Proposed Evaluation Plan for Assessing Implementation of the Clinical Trials Working Group (CTWG) Initiatives

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Report of the CTWG Evaluation Working Group of the Clinical Trials and Translational Research Advisory Committee July 13, 2011

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1. Executive Summary

The National Cancer Institute (NCI) Clinical Trials Working Group (CTWG) was convened in January 2004 to "advise the National Cancer Advisory Board (NCAB) on whether and in what ways the NCI-supported national clinical trials enterprise should be restructured to realize the promise of molecular medicine for advancing oncologic clinical practice in the 21st century."[1] The CTWG Report, published in June 2005, identified 22 initiatives intended to achieve this goal. The CTWG also recommended that an evaluation structure be created in order to assess the impact of the recommended initiatives, if implemented, on the NCI-funded clinical trials enterprise. Three levels of evaluation were proposed.

The first level of evaluation, tracking and evaluating the process of initiative implementation, is the responsibility of the Director of the Coordinating Center for Clinical Trials (CCCT), which was established to implement the CTWG initiatives. The latter two levels of evaluation, assessing the impact of the initiatives on the performance and outcomes of the NCI clinical trials system, are the subject of the evaluation plan proposed in this report.

As a prelude to this proposed evaluation plan, a baseline feasibility analysis, completed in October 2008, was conducted to determine the feasibility of data collection and also to report on certain measures of the state of the system before implementation of the CTWG initiatives.[2]

In 2010, NCI established the CTWG Evaluation Working Group under the Clinical Trials and Translational Research Advisory Committee (CTAC) to advise on the proposed evaluation plan. The Working Group included 10 extramural participants and five NCI staff, and conducted its deliberations between November 2010 and June 2011.

The proposed evaluation plan includes four components.

- System Outcomes
- Disease Steering Committees (includes Symptom Management and Health Related Quality of Life, Imaging, Pediatrics)
- Investigational Drug Steering Committee
- Collaboration

[1] National Cancer Institute, "Report of the Clinical Trials Working Group of the National Cancer Advisory Board: Restructuring the National Cancer Clinical Trials Enterprise", June 2005. Available at: http://transformingtrials.cancer.gov/files/ctwg-report.pdf. Last accessed March 1st, 2011.

[2] A summary of the baseline study is available at http://transformingtrials.cancer.gov/initiatives/ctwg/evaluation, last accessed March 1st, 2011.

The first component is a set of system outcome measures designed to assess the effectiveness of the overall NCI-funded clinical trials system. The other three components are directed at the impact of selected CTWG initiatives whose implementation is reasonably mature.

The proposed evaluation plan includes those early and late-phase trials conducted by CTEP and certain programs within DCP which are tracked either via the CTEP Enterprise System or the DCP DESK clinical trials databases. This includes trials conducted by the Cooperative Groups and the CCOP program as well as CTEP's early drug development trials and DCP's large chemoprevention and screening trials. Trials supported through other mechanisms (e.g., R01/P01, Cancer Center, SPORE awards) are not included. The evaluation plan, including the proposed measures and data collection approaches, is summarized below.

A. System Outcomes

Three specific outcomes were identified as suitable for evaluating the direction and productivity of the NCI-funded clinical trials system.

- Clinical trials should be of high quality
- Clinical trial results should be scientifically important and clinically relevant
- Trials should be efficiently initiated and conducted

Not surprisingly, there is no single measure that adequately captures any of these three outcomes. Therefore, for each outcome, a set of measures is proposed which, in aggregate, was judged able to provide a valid and reliable indication as to whether the NCI-funded clinical trials system is achieving that particular outcome.

1. Trial Quality

Four measures of quality were identified for evaluating this outcome.

- Percentage of trials that complete accrual
- Percentage of trials that definitively answer primary question
- Percentage of trials published in peer reviewed journals
- Percentage of early-phase trials that influence the design of a late-phase trial

Although three of these measures are amenable to quantitative data collection, a determination of whether trials definitively answer the primary question must rely on expert judgment. Moreover, the reasons why trials do not complete accrual must also be tracked as not all reasons reflect negatively on trial quality.

