

Report of the Operational Efficiency
Working Group
of the
Clinical Trials and Translational
Research Advisory Committee

Compressing the Timeline for Cancer
Clinical Trial Activation

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Executive Summary

In December 2008, the Operational Efficiency Working Group (OEWG) was established under auspices of the Clinical Trials and Translational Research Advisory Committee (CTAC) to advise the National Cancer Institute (NCI) on strategies to reduce the time required to activate NCI-sponsored Cooperative Group and early drug development trials as well as NCI-Designated Cancer Center investigator-initiated trials. The OEWG is a broadly constituted panel including Cooperative Group Chairs and Cancer Center Directors; clinical investigators, statisticians and protocol specialists; academic and community oncologists; clinical trials leadership and staff from all relevant NCI divisions, programs and centers; representatives of pharmaceutical and biotechnology companies and patient advocacy organizations; and representatives of the Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS) and NCI's Cancer Trials Support Unit (CTSU).

Establishment of the OEWG represents the realization of Operational Efficiency New Initiative 2 of the June 2005 Clinical Trials Working Group Report to the National Cancer Advisory Board: “Identify the institutional barriers that prolong the time from concept approval to accrual of the first patient, and develop solutions for overcoming these barriers.” In addition to this charge, the OEWG was also requested to identify strategies to increase the percentage of studies that reach their accrual targets in a timely fashion. The work of the OEWG was therefore divided into two phases, with the first addressing the reduction of trial activation time and the second addressing timely completion of activated studies. This report describes the first phase of the OEWG's activity and presents the recommended initiatives resulting from that phase.

To focus its deliberations, the OEWG made three initial decisions. The first was to exclude several matters that are beyond NCI's jurisdiction: trial elements, such as consent forms, that are regulated by the Office of Human Research Protections of the Department of Health and Human Services; state laws and requirements; and congressional funding mandates. The second, recognizing that different types of trials present different challenges, was to identify four separate trial categories to address: Cooperative Group Phase III trials, activation of Cooperative Group trials at Cancer Centers, NCI Investigational Drug Branch (IDB) early drug development trials implemented by Cooperative Groups and Cancer Centers and Cancer Center investigator-initiated trials. The third was to set a goal of reducing the time to trial activation for each category of trials by at least 50%.

The OEWG set a target of 300 days to complete the steps in Cooperative Group Phase III trial¹ activation that are under CTEP and Cooperative Group control. *However, the OEWG also set a “drop-dead” date by which all issues, including those controlled by industry partners or IRBs,*

¹ In this report, the term “Phase III trial” should be interpreted to include non-IDB Phase II trials with ≥ 100 patients.

must be resolved. If a protocol based upon a concept submitted to CTEP is not activated within a 24-month period, it will be terminated. For CTEP Phase II early drug development trial activation, the OEWG set a target of 210 days to complete the steps under CTEP/IDB and extramural control – Letter of Intent (LOI) review, protocol development, protocol review, and forms development. *The OEWG also set a “drop-dead” date of 18 months by which all external issues must be resolved. If a protocol based upon an LOI submitted to CTEP is not activated within an 18-month period, it will be terminated.* For investigator-initiated trials at Cancer Centers, the OEWG set two targets: 90 days for protocol review and revision, forms development, IRB review, and ancillary committee review and 180 days to complete all steps from protocol submission to trial activation including institutional financial review and industry negotiations.

To develop recommended initiatives for achieving the target activation times for each category of trials, the OEWG proceeded through a consensus building process involving four stages. First, the OEWG reached consensus on the component steps in the activation process for each trial category and the key barriers that delay each step. In the second stage, the OEWG developed new process descriptions for activation of trials in each category as well as timeline targets for each step in the respective processes. An important element of this stage was the commitment of the OEWG members to achieving the proposed timeline targets for steps under investigator and/or NCI control and the acceptance of firm dates to terminate protocol development if all issues, including those beyond NCI and investigator control, are not resolved.

In the third stage, the OEWG developed recommendations addressing key barriers that delay specific steps in the respective trial activation processes. In the fourth stage, the OEWG defined specific initiatives based on those recommendations and designed implementation plans for their practical realization.

This broad-based, strategically-driven effort, involving all the critical stakeholders in the cancer clinical trials community, resulted in the 14 initiatives and associated implementation plans detailed in this report on “Compressing the Timeline for Cancer Clinical Trial Activation”. These recommended initiatives and implementation plans, along with the new process descriptions and target timelines were presented to CTAC on November 4, 2009.

The proposed initiatives fall into two broad categories: management issues directly addressing time to trial activation and collateral issues judged sufficiently important to the vitality of the clinical trial system to warrant inclusion. Some of the initiatives directly relevant to trial activation time are specifically targeted at one of three trial categories – Cooperative Group Phase III trials, early drug development trials or Cancer Center investigator-initiated trials – while others apply across all trials.

The initiatives, which are described in detail in the report, are summarized below.

Cooperative Group Phase III Trial Process Improvements

- Develop Group-specific Action Plans to achieve the agreed OEWG target timeline for each step in Phase III trial activation impacted by the Cooperative Group
- Develop a CTEP Action Plan to achieve the agreed OEWG target timeline for each step in Cooperative Group Phase III trial activation impacted by NCI
- Develop collaborative CTEP/Group processes for meeting the OEWG target timeline for revision of concepts and protocols
- Develop approaches to reward performance against timelines through a collaborative, empirically based process involving both CTEP and the Groups

Early Drug Development Trial Process Improvements

- Develop a CTEP Action Plan to achieve the agreed OEWG target timeline for each step in early drug development trial activation impacted by NCI
- Develop collaborative processes involving CTEP, N01 contractors, Cooperative Groups and other Phase II early drug development trial performance sites for meeting the OEWG target timeline for revision of LOIs and protocols

Cancer Center Investigator-Initiated Trial Process Improvements

- Develop a Center-specific Action Plan to achieve the agreed OEWG target timeline for each step in investigator-initiated trial activation impacted by the Cancer Center
- Develop and implement new NCI and Cancer Center initiatives designed to streamline university contracting and financial review processes

Process Improvements Applicable Across Trial Categories

- Develop a coordinated approach to standardization of protocol elements and protocol development tools involving NCI, the Cooperative Groups and the Cancer Centers in order to speed development and review of protocols
- Enhance funding and capabilities for use of biomarkers in clinical trials in order to speed activation of trials designed to incorporate integral and integrated biomarkers
- Perform a rigorous Cancer Center review of each proposed clinical trial concept in advance of protocol development in order to optimize use of clinical trial resources, speed trial development and improve trial quality

Process Improvements to Enhance Overall Clinical Trials Program

- Provide incentives to enhance Cancer Center participation in Cooperative Group and other multi-site clinical trials in order to speed trial development and accrual

- Develop a Center-specific process for the periodic strategic review of Cancer Center clinical trial activity to enhance the coherence, focus and impact of the clinical trial program
- Develop enhanced NCI-funded clinical research mentorship and training programs at Cancer Centers to facilitate skill development for junior investigators and clinical research office staff

For each of these initiatives, the OEWG developed an implementation plan to realize its goals. The individual plans were developed through many hours of iterative discussion and deliberation by the OEWG, first within the subcommittee that generated the initiative and then in plenary session. On specific initiatives, input was also obtained from members of the cancer clinical research community who were not represented on the OEWG. While complete consensus was not achieved on all specific points, there was widespread support for all of the proposed plans.

Implementing these initiatives will require considerable commitment and effort by the extramural clinical trials community and NCI program staff to modify current processes to achieve the agreed upon goals. Although most of the work will be in doing things differently rather than undertaking new activities, a modest NCI investment in certain targeted initiatives will be required. Such new commitment and investment will result in a more efficient clinical trials system and is crucial for ensuring that the large, ongoing national investment in cancer clinical trials achieves the goal of bringing effective new therapies to patients as rapidly as possible. By embracing these initiatives, NCI and the cancer clinical trials community will demonstrate their strong commitment to achieving this shared goal.

Introduction

In December 2008, the Operational Efficiency Working Group (OEWG) was established under auspices of the National Cancer Institute (NCI) Clinical Trials and Translational Research Advisory Committee (CTAC). The OEWG was charged with recommending strategies and implementation plans for reducing the time to activation of NCI-sponsored Cooperative Group and early drug development trials as well as Cancer Center investigator-initiated trials, with the goal of reducing study activation time by at least 50 percent. The creation of and charge to the OEWG represent the realization of Operational Efficiency New Initiative 2 of the June 2005 Clinical Trials Working Group Report to the National Cancer Advisory Board: “Identify the institutional barriers that prolong the time from concept approval to accrual of the first patient, and develop solutions for overcoming these barriers.” Additionally, the OEWG was requested to identify strategies to increase the percentage of studies that reach their accrual targets in a timely fashion.

The 63 members of the OEWG represent a broad spectrum of stakeholders in the cancer clinical trials system, including Cooperative Group Chairs and Cancer Center Directors; clinical investigators, statisticians and protocol specialists; academic and community oncologists; NCI clinical trials leadership and staff from all relevant divisions, programs and centers; representatives of pharmaceutical and biotechnology companies and patient advocacy organizations; and representatives of the Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS) and NCI’s Cancer Trials Support Unit (CTSU).

The work of the OEWG was divided into two phases, with the first addressing the reduction of study activation time and the second addressing timely completion of activated studies. This report describes the first phase of the OEWG’s deliberations and presents the recommended initiatives resulting from that phase.

The scope of the OEWG’s initial activity was further refined by excluding several matters that are beyond NCI’s jurisdiction: trial elements, such as consent forms, that are regulated by the Office of Human Research Protections of the Department of Health and Human Services; state laws and requirements; and congressional funding mandates.

Recognizing that different types of trials present both common and distinctive challenges to timely trial activation, the OEWG identified four separate trial categories to address: Cooperative Group Phase III trials, activation of Cooperative Group trials at Cancer Centers, NCI Investigational Drug Branch (IDB) early drug development trials implemented by Cooperative Groups and Cancer Centers and Cancer Center investigator-initiated trials.

At its initial plenary meeting in December 2008, the OEWG reviewed available empirical data on clinical trial timelines, identified component tasks in trial activation and barriers to timely

activation, and discussed specific issues arising in the Cooperative Group and Cancer Center settings. Based on these deliberations, the OEWG members were organized into six subcommittees addressing issues related to the following:

- Cooperative Group clinical trial prioritization
- Cooperative Group clinical trial process management
- Cancer Center clinical trial prioritization
- Cancer Center clinical trial process management
- Academic and institutional incentives related to clinical trials
- Inclusion of correlative studies in clinical trials

The subcommittees conducted their deliberations through a series of conference calls as well as breakout sessions at two additional plenary meetings, held April 30–May 1, 2009 and September 16–17, 2009. Based on a determination at the spring meeting that no specific recommendations were warranted with regard to Cooperative Group trial prioritization, that subcommittee was dissolved and its members joined the Cooperative Group process management subcommittee. To gain additional Cancer Center input on process and prioritization issues, conference calls were held with the clinical trials leadership of five Cancer Centers not represented on the OEWG.

Additionally, during the summer of 2009, the OEWG requested a series of updated analyses of clinical trial activation timelines. Findings from these analyses were used to inform discussions about new process descriptions and timeline targets for individual steps in trial activation as well as recommendations for specific improvements. These data and the timeline targets for different trial activation steps are presented in the sections of this report addressing specific trial categories.

Over the course of their deliberations, the OEWG subcommittees created and refined a list of recommendations that fall into two broad categories: management issues directly addressing time to trial activation and collateral issues judged sufficiently important to the vitality of the clinical trial system to warrant inclusion. The core of this report is a presentation of the 14 specific initiatives and associated implementation plans developed by the OEWG for realizing those recommendations.

