

**Toward a Fully Integrated Clinical Trials System****PROGRESS REPORT on NCI IMPLEMENTATION  
of the****Report of the Ad hoc Guidelines Harmonization Working Group** (July 2009)  
(Coordination Subcommittee, CTAC)**Clinical Trials and Translational Research Advisory Committee (CTAC)  
December 2010****I. Introduction**

In July 2009, the Guidelines Harmonization Working Group (Coordination Subcommittee, CTAC) presented a report with recommendations to the Clinical Trials and Translational Research Advisory Committee (CTAC). The charge of the Working Group was to develop recommendations to harmonize program guidelines and develop incentives to foster collaboration among all components of the clinical trials infrastructure. The intent was to promote collaborative team science by ensuring that guidelines for different clinical trials funding mechanisms are aligned and to eliminate redundancy and duplication while proactively encouraging collaboration.

**A. Background and Rationale**

The Clinical Trials Working Group (CTWG) envisioned that in a fully integrated clinical trials system, the Cooperative Groups, Cancer Centers, SPOREs, phase I U01 grants, phase II N01 contracts, and individual investigators will participate collaboratively in a joint enterprise guided by scientific priorities and informed by input from basic and translational scientists, community oncologists, and patient advocates. Sharing of data and ideas, and the development of true team science will become a new standard of excellence alongside individual and institutional achievement. One of the CTWG recommendations, which was the charge of the Guidelines Harmonization Working Group, was to "realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation."

The purpose of this document is to present an update of the NCI's proposed plans to modify clinical trials program and reviewer guidelines consistent with the vision and overarching goals put forth by members of the Guidelines Harmonization Working Group in their report to CTAC in July 2009. The report provided overall guidance and recommendations for the harmonization of NCI's clinical trials program guidelines (Cancer Center, SPORE, Cooperative Groups, phase I U01s, phase II N01s, etc.) in order to achieve the aims described above.

Additionally, the members of the Working Group agreed that changes in guidelines for funding mechanisms will not, alone, provide incentives to overcome the structural and cultural barriers to collaboration across the spectrum of translational and clinical research. The 'vision' document includes recommendations for consideration that go beyond revisions of guidelines. This document describes approaches to some, but not all of the Working Group's proposed incentives.

## II. Approach

The Guidelines Harmonization Working Group focused its deliberations on the major mechanisms that the NCI utilizes to support clinical trials; Cooperative Groups, Specialized Programs of Research Excellence (SPOREs), Cancer Centers, and Community Clinical Oncology Programs (CCOPs) and Minority-Based CCOPs (MB-CCOPS). Other mechanisms for clinical trials and infrastructure support were included in the discussions as elements of the clinical and translational research system, however specific guidelines were not proposed since these grants do not constitute “stand alone” programs, per se.

NCI Program Leaders have proposed guidelines revisions to actualize the recommendations of the Working Group (GHWG). Key changes are summarized below. These revisions will be integrated, along with more extensive proposed revisions, to the full guidelines which are in development for Cancer Centers and SPORE programs. When the NIH has reviewed and approved the revised guidelines, Funding Opportunity Announcements (FOAs) for each of the programs will be released and implemented for new and renewal applications and in review. It should be noted that, since CCOP and MB-CCOPS do not utilize standing guidelines, related changes will be integrated into future funding announcements once guidelines revisions are finalized for the other major clinical trials mechanisms.

Reviewer, as well as program and review staff orientation will be critical to implementing the revised guidelines and review criteria in a way that will affect change.

## III. PROPOSED IMPLEMENTATION PLANS

### GUIDELINES REVISIONS:

Proposed guidelines revisions are summarized below and include the following key changes which support the breadth of the Working Group recommendations:

- SPORE and Cooperative Group guidelines will include separate sections on collaborations across clinical trials mechanisms to facilitate the movement of studies from the discovery phase to early clinical trials and to later phase studies and beyond. These sections will receive separate review and scoring.
- Collaboration is integrated into multiple sections of the Cancer Centers guidelines, including several that have a major impact on priority score.