2. Scientific Importance and Clinical Relevance of Trial Results

Because it is difficult to identify quantitative measures for evaluating this outcome, judgment by an expert panel is recommended. Four preliminary measures were proposed for operationalizing the terms "scientific importance" and "clinical relevance" for use by the expert panel.

- Novelty of trial results
- Results sufficiently meaningful to warrant practice changes
- Results led to real-world practice changes
- Results led to stand alone publication based on secondary aims

It is further recommended that NCI convene an initial expert panel to expand and refine the preliminary measures, establish criteria for judging whether the measures had been achieved, and pilot the proposed measures and criteria.

In addition to the expert panel process, five quantitative measures are proposed to evaluate clinical relevance, especially with regard to therapeutics.

- Percentage of NDA/sNDA submissions and FDA approvals supported by NCI-funded trials
- Percentage of NCI-funded trials that support NDA/sNDA submissions and FDA approvals
- Percentage of NCI-supported trials referenced in clinical practice guidelines
- Percentage of recommendations in clinical practice guidelines that reference NCI funded trial publications
- For recommendations in clinical practice guidelines with at least one NCI trial reference, percentage of total references represented by the NCI reference(s)

3. Efficiency of Trial Initiation and Conduct

Building on the report of the NCI Operational Efficiency Working Group, whose report was released in March 2010[3], two measures of the efficiency of trial initiation are recommended.

- Time from Letter of Intent receipt by NCI to trial opening for accrual (CTEP early drug development trials)
- Time from concept submission to a Steering Committee to trial opening for accrual (CTEP late-phase and DCP symptom management trials)

With regard to the efficiency of trial conduct, two categories of measures are proposed. The first is accrual rates compared to projected rates as well as revisions of projected rates over time. The second relates to protocol amendments, as the processing of non-administrative amendments imposes burdens on sites and delays trial conduct.

- Percentage of trials meeting originally projected accrual rate
- Percentage of trials with revisions to the projected accrual rate

[3] National Cancer Institute, " Report of the Operational Efficiency Working Group Clinical Trials of the Clinical and Translational Research Advisory Committee: Compressing the Timeline for Cancer Clinical Trial Activation", March 2010. OEWG report available at: http://ccct.cancer.gov/files/OEWG-Report.pdf.

- Percentage of trials meeting a revised projected accrual rate
- Percentage of trials with substantive amendments not resulting from new safety information
- Average number of substantive amendments per trial not resulting from new safety information

B. Disease Steering Committees

In response to the CTWG Report, NCI has established a series of Scientific Steering Committees covering major disease areas as well as pediatric oncology and symptom management/health related quality of life. The high-level goal of the Steering Committees is to ensure that NCI supports the best-designed trials, addressing the most important questions and leveraging the most significant scientific advances. Steering Committee membership includes Cooperative Group disease committee chairs, leaders of other relevant clinical trials networks, SPORE, Cancer Center and R01/P01 investigators, community oncologists, biostatisticians, patient advocates and NCI staff. Steering Committees may form Task Forces or Working Groups that focus on specific scientific topics or on clinical trial concepts in particular disease areas.

The recommended Disease Steering Committee evaluation plan addresses the extent to which the first years of implementation have met the expectations of extramural late-phase clinical trialists (both Committee members and other trialists) and NCI staff. The proposed measures are designed to assess the Committees along five dimensions:

- Timeliness of Concept Review
- Quality of Concept Review
- Influence on Concept Development
- Portfolio Management
- Collaboration

With the exception of the Timeliness of Concept Review, the data required for the evaluation is largely qualitative, collected through interviews with Steering Committee and Task Force members; NCI staff involved in Steering Committee operations; Cooperative Group leadership; and investigators who submitted concepts. In addition, the performance of trials approved by each Steering Committee on the System Outcome measures of Trial Quality and the Scientific Importance and Clinical Relevance of Trial Results will be included in the evaluation.