The initiatives are organized into five categories which represent major sections of this report: Cooperative Group Phase III Trial Process Improvements, Early Drug Development Trial Process Improvements, Cancer Center Investigator-Initiated Trial Process Improvements, Process Improvements Applicable Across Trial Categories, and Process Improvements to Enhance Overall Clinical Trials Program.

Cooperative Group Phase III Trial Process Improvements

Introduction

Ten NCI-funded Cooperative Groups² are the primary publicly funded mechanism for conducting Phase III cancer clinical trials in the United States. Accordingly, the performance of the Cooperative Group system in implementing Phase III trials is a major determinant of progress in advancing the state of the art in cancer treatment. The Clinical Investigations Branch (CIB) of the Cancer Therapy Evaluation Program (CTEP) plays an active role in overseeing the Cooperative Groups, and is itself an important element of the system and its performance.

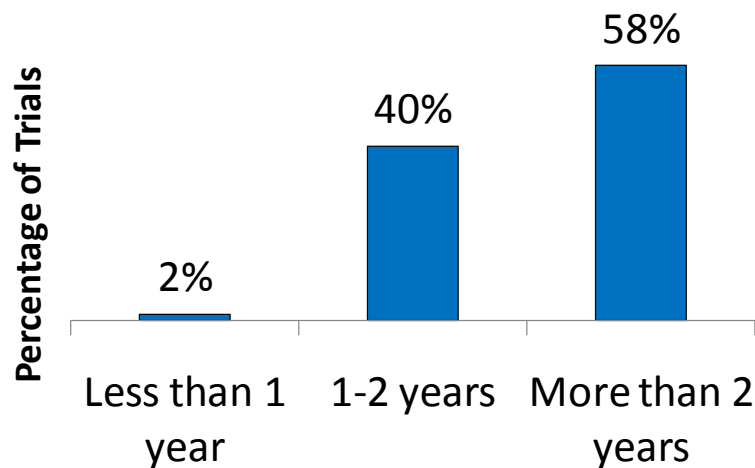


Figure 1: Time to Activation, Cooperative Group Phase III Trials Activated 2006-2008

Previous analyses by Dilts and colleagues³ documented substantial delays within both the Cooperative Groups and NCI in the process of advancing a Phase III clinical trial from concept to activation. Analysis of Cooperative Group Phase III trials⁴ activated between 2006 and 2008

² The ten Cooperative Groups are: American College of Radiology Imaging Network (ACRIN), American College of Surgeons Oncology Group (ACOSOG), Cancer and Leukemia Group B (CALGB), Children's Oncology Group (COG), Eastern Cooperative Oncology Group (ECOG), Gynecologic Oncology Group (GOG), National Surgical Adjuvant Breast and Bowel Project (NSABP), North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG), and the Southwest Oncology Group (SWOG). NCI also supports two non-U.S.-based Cooperative Groups: European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada, Clinical Trials Group (NCIC).

³ Dilts DM, Sandler AB, Baker M et al. Processes to activated phase III clinical trials in a Cooperative Oncology Group: the case of Cancer and Leukemia Group B, *J Clin Oncol* 2006 Oct 1;24(28):4553-7; Dilts DM, Sandler A, Cheng S et al. Development of clinical trials in a Cooperative Group setting: the Eastern Cooperative Oncology Group. *Clin Cancer Res* 2008 Jun 1;14(11):3427-33; Dilts DM, Sandler AB, Cheng SK et al. Steps and time to process clinical trials at the Cancer Therapy Evaluation Program. *J Clin Oncol* 2009 Apr 10;27(11):1761-6.

confirmed that such delays persist, with the majority of those trials requiring more than two years from concept submission to trial activation (Figure 1). Only two percent were activated in less than one year, while 40% required between one and two years.

As shown in Figure 2, the interval from protocol receipt by NCI to protocol approval was generally the most time-consuming step in the process, at a median of 348.5 days. The processes of concept approval and of trial activation following protocol approval required a median time of approximately three months each, while a median time of approximately 4.5 months elapsed between concept approval by NCI and receipt by NCI of the draft protocol.

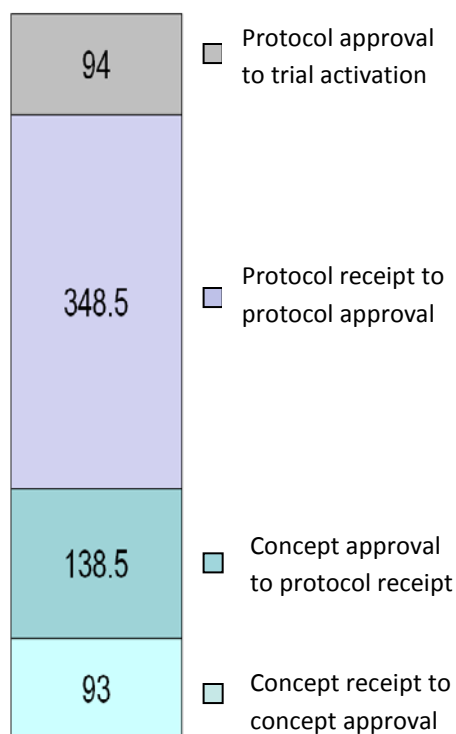


Figure 2: Median Days per Step, Cooperative Group Phase III Trials Activated 2006-2008

The analysis further determined that virtually all activated Phase III protocols went through two or more revisions (68 of 70 or 97%), while more than one-third (24 of 70 or 34%) went through four or more revision cycles (Figure 3).

⁴ Source: Analysis of information from CTEP CDUS database on 70 Phase III trials activated 2006-2008. 67 were Cooperative Group trials, plus one study each from NCIC, the Program for the Assessment of Clinical Cancer Tests, and the Bone Marrow Transplant Clinical Trials Network.

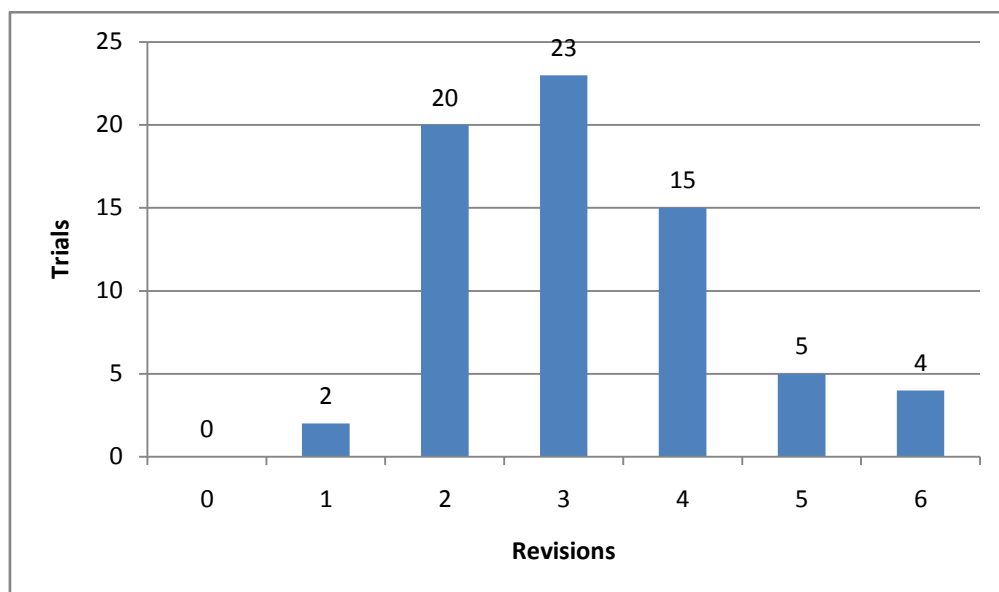


Figure 3: Revisions to Protocols, Cooperative Group Phase III Trials Activated 2006-2008

Improvement Targets

The OEWG set a target of 300 days to complete the steps in Phase III trial activation under CTEP and Cooperative Group control. As a supporting goal, the OEWG established the principle that revision of a submitted concept or protocol should be performed by CTEP and the Group in a collaborative manner such that only one formal submitted revision is necessary. Steps under CTEP and Cooperative Group control were specified as concept review, protocol development, protocol review, and forms development. The 300-day target timeline thus excludes contract and drug supply negotiations with industry partners as well as Institutional Review Board (IRB) approval. *However, the OEWG also set a “drop-dead” date by which all issues, including those controlled by industry partners or IRBs, must be resolved. If a protocol based upon a concept submitted to CTEP is not activated within a 24-month period, it will be terminated.*

Figure 4 shows the trial activation timeline proposed by the OEWG including timeline targets for individual steps in the process. The activities involved with each step, as well as activities prior to concept submission, are described in greater detail in Appendix A.

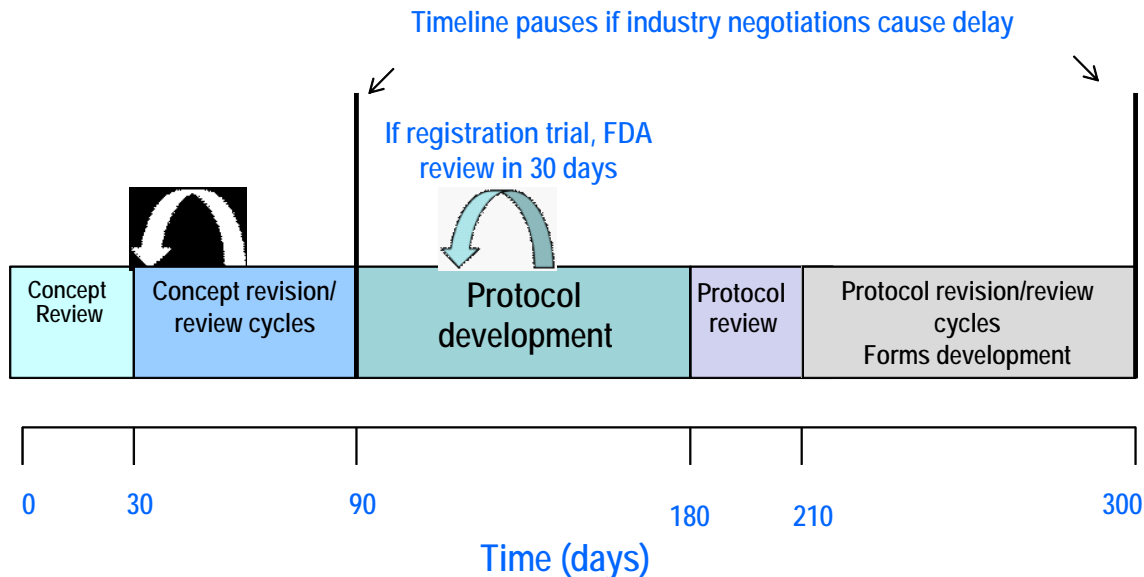


Figure 4: OEWG Proposed Timeline for Cooperative Group Phase III Trial Activation

Achieving the Targets

To reduce the time for activation of Cooperative Group Phase III trials, the OEWG proposes four initiatives.

- Initiative A1: Each Cooperative Group will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation
- Initiative A2: CTEP will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation
- Initiative A3: CTEP and the Groups will develop collaborative processes for revision of concepts and protocols that meet the agreed OEWG timeline
- Initiative A4: NCI and the Groups will collaborate in developing approaches to reward performance against timelines

A critical feature of these initiatives is the shared responsibility of the Cooperative Groups and CTEP for achieving the required improvements. Recognizing that Cooperative Group clinical trials are not developed in isolation, but rather through a process of extensive interaction with CTEP, the OEWG recommendations systematically address management issues within both the Cooperative Groups and CTEP as well as interactions between the Groups and CTEP.