### CANCER CENTERS:

- Transdisciplinary Coordination and Collaboration, one of the Six Essential Characteristics, will expand to include a section on movement of studies through the translational pipeline and collaboration across clinical and translational mechanisms.
- Senior Leaders in Cancer Centers will be asked to describe how they work together to address overall center goals and develop and implement strategies for a translational continuum that advances early scientific findings.
- Similarly, research program members should receive recognition for contributions to development and implementation of the center’s clinical activities, including authorship of clinical trials, accrual of patients on interventional trials, and leadership roles in cooperative group studies. The category of support for clinical staff investigators will also continue.

- Clinical and Translational programs in Cancer Centers, which receive merit descriptors for each program, will be asked to describe their effectiveness in activating and accruing to a diverse portfolio of clinical trials; the extent of coordination and collaborations across NCI and other translational and clinical funding mechanisms and partnerships; transition of findings through the translational continuum; effectiveness in mounting meritorious feasibility and early phase trials and moving findings into externally peer-reviewed or other funding mechanisms where appropriate; and the extent of leadership roles in and/or accrual to Cooperative Group phase III trials. Reviewers will be asked to assess the general quality of science in the program, as well as the potential import of clinical trial research being conducted by the center.
- In the second stage review of comprehensiveness, centers will be asked to describe efforts relevant to training, continuing education, and dissemination activities in clinical research.

#### COOPERATIVE GROUPS:

- Cooperative Group guidelines will include a new separate section on Collaboration and Coordination that will receive a separate review score. The Cooperative Group will be asked to discuss how it has worked strategically to address overall research goals and implement clinical trials that capitalize on collaborations across various NCI-funded mechanisms and institutions, as well as other clinical trials networks. This will include evidence of leadership and accrual to other Cooperative Groups trials as well as evidence of collaborations that facilitate transition of novel interventions through the translational/clinical continuum.
- Meaningful participation in Cooperative Group trials is defined as 5 – 10% of total accrual, depending on the size of the Group. Key scientific contributions to the development of a clinical trial are to be considered positively in review.
- Cooperative Groups' collaborative interactions with other NCI-funded programs and promotion of those collaborations which support transition through the translational pipeline will be considered important and to be viewed favorably in review.
- High value in review of Cooperative Groups will be placed on innovative collaborative interactions between Groups with early phase clinical trials mechanisms.
- Credit will be given to a Cooperative Group for accrual to trials even though those trials are not led or endorsed by that Cooperative Group. This will be considered as a reflection of the commitment of the Group members to actively seek trials for patients and to contribute to the research of the Cooperative Group Program.

#### SPORES:

- Though promotion of inter-SPORE research has always been a hallmark of the SPORE, SPOREs must now conceive and initiate research that is further linked to other key programs of the NCI, NIH, and non-governmental programs in order to accelerate translational research along the pathway to the clinic, either directly in the case of therapeutic agent development or indirectly through the various steps of validation in the case of biomarker development. SPOREs guidelines now define 2 types of collaborations: Horizontal and Vertical:
  - *Horizontal* Collaboration: Collaboration in which groups work together coordinately to accomplish a set of research aims or goals on a single level, that is, in the laboratory, or at the clinical trial stage, or as a population clinical study. This is the type of collaboration in which SPOREs have traditionally participated.
  - *Vertical* Collaboration: Collaboration in which groups work together sequentially, or with some overlap, to move up the translational research pathway, that is, from discovery, to pre-clinical development, to Phase I trials or studies, to later phase studies, and possibly to a final hand-off to a commercial company.