1. Timeliness of Concept Review

Steering Committee performance in this dimension is easily captured by one quantitative measure.

- Time from initial concept receipt to final decision by the Steering Committee

2. Quality of Concept Review

Because there is no objective measure of quality by which to judge Steering Committee performance in concept review, the evaluation must depend primarily on judgments by stakeholders as to whether the Steering Committee process is effective. Therefore, eight qualitative measures are proposed.

- Transparency and whether there has been improvement since implementation of the Steering Committee
- Fairness and whether there has been improvement since implementation of the Steering Committee
- Efficiency and whether there has been improvement since implementation of the Steering Committee
- Roles played by patient advocates, community oncologists, translational researchers, clinical researchers and NCI staff
- Procedures for ensuring accountability
- Procedures for conflict resolution
- Potential for double jeopardy due to Task Force and then Steering Committee review
- Whether concepts rejected by Task Forces or the Steering Committee have been implemented by others and led to scientifically important/clinically relevant results

3. Influence on Concept Development

Because the extent and nature of Steering Committee and/or Task Force contributions to trial concepts is highly variable, again there are no objective measures by which to judge performance. Hence, five qualitative measures are proposed.

- Role and value of Task Force deliberations
- Role and value of Steering Committee deliberations
- Responsibilities of Groups versus Task Forces/Steering Committee
- Value of translational science and correlative studies proposed by Task Forces/Steering Committees
- Role played by patient advocates, community oncologists, translational researchers, clinical researchers and NCI staff

4. Portfolio Management

Steering Committees do not just review concepts. They also contribute to setting new strategic directions and to the overall character of the trial portfolio in their disciplines. To evaluate this aspect of performance, six qualitative measures are proposed.

- Influence of Clinical Trials Planning Meetings on trial priorities and strategic directions
- Role of Steering Committee in identifying new trial priorities and strategic directions
- Extent to which trial portfolio reflects state of science with regard to biological basis of disease
- Extent to which trials are based on new innovative scientific hypotheses rather than more standard, previously studied hypotheses
- Extent to which trials are designed to identify practice changing improvements rather than incremental improvements
- Value of Steering Committee in reducing competition for patient populations among NCI-funded trials and trials supported by others

5. Collaboration

NCI considers the fostering of collaboration, whether in trial design or among Steering Committees, to also be an important performance attribute. To evaluate the Steering Committees in this dimension, four qualitative measures are proposed.

- Incentives and disincentives for collaboration in the design of trials and whether there has been improvement since implementation of the Steering Committee
- Collaborations between Steering Committees, including between modality Steering Committees and Disease Steering Committees
- Collaborations between Steering Committee and the IDSC
- Influence of IDSC reports and guidelines on design of Phase III trials with CTEP agents

C. Investigational Drug Steering Committee

The CTWG also recommended that NCI establish an Investigational Drug Steering Committee (IDSC) to provide NCI with broad external scientific and clinical input with regard to the CTEP early drug development program. The goal is to increase the predictive value of these early phase trials, resulting in the design of more successful Phase III trials. The IDSC, which was established in late 2005, includes Principal Investigators of the CTEP Phase I U01 grants and Phase II N01 contracts, representatives from the Cooperative Groups, liaisons from the Disease Steering Committees, a patient advocate, biostatisticians, and NCI staff.

The recommended evaluation plan addresses the extent to which the IDSC has met the expectations of the extramural community and NCI by assessing IDSC performance along four key dimensions.

- Strategic input to NCI's early drug development priorities
- External input into Clinical Development Plans for CTEP investigational agents
- Open forum for interaction among extramural early drug development investigators and NCI staff
- Reports and guidelines that address key issues in early drug development trial design.