Initiative A1: Each Cooperative Group will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation

Rationale

The creation of Group-specific Action Plans will achieve the benefits of a commitment to a clearly defined improvement plan while acknowledging the legitimate differences in Cooperative Group processes and procedures. Each Group can thus design a plan tailored to its own needs and resources.

Implementation Plan

Each Group's Action Plan should:

- Identify specific changes in task responsibilities and operational processes to speed trial development and activation
- Focus on developmental steps directly impacted by the Group – concept development and revision, protocol development and revision, and protocol activation following final CTEP approval
- Specify where existing resources can be rearranged to implement changes and where new resources are required

Action Plans should not be elaborate documents with extensive supporting material. Rather, the intent is for each Group to develop a concrete plan that properly focuses its implementation efforts and to present that plan in a concise, straightforward manner. NCI will provide supplemental funding to support development and implementation of the Action Plans.

The OEWG identified several management practices as important components in achieving the timeline targets. Each Action Plan should address these practices as well as any others the Group deems important.

Project Management

Establish one or more Trial Development Manager positions with primary day-to-day responsibility for managing trial development tasks including assuring that adequate resources are available and that activities are well coordinated within the Group and in interactions with NCI.

Project Tracking System

Deploy an electronic, interactive, real-time project management/protocol tracking system that provides the following capabilities:

- Track status of individual trial development steps and the responsible parties
- Identify individual concept or protocols that are falling behind the timeline and send reminders to the responsible individuals
- Monitor timeline performance of individual trial development steps and the complete concept-to-activation process, both for individual trials and across the Group's trial portfolio
- Facilitate identification of the reasons for any delays and suggest corrective actions

Protocol Chair Support

Provide direct support to Protocol Chairs that will reduce the time and effort required on their part for trial development. Options for providing such support include but are not limited to the following:

- Use specialist medical writers to draft initial protocols and protocol revisions in coordination with the Protocol Chair
- Establish one or more Physician Senior Protocol Officer positions; these individuals, coordinating with the Protocol Chair, will have primary responsibility for assembling the scientific and clinical content of the protocol and for coordinating resolution of outstanding scientific and clinical issues in protocol development and revision
- Establish a mentorship program for inexperienced clinical investigators that develops the skills needed to prepare a protocol and guide it through the review and approval process

Workflow Management

Establish trial development workflow processes such that, whenever possible, trial development steps are performed in parallel rather than sequentially. A good example is proceeding with forms development while a protocol is undergoing revision.

Direct, Coordinated Interactions

Establish policies and procedures that result in direct, coordinated interactions among members of the Group when conducting scientific/clinical review as well as when addressing budgetary and administrative matters. This should include scheduling regular, standing meetings or calls with all staff involved in the protocol development process to review status and address problems and structuring all communication processes for rapid, interactive feedback and response.

Identification and Resolution of Issues

Establish procedures to assure that issues requiring action are identified, prioritized, and assigned for resolution in a timely and effective way. This should include identifying, prioritizing and communicating key issues as early as possible, specifying clear responsibility and action steps for resolution, including coordinated interactions as necessary. It will also be important to identify types of corrections and revisions to trial protocols that are considered routine and appropriate for resolution by non-physician protocol development staff, and others that require involvement of the Protocol Chair or Physician Senior Protocol Officer.

Initiative A2: CTEP will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation

Rationale

The OEWG views CTEP as having a parallel and shared responsibility with the Cooperative Groups for achieving the targeted reduction in time to trial activation. As with the Groups, an explicit Action Plan is an important element in achieving commitment to a set of concrete improvements and attaching a high priority to their implementation.

Implementation Plan

The leadership of CTEP and CIB, with the support of the Director of the NCI Division of Cancer Treatment and Diagnosis (DCTD) and other DCTD programs and branches as required, will analyze CTEP's operating procedures for advancing Phase III trials to activation. Particular attention will be paid to identifying internal bottlenecks in staff and procedures that delay concept and protocol review, revision and approval. Based on this analysis, CTEP will develop an Action Plan that will:

- Identify specific changes in task responsibilities and operational processes to speed trial activation
- Encompass concept review, protocol review, coordination of all necessary interactions and sign-offs across units within NCI (e.g., statistical review, drug supply) and communication of review results and comments
- Specify where existing resources can be rearranged to implement the changes and where additional resources are required

As with the Group Action Plans, the CTEP Action Plan should be concrete, concise and straightforward. NCI will provide supplemental funding for development and implementation of the Action Plan.

The OEWG has identified several management practices, parallel and complementary to those identified for the Cooperative Groups, as important components in achieving CTEP's timeline goals. CTEP's Action Plan should address these practices as well as any others CTEP deems important.

Project Management

CIB will establish positions within CTEP for individuals with project management experience who will have responsibility for facilitating all aspects of the trial activation process.

- Coordinating the review of concepts and protocols and the preparation of written responses by CIB Medical Officers and others within DCTD (e.g. statistics staff) such that all issues are identified at the time of initial review for both concepts and protocols
- Facilitating interactions between NCI and the Groups to resolve issues promptly, reaching compromise and consensus among the parties
- Serving as a Group's NCI point of contact for all matters relevant to concept and protocol review and revision
- Facilitating interactions, as necessary, with FDA and industry partners on concept and protocol content
- Monitoring progress of trial activation with responsibility and authority to keep the process on track

Project Tracking System

The CTEP Clinical Data Update System (CDUS) database contains a wealth of information regarding the status of individual concepts and protocols, but that system is not designed for real-time management of the review, revision and approval process. CTEP will deploy either an independent system that draws on information from CDUS or a CDUS enhancement, whereby project managers can track status of the concepts and protocols under their jurisdiction. Such a system will need the following capabilities:

- Track status of review, revision and approval for individual concepts and protocols and the responsible parties
- Identify individual concept or protocols that are falling behind the timeline and send reminders to the responsible individuals

- Monitor timeline performance of individual steps in the review and approval process as well as the overall process, both for individual concepts and protocols and across the entire portfolio
- Facilitate identification of the reasons for any delays and suggest corrective actions

Streamlined Communication

CIB will implement streamlined methods for communicating to the Groups comments and required responses about trials in development. Options for such streamlined methods include but are not limited to the following:

- Communicate critical issues to the Groups verbally or by email in advance of a formal written response
- Consolidate comments from CTEP and other DCTD units into a comprehensive, integrated response that invites discussion and dialogue
- Distinguish clearly between critical comments that must be addressed and those that are only suggestions for consideration
- Allow changes made in the protocol document in response to comments to be highlighted and annotated with any necessary explanation without the requirement to create a separate document outlining the changes and/or response to comments

Initiative A3: CTEP and the Groups will develop collaborative processes for revision of concepts and protocols that meet the agreed OEWG timeline

Rationale

The analyses and deliberations of the OEWG highlighted interactions between the Cooperative Groups and CTEP in revising concepts and protocols as a significant source of delay in trial development. A collaborative effort to streamline these interactions is essential to achievement of the 300 day target timeline as improving such interactions cannot be addressed by internal initiatives undertaken individually by the Groups or CTEP.

Implementation Plan

An informal working group encompassing leadership and senior operations staff from both CTEP and the Groups will be convened to develop collaborative approaches for concept and protocol revision. The working group will share information on perceived bottlenecks in their interactions, jointly review data on the time required to revise concepts and protocols, identify possible factors contributing to delays, and share information on respective internal process

analyses and improvement initiatives that may have relevance. The goal is to identify concrete actions that will allow the revision process to be completed in 30 days for concepts and 90 days for protocols. The OEWG recommended that the following actions be considered.

Collaborative Concept Revision

NCI and the Groups will establish procedures for direct, coordinated interactions to resolve any issues in the revision of a concept where there is not rapid agreement between CTEP, other relevant DCTD units, the Scientific Steering Committee and the Group.

Resolve Key Issues at Concept Stage

CTEP and the Groups will accept and enforce the principle that outside of exceptional circumstances, such as a substantial late change in relevant scientific or clinical knowledge, disagreements about basic elements of the study design are resolved at the concept stage and changes in these elements are not requested or introduced at the protocol stage.

Collaborative Protocol Development

CTEP and the Groups agree that interactions between them at the protocol stage should reflect a partnership focused on the shared goal of timely completion of a protocol embodying the agreed concept. Toward that end, the following principles will be adopted and implemented:

- CTEP, other DCTD, and Group staff place a high priority on meeting the required timeline for protocol review and revision and rearrange schedules as needed to jointly resolve important issues
- All major issues are identified and communicated promptly
- Issues requiring resolution are clearly distinguished from comments presented only for consideration
- Direct, coordinated interactions employed to resolve any issues on which there is not rapid agreement between CTEP, other relevant DCTD units and the Group
- CTEP and the Groups adopt methods and tools to minimize the time and effort required to make routine or *pro forma* revisions

Rapid Arbitration

CTEP and the Groups establish procedures for rapid arbitration of any issues on concepts or protocols that cannot be resolved in a timely fashion by direct discussion between the parties.

Industry Outreach

CTEP and the Groups will work with industry to develop processes and procedures for achieving industry input and concurrence on concepts and protocols within the agreed 300-day timeframe. Possible efforts include:

- Collaborate with the Life Sciences Consortium of the CEO Roundtable on Cancer to identify barriers and solutions to obtaining industry cooperation in meeting the target timelines
- Modify Cooperative Research and Development Agreement (CRADA) language to stipulate the target timelines and industry's cooperation in achieving them
- Develop a standard cost structure for typical elements of a Phase III Cooperative Group trial to simplify and standardize budget negotiations

FDA Outreach

CTEP and the Groups will work with FDA to develop processes and procedures for achieving FDA input and concurrence on concepts and protocols within the agreed 300-day timeframe.

Possible efforts include:

- Implement a process involving FDA, industry, NCI and the Groups for defining standards concerning which categories of trials should routinely be managed as potential registration studies
- Develop a standard set of requirements for various aspects of a protocol, as well as the required minimum data set, if the trial is to support registration
- Develop procedures for timely scheduling of Group/CTEP/FDA meetings for review of approved concepts for those trials considered potential registration studies. The Groups, CTEP and FDA commit to the principle that, barring exceptional circumstances, the goal of these meetings will be to resolve all fundamental issues of trial objectives and design, so as to permit rapid and efficient protocol development and facilitate timely and definitive FDA protocol review

Initiative A4: NCI and the Groups will collaborate in developing approaches to reward performance against timelines

Rationale

To the extent that timely trial activation is considered an important performance objective, Cooperative Group review criteria as well as other incentives implemented by NCI should encourage timely trial activation and achievement of the OEWG target timelines. However, bearing in mind the counterproductive effects of poorly-designed incentives, the OEWG believes that any such system should be developed through a collaborative, empirically-based effort.

Implementation Plan

Empirical Foundation

In collaboration with the Groups, NCI will develop a system to routinely and comprehensively collect and report information on the time required to complete each step in the activation of Phase III, large Phase II, and Phase II IDB trials by the Groups with the goal of assessing current performance against the OEWG target timelines. Group-specific performance metrics should be reported on a routine basis to CTEP management, and data on individual Groups should be reported to the respective Group chairs. Because timeline commitments are defined in terms of tasks that are under the control of CTEP and the Groups, the system should clearly indicate when performance against chronological time is placed on hold because of delays due to a third party such as an industry partner or FDA. Moreover, because concept and protocol revision is expected to be a collaborative CTEP/Group endeavor, the system should identify which party is responsible for a given time delay.