- A new reviewed and scored section, Scientific Collaboration (SC) will be included in the SPORE guidelines. The SC includes descriptions of both horizontal and vertical collaborative efforts across NCI and other supported clinical trial and translational science mechanisms (planned activities for new applications; planned and current activities, as well as accomplishments for renewal applications) that will move studies through the translational pipeline. The SC section will focus on the arrangements, plans, milestones, agreements, and leadership involved in the collaborations as well as the overall accomplishments. Specific scientific data will be described and reviewed in the individual project sections, not in the SC.
- SPORE applicants will be asked to describe planned, ongoing, and/or completed collaborative projects and programs with set milestones to explain how the joint effort(s) will further translational goals. Additionally, the application should describe the efforts, arrangements, or the milestones toward, and the accomplishments of collaborations where promising SPORE results are handed off to other NCI-supported clinical trial mechanisms or to non-governmental mechanisms.
- New scoring for the overall SPORE will eliminate the previous 70%:30% ratio of formulaic weighting. However, the overall impact/priority score should focus on the likelihood that the proposed scientific projects will have a high translational impact as they are supported by the shared cores in the context of the overall programmatic organization and capabilities, developmental programs and scientific collaborations, and not just a simple average of the scores for the projects, resources, and developmental programs.
- A clinical trial will not be the goal of many SPORE projects, which reach a human endpoint by using human specimens in the laboratory to expand upon observations made in the clinic in a process known as “reverse translation”. Review criteria for SPORE renewal applications will include consideration of whether a “forward” translational project has been completed and moved to a later phase of product or intervention development on the translational continuum; and whether milestones have been met or if progress toward milestones has been shown for specific research projects. When biomarkers studies are ready for clinical trials in such studies, SPOREs are encouraged to collaborate with trans-NCI clinical trials mechanisms to validate the biomarkers clinically.
- New SPORE applicants will be asked to envision and describe potential collaborative arrangements beyond the limits of the SPORE should early clinical studies prove to be successful. First renewal applications that have not yet reached the 5-year period in which they must show a human endpoint will be asked to give a timeline with milestones of where each project is on the translational continuum and what collaborative arrangements will be made if the SPORE studies are successful.
- Only Phase I and early Phase II clinical trials (generally non-randomized, small accrual of less than 100 patients, investigating the activity of a single agent in a single disease), may be supported by the SPORE mechanism without collaboration. However, SPOREs are strongly encouraged to establish collaborative clinical trial activities across NCI-funded mechanisms early in the development of projects that have clinical trials/studies as their goals.
- For multicenter, randomized Phase II therapeutic trials ( $\geq 100$  patients), SPOREs wishing to collaborate as an inter-SPORE endeavor or with investigators funded by other grant mechanisms, should use the appropriate NCI Disease-Specific Steering Committees and their Task Forces (<http://restructuringtrials.cancer.gov/steering/overview> ) working together to develop clinical concepts from early SPORE trials that could move forward to the Clinical Trials Cooperative Groups. Upon the recommendation of a Steering Committee, requests for

use of NCI Cancer Trials Support Unit (CTSU) (<https://www.ctsu.org/public>) will be considered when it is not possible to use the Cooperative Group mechanisms.

## **INCENTIVES to COLLABORATION:**

Proposed plans and implementation progress in support of several of the recommendations to stimulate collaborations are described below. NCI Staff and Working Group members recognized that many of the recommendations for incentives to collaboration require future funding commitments and, thus, will need further deliberation by NCI. These recommendations are noted in this document and continue to be considered in the development of more extensive and long term programmatic changes.