A wide range of sources is recommended for data collection: independent expert panel review; interviews with IDSC members, NCI staff involved in IDSC operations, non-IDSC extramural early drug development investigators, Disease Steering Committee liaisons, and industry early drug development investigators; database analysis; and review and bibliometric analysis of IDSC reports and guidelines.

1. Strategic Input

To assess IDSC performance in providing strategic input, four qualitative measures are proposed. The first three would be addressed by an expert panel and the fourth through stakeholder interviews.

- Value of IDSC recommendations regarding targets
- Degree to which trials address biological opportunities and/or patient populations identified by a Disease Steering Committee as needing early phase trials
- Degree to which trials are designed to expand knowledge around particular agents in response to IDSC recommendations
- Transparency and quality of early drug development trial prioritization before and after implementation of the IDSC.

2. Clinical Development Plans

To assess IDSC performance in providing input to CTEP Clinical Development Plans (CDPs) as well as to assess overall CDP quality, four qualitative measures are proposed. The first two would be addressed by the expert panel, the third by a combination of the expert panel and stakeholder interviews, and the fourth by interviews alone.

- Degree to which trials based on the CDP, if successful, are likely to lead to a Phase III trial
- Degree to which trials based on the CDP address gaps in knowledge about the tested agent
- IDSC role in improving CDP quality with regard to: enhanced innovation in therapeutic approaches; enhanced incorporation of biomarker studies; and enhanced clarity and specificity
- Quality of the process by which NCI develops, and IDSC reviews, CDPs

3. Collaboration

To assess IDSC performance in promoting collaboration in early drug development trials, four measures are proposed. Three are qualitative, addressed through interviews, and the fourth is quantitative based on NCI data.

- Degree to which the IDSC process has changed incentives for collaboration among IDSC participants
- Degree to which the IDSC process has increased involvement of new investigators (e.g., SPORE investigators) in CTEP early drug development trials
- Role, activities and effectiveness of the IDSC/Disease Steering Committee liaisons
- Percentage of CTEP early drug development trials (and patients on trials) that involve collaboration in accrual across multiple institutions

4. Reports and Guidelines

To assess the value of IDSC reports and guidelines, four measures are proposed. The first is quantitative, addressed through bibliometric analysis. The second and third are qualitative, addressed through stakeholder interviews. The fourth is also qualitative but is addressed through document analyses.

- Number of citations to published IDSC reports and guidelines
- Impact of IDSC reports and guidelines on the design of NCI supported early drug development trials
- Impact of IDSC reports and guidelines on the design of industry early drug development trials
- Extent to which NCI early drug development guidance documents reflect elements of IDSC reports and guidelines

D. Collaboration

The CTWG recommended a variety of changes to promote greater collaboration in the design and conduct of clinical trials. However, in developing useful measures for assessing the extent of collaboration, several limitations emerged. First, collaborations among academic researchers and between academia and industry are hard to capture in quantifiable fashion. Who participates in the design of a clinical trial, or what funding mechanisms and other resources support a clinical trial, are not easy to identify in a comprehensive and reliable fashion. Furthermore, some measures of collaboration (e.g., bringing forward a drug from earlier stage development) are included under System Outcomes.

As a result, only three aspects of "collaboration" are addressed in this section of the evaluation plan. The first is assessment of the revisions made to guidelines covering NCI translational and clinical research programs to promote collaboration. The second is collaboration in clinical trial accrual and the third is collaboration between NCI/CTEP and industry. Data collection involves

analysis of NCI program documents and database analyses for accrual and industry/NCI interactions.

1. Funding Incentives for Collaboration

Cancer Center, SPORE, and Cooperative Group Guidelines, Funding Opportunity Announcements and other program documentation will be analyzed for the presence of direct incentives for collaboration. Examples might include the following:

- Scored review criteria associated with an aspect of collaboration
- Availability of award funds to conduct or promote collaborative activities
- Availability of supplemental funds for collaborative activities

The analysis will include a detailed comparison of corresponding documents prior to the revisions inspired by the CTWG to assess the degree and scope of the changes.