Collaborative Design of Incentive System

At the end of one year of data collection, CTEP and the Groups will discuss performance of the timeline collection and reporting system, lessons learned from the data obtained to date, and the development of incentives to reward meeting of target timelines. Topics for discussion may include:

- Changes to the target timelines for each step in the process
- Definitions of “on hold” status for industry or FDA delays, and/or designation of responsibility for delays in concept and protocol revision
- Accuracy and value of timeline data reports
- Value of transparent reporting of comparative performance data across the Groups
- Reasonableness of establishing incentives for the Groups linked to achieving the timeline targets
- Guidance to Subcommittee H on incorporating success in meeting timeline targets as a scored review criteria

CTEP Internal Performance Management

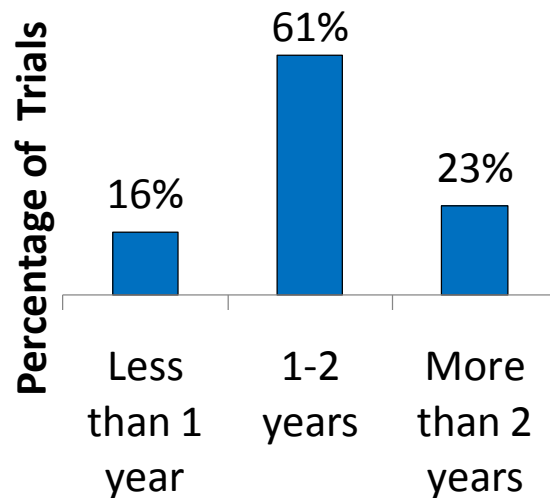
CTEP management will use timeline performance data on activities involving CTEP staff as a key element in annual performance evaluations.

Early Drug Development Trial Process Improvements

Introduction

In addition to the Cooperative Group and Cancer Center clinical trials programs, NCI also supports Phase I and Phase II early drug development trials through the CTEP IDB program. This program supports clinical trials of investigational agents held under CTEP Investigational New Drug Applications (INDs), in collaboration with industry, academia, and the NCI intramural program. CTEP holds approximately 80 active INDs and approximately 500 Phase I and Phase II clinical trials are active at any given time. The funded components of the early drug development program include the Phase I U01 grantees and Phase II N01 contractors. However, Cooperative Groups, Cancer Centers and the NCI intramural program conduct approximately half of the Phase II trials using CTEP IND agents.⁵

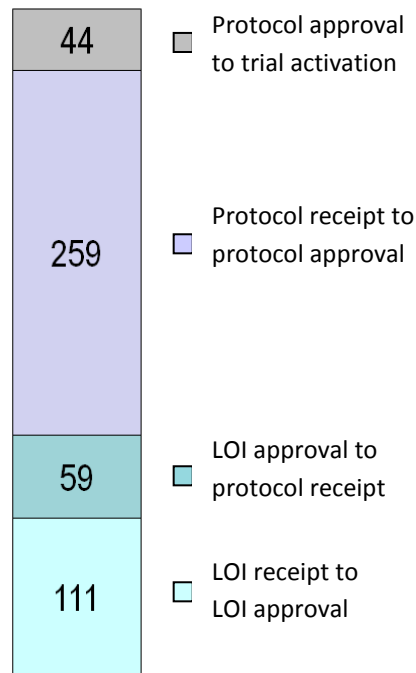
Analysis of Phase II CTEP early drug development trials⁶ activated by Cooperative Groups and N01 contractors between 2006 and 2008 revealed that the majority of those trials required 1-2 years from Letter of Intent (LOI) submission to trial activation (Figure 5), while approximately one-sixth were activated in less than one year, and nearly one-quarter required more than two years to be activated.



**Figure 5: Time to Activation, Early Drug Development Trials Activated 2006-2008
Cooperative Groups and N01 Contractors**

⁵ Source: http://ctep.cancer.gov/MajorInitiatives/Phase_1-2_Early_Drug_Development.htm and data from CTEP.

⁶ Source: Analysis of information from CTEP CDUS database on 137 CTEP Phase II trials conducted by Phase II holders or Cooperative Groups activated 2006-2008.



**Figure 6: Median Days, Early Drug Development Trials Activated 2006-2008
Cooperative Groups and N01 Contractors**

As shown in Figure 6, the time from protocol receipt to protocol approval was the longest step in the process, with a median completion time of 259 days. The process of LOI approval required approximately four months, while the median times from LOI approval to protocol receipt and from protocol approval to trial activation were less than two months. The analysis further determined that nearly three-quarters of activated Phase II protocols went through two or more revisions (101 of 137 or 74%), while more than one-fifth (29 of 137 or 21%) went through four or more revision cycles. (Figure 7)

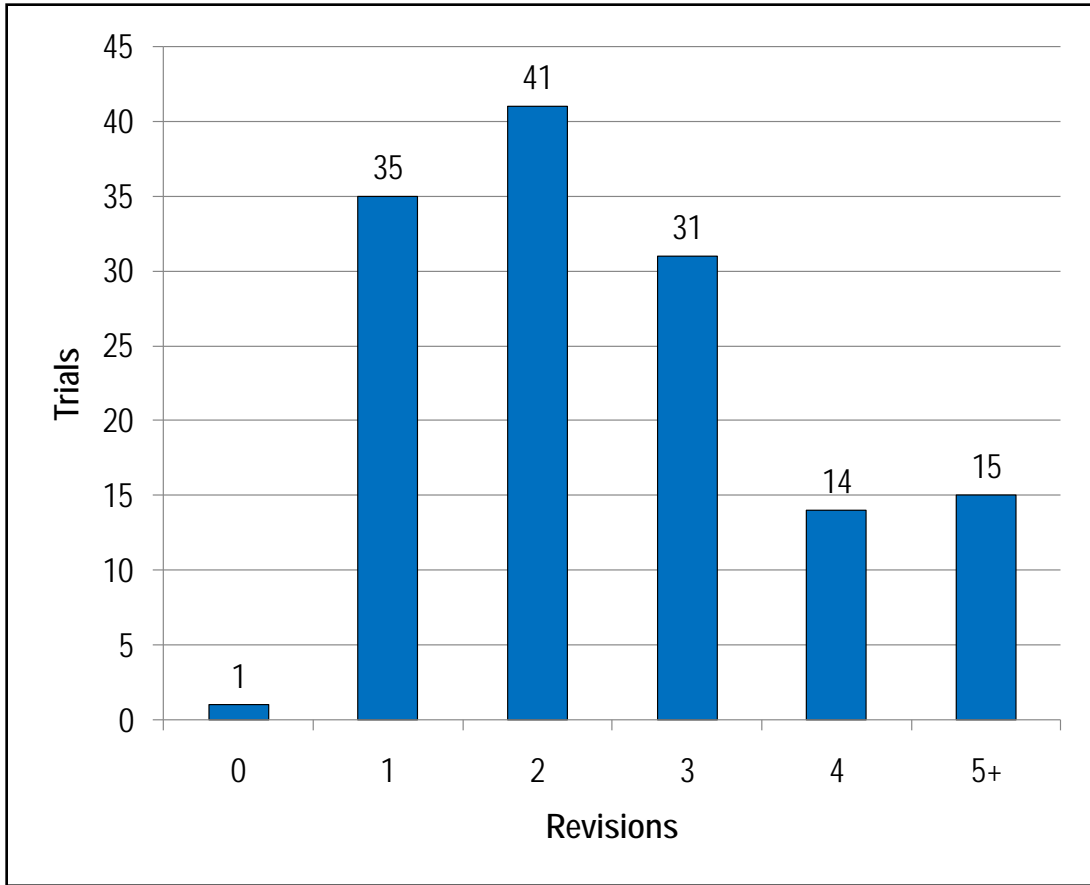


Figure 7: Protocol Revisions, Early Drug Development Trials Activated 2006-2008 Cooperative Groups and N01 Contractors

Improvement Targets

To reduce the time for CTEP Phase II early drug development trial activation, the OEWG set a target of 210 days to complete the steps under CTEP/IDB and extramural control – LOI review, protocol development, protocol review, and forms development. A supporting goal is to revise LOIs and protocols in a collaborative manner such that only one formal submitted revision is necessary. The timeline excludes industry negotiations, arranging drug supply, and IRB and FDA approval. *However, the OEWG also set a “drop-dead” date of 18 months by which all external issues must be resolved. If a protocol based upon an LOI submitted to CTEP is not activated within an 18-month period, it will be terminated.*

Figure 8 shows the trial activation timeline proposed by the OEWG including timeline targets for individual steps in the process. The activities involved in each step, as well as activities prior to LOI submission and variations due to LOI volume, are described in greater detail in Appendix B.

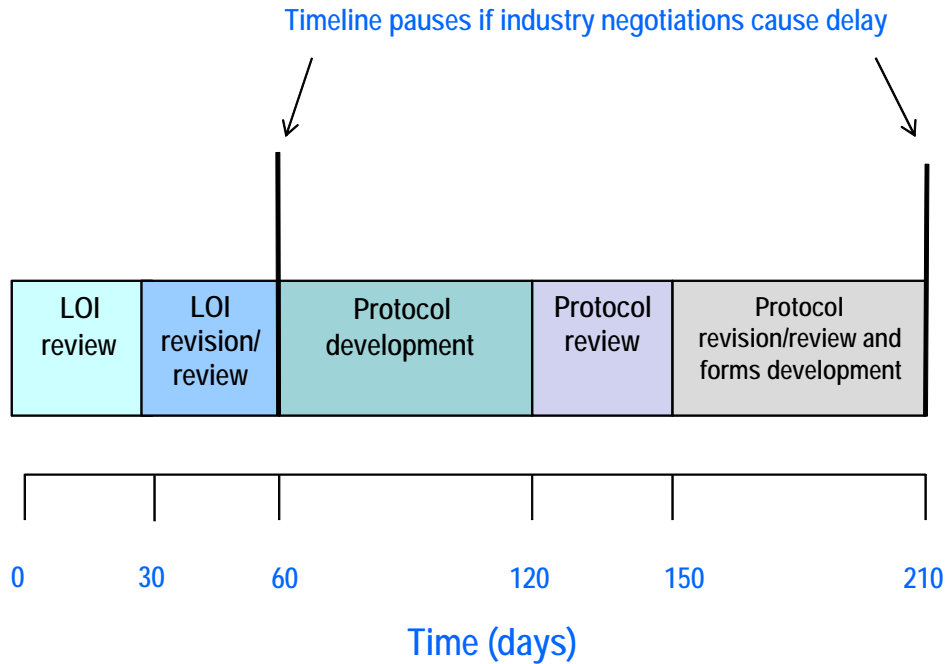


Figure 8: OEWG Proposed Timeline for CTEP Phase II Early Drug Development Trial Activation

Achieving the Targets

To reduce the time for activation of CTEP Phase II early drug development trials, the OEWG proposes two initiatives.

- Initiative B1: CTEP will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation
- Initiative B2: CTEP will collaborate with Phase II early drug development trial performance sites to develop processes for revision of LOIs and protocols that meet the agreed OEWG timeline

Initiative B1: CTEP will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation

Rationale

Of the four stages of Phase II protocol development shown in Figure 6, the median time to complete the stage from LOI approval to protocol submission already matches the OEWG's proposed timeline while the time from protocol approval to protocol activation is relatively short, at just over one month. It is at the other two stages – from LOI receipt to LOI approval and from protocol receipt to protocol approval –that substantial improvements are needed to meet the OEWG target timeline. Each of these stages involves a review process by CTEP and then a revision process involving both CTEP and the investigator. Therefore, a CTEP Action Plan to address delays in the review process is an important element in reducing the time to trial activation.

Implementation Plan

The Action Plan will address the following topics:

- Identify internal bottlenecks in staff and procedures that delay LOI and protocol review
- Identify specific changes in task responsibilities and operational processes to address these bottlenecks
- Identify actions to achieve better coordination of interactions and sign-offs across units within NCI (e.g., statistical review, drug supply) and improved approaches to communication of review results and comments
- Specify where existing resources can be rearranged to implement the needed changes and where additional resources are required

NCI will provide supplemental funding for development and implementation of the Action Plan.

