher level, ambiguity surrounding metrics and the lack of baselines and targets threatens to confound this intent. Essentially, we have no effective way of measuring performance levels for the status quo and no definition of what constitutes success (i.e., the targeted level of improvement.) It is important to note that metrics played a crucial role in recent successes with protocol development timeframes and CIRB throughput. Metrics can be difficult to develop and often aren't perfect, but they inform action and provide clear incentives and feedback

- Reliance on secondary endpoints—Trials are ideally designed to achieve primary endpoints that indicate clinical benefit, such as overall survival. Secondary endpoints, like response rates, are viewed as not necessarily indicative of true clinical benefit and are frowned upon where there are primary endpoints that can readily be measured. There is a presumption of benefit from reducing the number of groups from ten to four. However, there is no evidence that there will be benefits. We have not seen analyses to project the magnitude of any benefits and

what specifically will be required to achieve them. Similar assumptions are made relative to consolidation of decision-making into national committees. However, the is no evidence that this will be the case and no metrics defined to assess the effect on outcomes

Some redundancy may be required to achieve an optimal result

When manufacturing Toyotas or purchasing computers, there are clear economies of scale. Redundancy is anathema, a good and evil issue. In a creative process subject to serendipity and dependent on creative development and testing of hypotheses, competing (i.e., redundant) efforts are often necessary to hedge against the risk of failure and to avoid stifling innovation. Centralized planning and prioritization for scientific research has value to focus investment of scarce resources. However, it needs to accommodate independence of thought and innovation, and extend to the entire portfolio of research, which includes cancer centers and RO1's.

It is unclear how NCI plans to address the IOM recommendations that relate to changes at NCI

The IOM report suggested numerous changes to NCI's management of the clinical trials enterprise. Examples of these changes include:

- Re-evaluating NCI's role in the clinical trial system and shifting from hands-on leadership and oversight to funding the clinical trials process
- Allocating a larger portion of the NCI research portfolio to the Clinical Trials Cooperative Group Program
- Enhancing trial participant diversity through support for Minority-Based Community Clinical Oncology Programs, Patient Navigator Research Program and other NCI programs. Our constituents ask that NCI Enforce NIH Policy and Guidelines on the Inclusion of Women and Minorities in Clinical Research as prescribed in the NIH Revitalization Act of 1993, PL 103-43
- Increasing the per case reimbursement rate and adequately funding the costs of conducting trials
- Mandating the submission of annotated bio-specimens

In some areas, it is unclear if NCI plans to or is able to proceed with the recommended changes (e.g., funding/reimbursement.) In others (e.g., leadership/oversight), the direction appears to be counter to the IOM recommendation. It is important that these issues be dealt with early in the transition as they could have a significant impact on the ultimate outcome.

Cooperative group advocates should participate as full partners in the transition

As cooperative group advocates, we represent the patient and consumer communities. Most of us are cancer survivors and all of us have been touched by cancer. We work directly with the Cooperative Groups and NCI to design, conduct and evaluate clinical trials. Many of us have professional experience in related fields that we bring to bear in our advocacy work. We are committed, knowledgeable and have a unique point of view. We should be full partners in this implementation.

We are grateful for the incredible progress that NCI has engendered by involving advocates in all key management functions in its research enterprise. However, this undertaking to transform the system has not met the high standards for advocate involvement that NCI has set.

- There was no cooperative group advocate on the IOM task force that developed the recommendations
- Meetings to present the program and work out details have excluded cooperative group advocates from key sessions, most notably from NCI's many meetings with the Cooperative Group Chairs

Advocates are passionate about the NCI-funded clinical trials system and have a huge stake in its success. This passion sometimes translates into controversy, which we believe is healthy as long as it remains constructive. We have much to contribute and ask that the NCI ensure that we are fully-integrated into the implementation program and the on-going efforts that will follow.

We respectfully request a response to the nine recommendations listed above

As concerned stakeholders and representatives of the patient and consumer communities, the ultimate beneficiaries of the clinical trials enterprise, we respectfully request a timely response in the form of an action plan to the nine recommendations listed above. We believe these are critical to ensure that the implementation delivers on its promise and that timely action is required. Your thoughtful response will facilitate consensus and demonstrate transparency on critical elements of the implementation.

There are over ninety advocates working within the US Cancer Cooperative Groups. Most of us are cancer survivors and all of us have been touched by cancer. All of us are passionately committed to the success of NCI-funded clinical trials. We work assiduously with NCI, the Cooperative Groups, advocacy organizations, the patient community and industry to improve NCI-funded clinical trials and we applaud the efforts of the Institute of Medicine and the National Cancer Institute to revitalize them. This letter represents the consensus of approximately 75% of our advocates, listed on the next page with their Cooperative Group affiliations.

Thank you for your attention. We look forward to working with NCI as we jointly pursue this exciting opportunity.

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Legend: Advocate Affliation Codes

PAB: Coalition of Cancer Cooperative Groups Patient Advisory Board	
ACOSOG: American College of Surgeons Oncology Group	GOG: Gynecologic Oncology Group
ACRIN: American College of Radiology Imaging Network	NCCTG: North Central Cancer Treatment Group
CALGB: Cancer and Leukemia Group B	NSABP: National Surgical Adjuvant Breast & Bowel Project
COG: Children's Oncology Group	RTOG: Radiation Therapy Oncology Group
ECOG: Eastern Cooperative Oncology Group	SWOG: Southwest Oncology Group