### **Proposed and ongoing initiatives:**

- *“Formalize a process to facilitate development, review, support, initiation, and conduct of collaborative randomized phase II cancer treatment and prevention clinical trial concepts.”* As forums comprised of multiple stakeholders engaged in discussion around multi-center clinical trials, Scientific Steering Committees are able to foster handoffs and collaborations encouraged in the harmonized guidelines. Some trial concepts may initially evolve into collaborations involving partners without trial coordination capabilities. Inclusion of groups with trial coordination capabilities (e.g., Clinical Trial Cooperative Groups) is strongly encouraged. For cases when a multi-center Phase II trial cannot be lead by a study team with multi-center coordination capabilities, NCI is developing a funding initiative to provide coordination support for highly meritorious and unique multi-center randomized Phase II therapeutic oncology trials lead by NCI Designated Cancer Center or SPORE institution investigators in order to enhance the pipeline of clinical trials leading to Phase III Cooperative Groups studies. Management of the program will be through the Coordinating Center for Clinical Trials in conjunction with the Cancer Centers Branch, the Translational Research Program, and the Cancer Therapy Evaluation Program. Most of the support will be in the form of in-kind resources provided by the CTSU.
- *“Mechanisms are needed to enhance recognition and career development for individuals who make substantive contributions to collaborative clinical trials efforts, but are not currently Principal Investigators (PIs).”* The NCI issued the first Cancer Clinical Investigator Team Leadership Awards in FY2009 as supplements to 11 Cancer Center Support Grants. It is planned that 12 awards will be issued in FY2010. The award is designed to provide recognition and support for outstanding mid-level clinical investigators whose participation and activities promote successful clinical research programs as well as to promote retention of clinical investigators in an academic career in clinical research. The two year award provides investigators with partial salary support for their leadership roles in clinical trials at NCI-designated Cancer Centers.
- *Evaluate the effectiveness of the ARRA Grand Opportunities (GO) Grants: “Coordination of Clinical/Translational Research Across the NCI” with the intent of developing an initiative for the long term support of similar grants.* The “GO” initiative presents a unique opportunity for groups of scientists with diverse expertise, and original, creative ideas to work together on translational cancer research projects of significant scope and consequence that, nonetheless, can be completed within two years. Nine grants were funded in 2009 through this mechanism. Two years of support was provided teams of investigators proposing focused, evidence-based, hypothesis-

driven correlative studies associated with either an ongoing clinical trial or a new (ready to proceed) clinical trial in a multi-institutional setting.

The Working Group members agreed that it would be valuable to build on this initial investment as a model to develop a new mechanism to move exciting, novel, clinically applicable ideas from bench to bedside through the clinical trials system. Grants for Coordination of Clinical/Translational Research, funded for two years through the ARRA “Grand Opportunities” initiative, will undergo an interim evaluation to determine whether this initiative should be expanded.

### **Recommendations for Incentives to Collaboration requiring further NCI consideration:**

- Increase or provide for support of Principal Investigator and individual investigators to collaborate across mechanisms on various aspects of clinical trials development and implementation, including the expansion of U10 grants to qualifying institutions that participate in Cooperative Group trials.
- Utilize current K-award mechanisms to tailor an award for senior investigators that would provide salary support, primarily for the facilitation of collaboration across institutional programs.
- Increase per patient reimbursement for participation in clinical trials.

### **OUTCOMES MEASURES**

The Guidelines Harmonization Working Group members proposed that the Outcomes Measures listed below be used to measure the effectiveness of the recommendations, as implemented, in addressing the goals of the Clinical Trials Working Group (CTWG) initiative to “*Realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation.*” The CTWG Evaluation Working Group to be constituted in late 2010 will include these proposed measures as part of planning for subsequent evaluations of progress in implementation of the CTWG Report.

Anticipated measurable outcomes of the recommendations of the Working Group, when implemented, include:

1. Guidelines for all NCI-supported clinical trials mechanisms promote collaboration with other clinical trials programs, e.g., Cancer Centers and Cooperative Groups.
2. Guidelines are consistent across mechanisms regarding collaborative activities in clinical trials.
3. Reviewer credit is reflected in overall priority scores for active collaborations across clinical trials and translational research programs and mechanisms.
4. Collaborative activities in early clinical interventions are demonstrated between Cancer Centers, SPOREs, P01s, and other programs that offer access to novel clinical interventions.
5. Cooperative Groups activate phase III trials based on results from early phase studies in other NCI-supported clinical trials programs.

- The goal is to document a steady increase in SPORE/Cancer Center-generated late phase II and phase III clinical trials with an increasingly significant role of SPORE and Cancer Center scientific contributions to phase III Cooperative Group trials.
6. Incentives and rewards are instituted to promote early clinical research activities between Cancer Centers, SPOREs, P01s and other clinical research programs.
  7. Performance criteria and rewards include individual contributions to collaboration on clinical trials.
    - The goal is to document increased contributions by SPORE and Cancer Center leadership to early phase NCI-sponsored trials and Cooperative Group late Phase II and phase III trials.