While the OEWG focused on Phase II trials, it should be noted that operational improvements that enhance the efficiency and timeliness of Phase II trial activation will be implemented to improve activation of IDB Phase I trials as well.

The OEWG identified several management practices as important components in achieving CTEP's timeline goals. CTEP's Action Plan should address these practices as well as any others CTEP deems important.

Project Management

IDB will establish positions for individuals with project management experience who will have responsibility for facilitating all aspects of the trial activation process.

- Coordinate responses to LOIs and protocols from IDB Drug Monitors and others within DCTD (e.g. statistics staff) such that all issues are identified at the time of initial review for both LOIs and protocols
- Facilitate interactions between NCI and LOI/protocol submitters to resolve issues promptly, reaching compromise and consensus among the parties
- Serve as the investigators' NCI point of contact for all matters relevant to LOI and protocol review, revision and approval
- Facilitate interactions, as necessary, with FDA and industry partners on LOI and protocol content
- Monitor progress of trial activation with responsibility and authority to keep the process on track

Currently, such activities are performed by IDB technical staff (e.g., Drug Monitors) whose training and skills lie in the conduct of clinical trials rather than the management of complex organizational processes.

Project Tracking System

The CTEP CDUS database contains a wealth of information regarding the status of individual LOIs and protocols, but that system is not designed for real-time management of the review, revision and approval process. CTEP will deploy either an independent system that draws on information from CDUS or a CDUS enhancement, whereby project managers can track status of the LOIs and protocols under their jurisdiction. Such a system will need the following capabilities:

- Track status of review, revision and approval for individual LOIs and protocols and the responsible parties
- Identify individual LOIs or protocols that are falling behind the timeline and send reminders to the responsible individuals
- Monitor timeline performance of individual steps in the review and approval process as well as the overall process, both for individual LOIs and protocols and across the entire portfolio
- Facilitate identification of the reasons for any delays and suggest corrective actions

Streamlined Communication

The early drug development timeline sets as its goal that LOIs requiring revisions be approved within 30 days of the “hold” decision and that protocols requiring revisions have them completed

within 60 days. The timeline also calls for rapid notification of investigators whose LOIs have been disapproved. These requirements suggest that CTEP will need to streamline its practices for communicating with investigators. Options for such streamlined practices include but are not limited to the following:

- Communicate a decision not to accept an LOI to the investigator at the point of decision, perhaps via email, in advance of preparing a formal written communication and critique
- Communicate critical issues to investigators verbally or by email in advance of the formal written review
- Consolidate comments from CTEP and other DCTD units into a comprehensive, integrated response that invites discussion and dialogue
- Distinguish clearly between critical comments that must be addressed and those that are only suggestions for consideration
- Allow changes made in the protocol document in response to comments to be highlighted and annotated with any necessary explanation without the requirement to create a separate document outlining the changes and/or response to comments

Initiative B2: CTEP will collaborate with Phase II early drug development trial performance sites to develop processes for revision of LOIs and protocols that meet the agreed OEWG timeline

Rationale

The analyses and deliberations of the OEWG highlighted interactions between investigators and CTEP in revising LOIs and protocols as a significant source of delay in trial development. A collaborative effort to streamline these interactions is essential to achieve the target of 210 days for Phase II early drug development trial activation.

Implementation Plan

CTEP and, as applicable, investigators and their institutions should address the following aspects of trial activation.

Resolving “on hold” LOIs

CTEP and investigators should establish procedures for direct, coordinated, interactions to resolve issues in the revision and approval of an LOI that is placed “on hold” for issues other than the need for new information, such as the completion of additional studies. In order to resolve issues rapidly, CTEP and LOI submitters will commit to conduct conference calls or other communications within two weeks of CTEP’s initial decision to place an LOI on hold, with

the goal of resolving all issues within 30 days of CTEP's initial response. For LOIs placed on hold to establish a collaboration with two or more LOIs submitters, CTEP will work with extramural investigators to define a formal process for forging such collaborations and creating multi-center studies from individual LOIs.

Resolve Key Issues at LOI Stage

CTEP and the early drug development investigator community will accept and enforce the principle that outside of exceptional circumstances, such as a substantial late change in relevant scientific or clinical knowledge, disagreements about basic elements of the study design are resolved at the LOI stage and changes in these elements are not requested or introduced at the protocol stage. To implement this action, both CTEP and the investigator community should review the current CTEP/IDB LOI template to determine whether it provides sufficient clarity regarding concept and study design.

Collaborative Protocol Development

CTEP and the investigator community agree that interactions between them at the protocol stage should reflect a partnership focused on the shared goal of timely completion of a protocol embodying the agreed LOI concept. Toward that end, the following principles will be adopted and implemented:

- CTEP, other DCTD staff and investigators place a high priority on meeting the required timeline for protocol review and revision and rearrange schedules as needed to jointly resolve important issues
- All major issues are identified and communicated promptly
- Issues requiring resolution are clearly distinguished from comments presented only for consideration
- Direct, coordinated interactions are employed to resolve any issues where there is not rapid agreement between CTEP, other relevant DCTD units and the investigator
- CTEP and investigators should adopt methods and tools to minimize the time and effort required to make routine or *pro forma* revisions

Rapid Arbitration

NCI, in consultation with the investigator community, will establish procedures for rapid arbitration of any issues on LOIs and protocols that cannot be resolved in a timely fashion by direct discussion between the parties.

Cancer Center Investigator-Initiated Trial Process Improvements

Introduction

The mission of NCI-Designated Cancer Centers includes development of more effective approaches for cancer therapy. Investigator-initiated trials, which rely upon internally-generated hypotheses and utilize funding sources including institutional funds, external awards, and industry sponsorship, are one component of that therapeutics development mission. Activation of investigator-initiated trials requires a number of steps: development of a protocol; review and acceptance by the Cancer Center's Protocol Review and Monitoring System (PRMS); budgeting and contracting; receipt of therapeutics to conduct the study; development of forms, consent statements, and regulatory documentation; and review by the IRB and other ancillary committees (e.g., radiation safety).

Analysis by Dilts et al of investigator-initiated trials at two selected Cancer Centers determined that those two institutions required an average of 211 and 243 days, respectively, to activate an investigator-initiated trial with a range of 110 to 908 days.⁷

Improvement Targets

To reduce the activation time for investigator-initiated trials at Cancer Centers, the OEWG set two targets:

- Complete protocol review and revision, forms development, IRB review, and ancillary committee review within 90 days
- Complete all steps from protocol submission to trial activation in 180 days

Figure 9 shows the trial activation timeline proposed by the OEWG, including timeline targets for individual steps in the process. The activities involved with each step, as well as the flexibility allowed Cancer Centers in the time allocated to each step, are described in greater detail in Appendix C.

⁷ Dilts DM and Sandler AB. Activating and Opening Oncology Clinical Trials: A Process and Timing Study, NCI CTAC meeting, November 14, 2007.

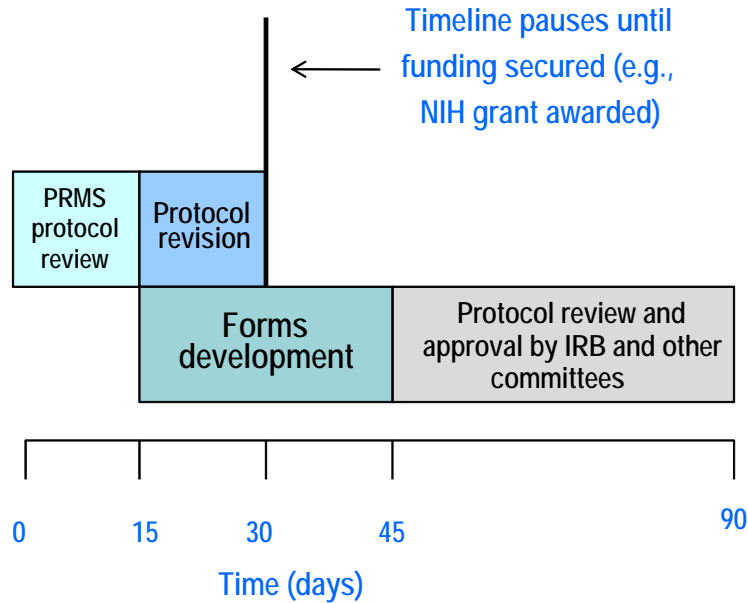


Figure 9: OEWG Proposed Timeline for Cancer Center Investigator-Initiated Trial Activation

Achieving the Targets

To reduce the time to activation for Cancer Center investigator-initiated trials, the OEWG proposes two initiatives.

- Initiative C1: Each Cancer Center will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation
- Initiative C2: NCI and the Cancer Centers will develop and implement new initiatives designed to streamline university contracting and financial review processes

Initiative C1: Each Cancer Center will develop an Action Plan to achieve the agreed OEWG target timeline for trial activation

Rationale

Cancer Centers have developed their own individual processes for developing and activating investigator-initiated trials. Those processes depend in part on structural factors such as whether the Cancer Center is an independent institution or a matrix Center within an academic medical center as well as the size of the Cancer Center and the size and character of its parent institution. The processes are also influenced by technical considerations such as the complexity of the

investigator-initiated trial portfolio and the origin of the therapeutics involved as well as Center-specific factors such as decision-making processes, protocol development infrastructure, and leadership. Improvement in time to activation thus requires Center-specific plans that take local conditions into account.

Implementation Plan

Action Plan Development and Content

The Action Plan must set trial activation timeline targets for investigator-initiated trials based on the OEWG proposed timelines shown in Appendix C. Delays beyond the control of the Cancer Center, such as institutional financial review, industry negotiations, and FDA review should not be included in the timelines. Each Cancer Center will report current times for trial activation when the Action Plan is submitted to NCI. Cancer Centers can propose target timelines that are longer than those specified by the OEWG. However, in that event the Center will identify specific processes (e.g., sequential review of draft protocols) and/or resource constraints (e.g., understaffed clinical trials office) that prevent meeting the OEWG target timelines as well as plans to address those limitations over time. Also, as part of its Action Plan, each Cancer Center should establish standards to judge success in meeting the target timelines (e.g. the median time to trial activation across a category of trials).

Each Center's Action Plan will identify concrete steps for improving the efficiency of protocol development and trial activation processes. Potential action steps identified by the OEWG include the following:

- Hire professional protocol writers and editors to assist investigators in preparing protocols
- Convene face-to-face meetings of all pertinent staff and the investigator to resolve differences and minimize serial tweaking of protocols
- Convene regular clinical trials office staff meetings for timeline management and problem solving
- Deploy project management software tools to track protocol development timelines

The Action Plans will also estimate the resources required to implement the proposed action steps.

Review of Action Plans

Given the heterogeneity of Cancer Centers, no specified action steps or timelines will be required of each. However, Cancer Centers will not be permitted to propose insufficient or excessively resource-intensive plans for improvement. To that end, Action Plans will be reviewed by NCI for reasonableness before individual Cancer Centers implement them.

To facilitate refinement of the respective plans, and for the benefit of the system as a whole, the proposed Action Plans, target timelines and progress to date will be discussed at Cancer Center Directors meetings to identify areas of variation and potential best practices.

Action Plan Implementation

Implementation will require a joint effort of NCI and the investigator community. The OEWG recommends that the NCI Cancer Centers program revise the Cancer Center Support Grant (CCSG) Guidelines to explicitly allow use of funds (including discretionary funds) for protocol development.⁸ However, if implementation of the Action Plans diverts significant funds from other CCSG-supported clinical trials activities, the OEWG's purpose would be thwarted. Reducing funds for clinical trial conduct would slow the completion of trials, and reducing funds for scientific infrastructure would reduce the number of new discoveries that could potentially be advanced to the clinic. NCI will therefore provide supplemental funds for implementing certain aspects of the Action Plan if the required investment is properly justified by the Center.

As Cancer Centers implement their Action Plans, they will track the time required for protocol development and activation and reasons for delays in specific steps, such as:

- Protocol writing by investigator
- Repeated iterations in the protocol review and approval process
- IRB review
- Contracting

Using these data, Cancer Centers should be able to identify areas of continuing delay and propose and implement actions to achieve further reductions in trial activation time.

NCI will require Cancer Centers to report trial activation timeline performance annually as part of their progress reports and competing renewal applications. NCI will compare individual Centers' results to the OEWG target timelines and to results across all Cancer Centers. Cancer Centers performing below expectations (e.g., X% above the OEWG target timeline; the slowest Y% of Cancer Centers) would be required by NCI to institute more rigorous corrective actions to reduce delays.

Each Cancer Center's progress reports and competing renewal applications should include an updated version of its Action Plan and report progress on its implementation. The updated Action Plan should identify types of trials upon which the Cancer Center will focus its improvement efforts (e.g., where target timelines had not yet been met or where the Cancer Center is different from others) and propose a benchmark for further improvement (e.g., reduce median time X% or decrease percentage of trials exceeding the OEWG targets by Y%).

⁸ Proposed guideline changes will be implemented under the auspices of the CTAC Guideline Harmonization Working Group.

Initiative C2: NCI and the Cancer Centers will develop and implement new initiatives designed to streamline university contracting and financial review processes

Rationale

Initiative C1 focuses on activities under the jurisdiction of the Cancer Center and its participating investigators. However, reducing the time spent on contracting and financial review is beyond the direct control of the Cancer Center. Addressing these processes will require institution-wide changes that have the potential to benefit all clinical trials across disease areas. NCI and Cancer Center leadership will therefore benefit from partnerships with NIH staff and trialists from other disease areas, perhaps through the NIH Clinical and Translational Science Award (CTSA) program, to define and achieve the required changes.

Implementation Plan

Given the magnitude of the challenge, this initiative includes separate activities for NCI and the Cancer Centers.

NCI Activities

NCI will work with academic institutions and other stakeholders towards system-wide changes in university contracting and financial review practices. Potential steps are described below.

- ***Standardized clinical trial agreement clauses.*** NCI will more proactively educate academic institutions concerning the Standardized Clauses for Clinical Trial Agreements developed by NCI as a result of the Clinical Trials Working Group Report. While the clauses are publicly available (e.g., on the Cancer Center Internet site), some Cancer Centers are not fully aware of the potential time savings that could be gained from their use.
- ***Common standards for reimbursable expenses.*** Policies regarding support from Medicare and Medicaid for clinical trial expenses currently are not clear. Moreover, even when policies exist at the Federal level, they are not necessarily interpreted in common fashion by regional CMS contractors. The lack of common standards creates uncertainty concerning the required clinical trial support budget, which slows the industry contracting process. NCI will work proactively with CMS to establish commonly accepted standards for reimbursable clinical trial expenses.
- ***Collaboration with CTSA program.*** The CTSA program is also concerned with improving clinical trials at awardee institutions, and the CTSA Clinical Research Innovation Key Function Committee includes improving contract management in its charge. NCI leadership will therefore work proactively with leadership of the CTSA

program to develop a coordinated action plan for streamlining university contracting and financial review.

- **Stakeholder outreach.** In approaching the leadership of academic institutions to advocate change, NCI will attempt to enlist the support of organizations such as the Association of American Medical Colleges (AAMC), the Association of American Cancer Institutes and the American Society of Clinical Oncology. As proposed changes have an impact beyond cancer research, it will be especially important to recruit general-interest organizations such as AAMC.

Cancer Center Activities

In addition to supporting the broader national initiatives, Cancer Center leadership will work with their institutions to adjust local practices to speed contracting and financial review. Potential steps are described below.

- **Implement standardized clauses.** In parallel with the NCI-wide educational activities, Cancer Center leadership will work to educate stakeholders within their own institutions concerning the Standardized Clauses for Clinical Trial Agreements developed by NCI.
- **Pursue master agreements.** Master agreements simplify contracting on individual trials, while the standardized clauses can facilitate the execution of master agreements. Cancer Center leadership will pursue master agreements with those companies with which their institutions most often collaborate, using the standardized clauses as the starting point.
- **Dedicated contracting and legal staff.** Institutions' contracting and legal resources are typically responsible for a wide range of agreements affecting different parts of the institution. Dedicated staff to support negotiation of cancer clinical trial agreements would encourage development of specialized knowledge, reducing the time for individual transactions, and reduce delays due to competing commitments. While it is not possible to use Cancer Center (or other Federal) funds to support dedicated contracting or legal staff, Cancer Center leadership should consider using non-Federal funds for the full or partial support of a staff position in the university legal and/or contracting office, where the funded time is to be devoted exclusively to negotiating Cancer Center clinical trial agreements.
- **Schedule joint meetings.** One hindrance to rapid resolution of contracting and financial issues within an institution is the dispersion of key decision-makers across different organizational units. Organizing meetings of all relevant parties to resolve issues is more efficient than conducting bilateral phone calls or using electronic mail to mark up documents. Cancer Center staff will therefore, wherever possible, organize meetings of all relevant stakeholders to resolve budget and contracting issues.
- **Collaborate with CTSA leadership.** Cancer Center leadership at CTSA institutions will work with the local CTSA leadership to develop a coordinated action plan for streamlining university contracting and financial review.

- ***Share best practices.*** Although each Cancer Center is different, common strategies that prove successful may be worth sharing and implementing broadly. Meetings of the Cancer Center Directors provide one potential venue for sharing experiences and identifying and disseminating best practices.

Process Improvements Applicable Across Trial Categories

Introduction

The OEWG's deliberations identified several process improvements that would speed time to activation for all categories of trials. Three improvements were judged to be of sufficient importance that the OEWG developed specific initiatives to address them.

- Initiative D1: NCI, Cooperative Groups and Cancer Centers will develop a coordinated approach to standardization of protocol elements and protocol development tools
- Initiative D2: NCI will enhance funding and capabilities for use of biomarkers in clinical trials
- Initiative D3: Cancer Centers will perform a rigorous review of each proposed clinical trial concept in advance of protocol development

Initiative D1: NCI, Cooperative Groups and Cancer Centers will develop a coordinated approach to standardization of protocol elements and protocol development tools

Rationale

Considerable effort has already been invested by NCI, Cooperative Groups and Cancer Centers in development of standard cancer clinical trial protocol elements and protocol development tools. However, to date there has been little coordination or integration of these efforts. As a result, there is a risk of both duplicated effort and the imposition of new standards that are unnecessary. The critical need is not for new standardization initiatives but for enhanced coordination of and communication about existing efforts and improved dissemination of information on the availability of standard elements and tools for operational use.

Implementation Plan

Standardization Working Group

NCI will establish a working group, with membership from CTEP, the Center for Bioinformatics and Information Technology (CBIT), the Cancer Centers Program, the Cooperative Groups and the Centers, to develop consistent and transparent policies on standardization. Representation from the Groups and the Centers should include individuals who have responsibility for protocol development and trial operations as well as individuals who have responsibility for the IT infrastructure supporting these activities.

Inventory of Existing Tools

In consultation with the working group, NCI will compile an inventory of current Cooperative Group, Cancer Center, CTEP and CBIIT software tools, protocol templates, data elements, case report form modules, etc. as well as relevant software available commercially. With guidance from the working group and expert contractor or consultant support as necessary, NCI will analyze this inventory to identify best-in-class products and tools, redundancies in current development efforts and unmet needs.

Once the inventory and analysis is complete, the working group, with input as needed from software vendors and from application developers in the Groups and Centers, will review the results and identify:

- Protocol elements and tools where it will be beneficial to standardize across the entire community as well as those where special requirements necessitate Group-specific or Center-specific standards
- Protocol elements and tools where standardization will be considered mandatory, those where it will be recommended and those where implementation is at the discretion of individual Groups and Centers
- Any needed standards for data interchange between protocol development tools used by the Groups, the Centers and NCI
- Existing products, templates, tools, etc. judged best for meeting specific functional needs as well as areas where new or redirected development efforts are needed

Developing and Implementing Standards

Once the inventory, analysis and above actions have been completed, the working group will develop a coordinated management process for developing and implementing standards across NCI, the Groups and Cancer Centers. The process will encompass the following:

- Implementing agreed-upon standards
- Monitoring implementation progress and identifying any corrective actions
- Monitoring evolving activities and needs in the Groups and Centers and identifying additional opportunities for process improvement through standardization
- Developing and disseminating new tools as needed

NCI and the leadership of the Groups and Cancer Centers should collaborate to promote awareness of and encourage adherence to agreed upon standards by investigators, scientific committees, PRMS committees, IRBs and sponsors.

In support of the standardization effort, CBIIT should establish and maintain a portal providing up-to-date information on the status of all standardized elements and tools relevant to Groups' and Cancer Centers' protocol development efforts, including:

- Links to standard templates, language, data elements, form modules, procedures, etc.
- Whether each element or tool is considered mandatory, strongly recommended, or optional
- Status and expected timeline of ongoing development and standardization efforts

Initiative D2: NCI will enhance funding and capabilities for use of biomarkers in clinical trials

Rationale

Given the increasing importance of biomarkers in cancer treatment and diagnosis, NCI's funding mechanisms and review processes should facilitate the inclusion of scientifically well-motivated integral and integrated biomarker studies⁹ both in Phase III and earlier phase trials. At present, however, the inclusion of such studies often slows the development of protocols, for any of several reasons:

- Need to seek outside funding for performance of biomarker tests
- Duplicative review due to different funding sources for clinical trial and the biomarker studies
- Inadequate detail concerning biomarker studies at the time of clinical trial concept review
- Need to complete validation studies before biomarker can be used in clinical trials
- Lack of access to laboratories certified by Clinical Laboratory Improvement Amendments (CLIA) for performing biomarker assays
- Lack of sites qualified to perform required imaging studies

NCI's funding and review processes for biomarker studies should be improved to reduce these delays in protocol development and trial activation.

⁹ This section uses the following definitions of biomarker-related terms:

- "Integral" biomarker study: Tests that must be performed in order for the trial to proceed. Integral studies are inherent in the design of the trial from the onset and must be performed in real time for the conduct of the trial. (e.g., AKT expression to enroll in trial)
- "Integrated" biomarker studies: Tests that are clearly identified as part of the clinical trial from the beginning and are intended to identify or validate assays or imaging tests that are planned for use in future trials. (e.g., % inhibition of AKT by inhibitor)

Implementation Plan

Expand and Enhance BIQSFP

NCI's Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP) supports studies that are integral to or integrated with Phase III clinical trials conducted by the Cooperative Groups and Community Clinical Oncology Program (CCOP) Research Bases. The OEWG recommends two enhancements to the program described below.

Include large, randomized Phase II trials. Allow integral and integrated biomarker studies associated with large (≥ 100 patient) randomized Phase II trials to be eligible for BIQSFP funds, and modify the program announcement to highlight this change. In addition, if there is strong scientific evidence for the importance of an integral or integrated biomarker study in association with a smaller or non-randomized Phase II trial, such studies could be proposed for BIQSFP funding in coordination with LOI submission for the trial.

Modify CTAC role. CTAC currently reviews each individual BIQSFP award. CTAC's role will be changed to focus on program planning and monitoring with responsibility for the following:

- Set overall goals for the program
- Define BIQSFP molecular biomarker eligibility criteria (e.g., "clinically validated")
- Identify study categories that should be eligible for BIQSFP funds (e.g., economic/cost-effectiveness studies)
- Recommend annually both overall funding and any specific funding for particular study categories (e.g., quality of life)
- Establish prioritization criteria (e.g., Phase III versus large randomized Phase II trials, integral versus integrated studies)
- Review program implementation annually

While funds allocated for BIQSFP were adequate in the program's first year, additional funding may be required as the use of integral and integrated biomarkers in clinical trials expands. NCI and CTAC will monitor the flow of applications and their quality to assess whether the program's current \$10 million annual funding level is appropriate.

Review of Biomarker Studies

NCI will change existing procedures for review of LOIs (for early drug development) and concepts (for Phase III studies) to provide more thorough review of proposed biomarker studies. NCI will require clinical trial concepts/LOIs to include information on proposed biomarker studies. Integral biomarker studies will require BIQSFP-level detail while integrated studies will require only a description of the biomarker assay to be employed and the biospecimens required.

Scientific Steering Committees, Task Forces, and CTEP currently include relevant molecular biomarker expertise during the review of concepts and associated BIQSFP proposals, but

increased involvement of imaging experts in the review of Cooperative Group (non-ACRIN) trials involving imaging biomarkers¹⁰ is required. However, trials that aim to validate imaging procedures (e.g., test of dynamic contrast-enhanced MRI) should not be reviewed by a disease-specific Scientific Steering Committee, but instead should be reviewed by current ACRIN or Cancer Imaging Program (CIP) procedures. IDB and Investigational Drug Steering Committee (IDSC) procedures should incorporate appropriate biomarker expertise in review of drug development plans and LOIs that incorporate biomarker studies.

Molecular Assay Support

NCI is establishing a Clinical Assay Development Program at NCI-Frederick and a Clinical Assay Development Network in the extramural community to provide laboratory resources for the development and analytical validation of clinical grade molecular assays for use in integral biomarker studies for Phase III trials. Assays will be approved for access to program resources by a collaborative process involving the extramural community and NCI. The OEWG supports the goals of these two new endeavors and recommends that they be expanded to include assays for earlier-stage trials.

NCI will also establish contracts with CLIA-certified laboratories to perform commonly used tests as a service to those performing integral molecular biomarker studies, and support the development of CLIA-certified laboratories at institutions. To disseminate knowledge regarding the availability of biomarker technologies, NCI will develop databases for the following resources:

- CLIA-certified laboratories and the biomarkers/technologies for which they are certified
- Assays currently being used in clinical trials with contact information for the trial and the assay

Imaging Site Qualification

CIP and ACRIN will develop a set of qualification standards for conduct of imaging studies associated with clinical trials and use these to prequalify institutions to participate in multisite imaging trials. Such standards need to be modality- and use-specific (e.g., CT for purpose of volumetric analysis is very different from dynamic CT to evaluate content of a liver lesion), and the process should build upon existing activities. CIP will then develop a database of the institutions qualified to perform specific modalities and technologies.

¹⁰ As of the time of the OEWG report, a new Imaging Steering Committee is under discussion, which may be a mechanism for providing the required expertise.

Initiative D3: Cancer Centers will perform a rigorous review of each proposed clinical trial concept in advance of protocol development

Rationale

Unlike Cooperative Group trial concepts, where prioritization is performed by NCI and the Scientific Steering Committees, or early drug development trials which are prioritized at the LOI stage by CTEP, there is not typically a proactive process for prioritization of investigator-initiated trials at the concept stage within a Cancer Center. Rigorous review of proposed clinical trial concepts by Cancer Centers in advance of protocol development would have three benefits. First, it would reduce the time spent by investigators in developing protocols that are eventually not taken forward or are opened and do not accrue well. Second, it would optimize use of protocol development resources by reducing the number of protocols in development at any one time. But most importantly, it would allow Cancer Centers to focus on activating those trials most likely to accrue well and provide results that advance the field.

Implementation Plan

The CCSG guidelines currently include a requirement for establishing a PRMS process for reviewing protocols before activation, but they do not include a comparable requirement for review at the concept stage. Therefore the guidelines will be revised to include a requirement that Cancer Centers develop a process for clinical trial prioritization at the concept stage. The process will be summarized in the competitive CCSG renewal application, with the full description available for the site visit. The process, at a minimum, should specify the following:

- Level at which approval/disapproval occurs (i.e. by “disease-specific group” or Center-wide)
- If approval is at disease level, how uniformity of reviews across diseases will be achieved
- Information included in the Center’s concept document
- Criteria by which concepts are reviewed

NCI should not mandate specific processes or criteria for concept reviews. Nevertheless, the OEWG recommends that the criteria adopted by Cancer Centers address the following elements:

- Scientific and operational feasibility
- Adequacy of patient population at the Center
- Absence of competition with other clinical trials open at the Center
- Impact of the trial results on advancing the field such as by providing the basis for a definitive Phase III trial or correlative study, disproving a clinical or correlative hypothesis or other measures of clinical or scientific impact

All clinical trial concepts – including those for externally peer-reviewed studies as well as for institutional and industry-funded studies – should be included in this process since they all draw upon patient and other resources. Cooperative Group trials should also be reviewed by this process before opening at the Center.

NCI will also charge Subcommittee A with establishing a review criterion measuring the impact of the Cancer Center's trials on advancing the field.

Process Improvements to Enhance Overall Clinical Trials Program

Introduction

The OEWG's deliberations identified three process improvements that while not directly reducing trial activation time, would enhance NCI's clinical trials program.

- Initiative E1: NCI and academic institutions will provide incentives to enhance Cancer Center participation in Cooperative Group and other multi-site clinical trials
- Initiative E2: Cancer Centers will develop a process for the periodic strategic review of their clinical trial program
- Initiative E3: NCI will develop enhanced clinical research mentorship and training programs at Cancer Centers

Initiative E1: NCI and academic institutions will provide incentives to enhance Cancer Center participation in Cooperative Group and other multi-site clinical trials

Rationale

The timely advancement of Cooperative Group trials would be facilitated by enhanced participation of Cancer Centers. The OEWG identified two barriers to participation by Cancer Center investigators in multi-site trials: collaborative design of large, multi-site trials is not recognized as a legitimate academic activity and accrual to multi-site trials developed by others is not recognized as an important service activity.

Implementation Plan

CCSG Guideline Modification

While the CCSG guidelines mention participation in Cooperative Group trials as an important element of Center activity,¹¹ the OEWG concluded the incentives for that participation could be improved. Therefore, NCI will revise the CCSG guidelines to make participation in Cooperative Group scientific leadership activities and accrual to Cooperative Group trials scored review criteria.

¹¹ See, for example, CCSG guidelines, September 2008, page 6, "Cancer centers with clinical components are expected to initiate and conduct investigator-initiated, early phase, innovative clinical trials and to provide leadership for, and participate in, the NCI cooperative groups."

Tenure and Promotion Criteria

The OEWG recommends the following changes for consideration by academic institutions:

- Include clinical trial leadership (e.g., leadership of Cooperative Group trials and/or participation in Group leadership and Scientific Steering Committee processes) as an “academic” criterion for tenure and promotion
- Include accrual of patients to clinical trials designed and led by others as a “service” criterion for tenure and promotion
- Encourage individual department chairs and deans of medicine to honor collaborative clinical trial participation through recognition of high-achieving investigators
- Provide enhanced relative value units (RVUs) to clinical investigators to encourage enrollment of patients on multi-site clinical trials

NCI will incentivize institutional adoption of these changes by encouraging their implementation in the CCSG guidelines.

Enhanced NCI Recognition

NCI will explore approaches for formal recognition of leaders of Cooperative Group trials, including the following:

- Group Chair writes a letter of commendation to the relevant department chair/dean when a Cancer Center investigator leads a Cooperative Group Scientific Committee or serves as a Protocol Chair
- NCI Director writes a letter of commendation to the relevant department chair/dean when a Cancer Center investigator leads a Cooperative Group Scientific Committee, serves as a Protocol Chair or chairs a NCI Scientific Steering Committee
- NCI expands the Clinical Investigator Team Leadership Award program to include support for the design and conduct of multi-site trials

Enhanced Support for Centers Participating in Cooperative Group Trials

The OEWG found that current Cooperative Group funding practices may not sufficiently incentivize Cancer Center participation. Separate U10 awards that provide Main Members with stable support for accrual, Principal Investigator status for the lead investigator and institutional overhead support are strictly limited. In addition, the standard \$2,000 per-patient reimbursement is only one-third the average cost of managing patients on a Cooperative Group study. To address these issues, NCI should implement the following:

- Expand U10 funding at Cooperative Group Main Member Cancer Centers
- Increase NCI per-patient reimbursement rates for Cooperative Group trials to \$6,000 per patient

Initiative E2: Cancer Centers will develop a process for the periodic strategic review of their clinical trial program

Rationale

Productive use of Cancer Center clinical trial program resources will benefit from enhanced coherence and focus in the Center's portfolio of clinical trial activity.

Implementation Plan

Each Cancer Center will establish a process for periodic strategic review of its clinical trial activities. The review should evaluate current activities, set new directions and focus on the following elements:

- Impact of recent scientific and clinical advances
- Changing research priorities in diseases and modalities
- Changes in unmet clinical needs
- Evolving character of the patient population served by the Center
- Portfolio balance among investigator-initiated, Cooperative Group and industry trials
- Alignment of clinical activities with programmatic directions and basic/translational research priorities
- Evolving clinical faculty interests
- Operational aspects including timelines for trial activation, accrual to studies and benefits of reviewing trials at the concept stage

Such a process might also determine whether new disease-specific groups should be formed and/or existing disease-specific groups eliminated and inform clinical faculty hiring decisions and basic/translational research directions.

The requirement to perform periodic clinical trial strategic reviews will be included in the CCSG guidelines. The process and the results of the most recent review will be summarized in the competitive CCSG application, with the full description available for the site visit.

Initiative E3: NCI will develop enhanced clinical research mentorship and training programs at Cancer Centers

Rationale

A final area of OEWG discussion concerned the difficulties faced by junior investigators wishing to participate in clinical research and by clinical research office staff in finding adequate mentorship and training. Enhancing training and mentorship would have several beneficial effects. It would enhance incentives for junior investigators to remain in academic medical centers and conduct clinical research and facilitate gaining the expertise to activate trials in a timely fashion. It would also facilitate skill-building by clinical research office staff.

Implementation Plan

CCSG Guideline Modifications

NCI will modify the CCSG guidelines to be more explicit in encouraging clinical research training and mentorship. Possible changes identified by the OEWG include:

- Allow Cancer Centers to use CCSG funds for training and mentorship of both junior investigators and clinical research office staff
- Define the “Staff Scientist” role at a Cancer Center as including clinical trial mentorship responsibilities and change review practices to highlight the importance of the role
- Include training grant awards in clinical research as part of the second stage review process for Comprehensive Cancer Centers

New Training Programs

NCI will create new training programs aimed specifically at clinical investigators. Of K-awards active in summer 2009, for example, only 82 of 597 (14%) had clinical research components, and 37% (14 of 38) of Comprehensive Cancer Centers had no K-series awards for clinical research. OEWG participants suggested a range of potential enhancements to NCI’s training programs:

- Create K-award programs (beyond the K23s) specifically supporting the design and conduct of a clinical trial
- Develop an online system to train young investigators and clinical research office staff in the protocol development process
- Develop a list of best practices related to clinical trials mentorship and training
- Develop a “Virtual Clinical Trial Institute” for junior investigators to interact online with senior investigator mentors from across the country
- Promote Master’s programs in clinical research administration

Clinical Trial Mentoring Programs

NCI supported clinical trials programs will enhance mentoring of junior investigators. To achieve this goal, OEWG participants suggested the following:

- Cooperative Group and CCOP guidelines will be modified to incentivize the mentorship of junior investigators, perhaps by incorporating a goal for the percentage of Cooperative Group and CCOP trials designed or led by junior investigators
- The IDB N01 and U01 early drug development programs will expand incentives for the mentorship of junior investigators beyond the mentored LOI, perhaps by incorporating a goal for the percentage of trials designed or led by junior investigators

CCSG-CTSA Synergies

Leaders at institutions participating in both the Cancer Center and CTSA programs will identify opportunities for synergy and economies of scale in training activities. One suggestion is that any training in clinical research (e.g., research ethics, biostatistics, clinical research design) offered by a CTSA or a Cancer Center be co-sponsored and made available to participants across both awards.

Appendix A: Cooperative Group Timeline¹²

Target Timeline: 300 days plus time for CIRB/IRB review, arranging drug supply/distribution and conducting industry contract negotiations. Small, non-systematic deviations from the times specified for individual steps will be acceptable providing there is a coordinated effort to achieve the 300-day target.

Drop-Dead Date: Because 300 days is a target, but not yet an absolute deadline, the OEWG further agreed that if a trial has not been activated two years from the date of concept receipt by CTEP, it will be terminated, regardless of the stage in the process that has been reached.

Proposed Process:

1. Investigators submit trial idea to Group Disease Committee or directly to relevant Disease-Specific Scientific Steering Committee (DS-SSC) Task Force if no Group Disease Committee exists.
2. Group Disease Committee members discuss trial ideas internally and with relevant DS-SSC Task Force if any. DS-SSC Task Force members discuss trial ideas if submitted directly by investigator.
3. For ideas approved by Disease Committee and/or Task Force, investigator submits a 3- to 5-page concept document to the Group “Leadership Committee” describing:
 - Study Rationale
 - Study Disease/Stage
 - Study Hypothesis
 - Primary and Secondary Aims
 - Study Design/Treatment Plan (drug, length of trial, endpoints, etc.)
 - Statistical Plan (sample size, power, analysis methods and schedule)
 - Eligibility Criteria
 - Critical Biomarker Tests and Quality of Life Assessments
 - Competing Trials/Patient Availability
 - IND Sponsor
 - Drug Supply
 - Industry Willingness to Participate (in principle and if relevant)

¹² Applies to Phase III trials and non-IDB Phase II trials with ≥ 100 patients.

4. If approved by Group “Leadership Committee”, concept submitted to CTEP/ DS-SSC and industry partner (if appropriate) simultaneously for review. Feedback on major challenges and key issues provided by all parties within **30 days**.
5. Coordinated investigator/Group/CTEP/ DS-SSC/industry resolution of issues and revision of the concept completed within an additional **60 days**. During the comment and revision process, all parties have one opportunity to recommend changes to the concept and subsequent input is limited to (a) accepting/rejecting the concept; (b) accepting/rejecting revisions recommended by others; and (c) commenting on revisions recommended by others.
6. If not approved by all parties as revised, concept is considered terminated.
7. If all agree on concept as revised, investigator/Group prepares protocol on an interactive basis with CTEP and any relevant industry partners. Protocol to be completed within **90 days**.
8. In the case of a registration trial, the concept is submitted to FDA simultaneously with initiation of protocol development. FDA comments are to be provided within 21 days. If needed, a teleconference or meeting with the Group, CTEP and the commercial sponsor is held within 30 days of concept submission to clarify FDA’s comments and discuss critical issues.
9. Protocol is submitted simultaneously to CTEP (and to FDA and industry if appropriate) for review. Feedback on major challenges and key issues is provided by all parties within **30 days**.
10. Coordinated investigator/Group/CTEP/FDA/industry resolution of issues and revision of the protocol are completed within an additional **90 days**. During the comment and revision process, all parties have one opportunity to recommend changes to the protocol and subsequent input is limited to (a) accepting/rejecting the protocol; (b) accepting/rejecting revisions recommended by others; and (c) commenting on revisions recommended by others.
11. If all agree on protocol as revised, the trial proceeds to activation.

Notes:

- If possible, negotiating any necessary contracts with industry should be conducted simultaneously with the 300 days

- Achieving trial activation within 300 days will require the following to be completed during the 210-day protocol development and approval period: CRF and database development, training, and development of ancillary study materials

Appendix B: Early Drug Development Timeline¹³

Target Timeline: 210 days plus time for IRB and industry approval. Small, non-systematic deviations from the times specified for individual steps will be acceptable providing there is a coordinated effort to achieve the 210 day target.

Drop-Dead Date: Because 210 days is a target, but not yet an absolute deadline, the OEWG further agreed that if a trial has not been activated¹⁴ 18 months from the timeline start point, it will be terminated, regardless of the stage in the process that has been reached.

Process:

1. IDB issues LOI solicitations.
2. The investigator¹⁵ prepares an LOI following the current NCI/IDB LOI template. Investigators may submit LOIs in response to a solicitation, or submit an unsolicited LOI. When IDB receives unsolicited LOIs, a “heads-up” message is sent to the relevant industry contacts.
3. The LOI is reviewed by IDB for up/down decision within **30 days**; timeline begins at the closing date for submission of LOIs to a solicitation or the date of LOI receipt by IDB for unsolicited LOIs. Should an LOI be disapproved, an email notice is sent immediately to the investigator, in advance of a final review letter.
4. If initial review indicates that additional information or other changes are required,¹⁶ a decision to “hold” is made. IDB sends written comments to the investigator and conducts conference calls and other communications with the investigator within two weeks to discuss information needs or questions with the goal of rapidly resolving all issues. Up to **30 days** are allowed for this LOI revision process which could involve more than one LOI revision and review cycle.¹⁷ Should an LOI be promising but a decision cannot be made because new information (e.g., the results of an ongoing trial) is required, IDB

¹³ Applies to IDB Phase II trials implemented by N01 contractors, Cooperative Groups and other early drug development trial performance sites.

¹⁴ For Cooperative Group studies, “activated” is defined as “at least one IRB has approved the study’s opening”.

¹⁵ For trials implemented by Cooperative Groups, the investigator will coordinate all trial activation steps with Cooperative Group leadership and staff.

¹⁶ For example, forging a collaboration between two LOI submitters proposing similar studies.

¹⁷ Should review of an LOI identify minor changes (operational definition of minor to be developed by IDB) to an otherwise-approvable LOI, those changes should be made during the protocol-writing stage rather than requiring a LOI revision.

classifies the LOI as “on hold pending new information” and the timeline pauses until the additional information is available.

(Note: If a large number of LOIs (>50) are received in response to a given solicitation, IDB may organize them into appropriate groups of 20-30 for review. The resulting LOI groups are reviewed in a back-to-back, staged fashion such that the review and revision of the LOIs in each group meets the 60-day timeline and the review and revision cycles are overlapped to reach all decisions as quickly as possible.)

5. If IDB does not approve the LOI as revised, the LOI is rejected, though the investigator has the right to request review of the decision through a rapid arbitration process to be created.
6. Upon approval of an LOI, IDB sends the LOI to the industry partner and the timeline pauses until the point of final industry decision. The timeline restarts at the point where the industry partner approves the LOI and commits to supply investigational agent for the study.
7. Once approved by the industry partner, the investigator writes protocol interactively with IDB and industry staff. Protocols are completed within **60 days** and submitted simultaneously to IDB and industry (if appropriate) for review.
8. IDB comments sent to investigator within **30 days**.
9. Coordinated investigator/IDB/industry resolution of issues and revision of protocol completed within an additional **60 days** resulting in conditional approval awaiting IRB approval¹⁸. IDB will facilitate conference calls and other communications with the investigator within two weeks of sending comments to discuss information needs or questions with the goal of rapidly resolving any issues. During this comment and revision process, all parties have one opportunity to recommend changes to the protocol and subsequent input is limited to (a) accepting/rejecting the protocol; (b) accepting/rejecting revisions recommended by others; and (c) commenting on revisions recommended by others. Should negotiations with industry over protocol content become a source of additional delay, the timeline pauses until industry issues are resolved.
10. If approved by all parties as revised, the trial proceeds to activation.

¹⁸ Typically, Cooperative Groups gain IRB approval after final protocol approval by CTEP rather than after conditional CTEP approval.

Appendix C: Investigator-Initiated Timeline

Target Timeline: 90 days plus time for budgeting/financial review, grant approval, FDA review and contracting/industry approval. Timeline begins with submission of the protocol to the Cancer Center's Protocol Monitoring and Review System (PRMS) and includes PRMS review and approval, forms development, approval from ancillary committees and approval by the IRB. Concept review and protocol development are not included in the timeline. Should negotiations with industry (or the FDA) over protocol content or budgeting/financial review become a source of additional delay, timeline pauses until issues are resolved.

Performance Benchmark Date: Given the variability of trial designs, the complexity of industry/contracting issues, and differences among Cancer Centers, 180 days from PRMS submission to trial activation should be made a performance benchmark but not a "drop dead" date. Clinical trials funded by NIH grants should be excluded from performance benchmarking, as no NIH-funded trials can meet the 180-day timeline.

Proposed Process:¹⁹

1. The investigator develops a protocol for an investigator-initiated trial to be supported by Cancer Center funds, an independent grant or industry. Cancer Center specific processes are used for review of concepts and draft protocols.
2. The investigator submits the protocol to the Cancer Center's PRMS. If any revisions are required to the protocol, the PRMS sends written comments to the investigator and conducts conference calls and other communications with the investigator to discuss information needs or questions with the goal of rapidly resolving any issues. The protocol is finalized within **30 days** of initial submission.
3. In parallel with review of the protocol by the PRMS, the investigator, in consultation with the Cancer Center clinical trials office, drafts consent forms, case report forms and other required documents for IRB submission or regulatory reporting. Forms are modified based upon PRMS feedback and completed within **45 days** of initial submission to the PRMS.
4. For trials requiring independent grant support, the timeline pauses after PRMS approval until the grant is approved for funding. Once approved, forms development proceeds and is complete within **15 days** of the award notice.

¹⁹ The time periods assigned to each step represent one way to achieve a 90 day timeline. The time allocated to each step may be different for different Cancer Centers.

5. Once the protocol and forms are complete, the protocol is sent in parallel for IRB review, review by any ancillary committees (e.g., radiation safety), and to the university financial/budgeting and contracting/legal offices, as appropriate.
6. Review of the protocol by the IRB occurs within **30 days** of the protocol's submission. Should the IRB require any modification to the protocol or attendant forms, the IRB sends written comments to the investigator and conducts conference calls and other communications with the investigator to discuss information needs or questions with the goal of rapidly resolving any issues. IRB approval occurs within **45 days** of submission.
7. Review of the protocol by any ancillary committees occurs within **30 days** of the protocol's submission for review. Should any changes be required, the ancillary committee sends written comments to the investigator and conducts conference calls and other communications with the investigator to discuss information needs or questions with the goal of rapidly resolving any issues. All ancillary committee approvals occur within **45 days** of submission.
8. Should both the IRB and ancillary committees provide comments that are inconsistent or difficult to rectify, or should these bodies require changes to the content of the protocol itself, the clinical trials office convenes a meeting of the investigator, members of the PRMS, and appropriate members of the IRB or ancillary committees to reconcile issues and agree upon a final version of the protocol and its accompanying forms. The meeting occurs such that any required changes can be made within the 45-day period.
9. University budgeting/financial review, FDA review, and any contracting with industry should begin once the PRMS has approved the protocol, but are not included in the timeline. Should negotiations with industry (or FDA) over protocol content become a source of additional delay, the timeline pauses until issues are resolved.
10. Once approved by all parties and contracting and budgeting are complete, the trial proceeds to activation.