2. Collaboration in Clinical Trial Accrual

Two quantitative measures of collaborations in clinical trial accrual were identified.

- Percentage of CTEP funded Phase II clinical trials (and patients on trials) involving collaboration in accrual across multiple institutions
- Percentage of Phase III clinical trials (and patients on trials) involving collaboration in accrual across multiple Cooperative Groups

3. Industry/CTEP Collaboration

There are potentially many forms of industry collaboration with regard to NCI funded trials. However, the only type of collaboration that was viewed as being amenable to reliable data collection was the interaction between CTEP and industry with regard to investigational agents. Four quantitative measures are proposed to capture this form of collaboration.

- Total number of investigational agents provided to CTEP by industry
- Year-over-year change in the number of agents
- Total number of companies collaborating with CTEP
- Year-over-year change in the number of companies collaborating with CTEP

E. Recommended Implementation Plan

The CTWG Evaluation Working Group recommends that evaluation activities begin as soon as possible. Several measures for assessing System Outcomes rely on data already collected in NCI databases and data collection and analysis could begin in 2011. However, several other measures require database modifications. It is therefore recommended that NCI analyze the time and effort required for these modifications during 2011 so that measures can be prioritized for inclusion and a timeline established for implementation.

It is further recommended that in 2011 NCI develop methodologies for the expert panel assessing scientific importance and clinical relevance of trial results and also the panel for evaluating IDSC impact with the goal of piloting these processes in 2012. Methodology development will also be required for measuring the impact of NCI-funded clinical research on practice and for the impact of IDSC reports and guidelines. Analysis of NCI program documents should occur once the current planned revision of the Cooperative Group guidelines is completed. With regard to both the Disease Steering Committee and IDSC evaluations, interview guides and protocols will need to be developed as soon as possible so that the initial evaluations can be conducted in late 2011 or early 2012.

In terms of ongoing evaluation, System Outcomes should be assessed on an annual basis, while assessment of collaboration should occur every one to three years. The Steering Committees (including the IDSC) should be assessed five years after inception and every five years thereafter. Thus, the IDSC, the Gastrointestinal Steering Committee, and the Gynecological Steering Committee would be evaluated first (as they were convened in 2006), followed by the other Disease Steering Committees chronologically in order of their initiation.

F. Evaluation Challenges

The proposed evaluation plan faces two primary challenges. The first is the limited availability of relevant quantitative data. As was discussed in detail above, there are only a few quantitative measures that are valid and feasible to collect and some of those measures are not very powerful. The second challenge is the complex and dynamic character of the NCI clinical trials system, which will likely lead to difficulties in proper interpretation of the evaluation results. For example, definitive attribution of observed changes in the system to implementation of specific CTWG initiatives will be difficult if not impossible to establish. These changes may have been influenced by other perturbations (e.g., budgetary constraints, responses to the IOM report).

The complexity of the system also requires thoughtful data interpretation. Given the large number of System Outcome measures proposed for evaluation, it is likely that at any given point in time individual trials, and perhaps even the NCI-funded trials system as whole, may score “well” on some measures and “poorly” on others. Nevertheless, the Working Group decided that despite these challenges, proactive collection of both quantitative and qualitative information on the “state of the enterprise” is essential to progress. However, it is essential that NCI analyze and interpret all data generated by the evaluation carefully, and that single measures never be focused upon in isolation by decision-makers and other stakeholders.

2. Introduction

A. Clinical Trials Working Group Report

The National Cancer Institute (NCI) Clinical Trials Working Group (CTWG) was convened in January 2004 to "advise the National Cancer Advisory Board (NCAB) on whether and in what ways the NCI-supported national clinical trials enterprise should be restructured to realize the promise of molecular medicine for advancing oncologic clinical practice in the 21st century."[4] The CTWG identified four goals for the restructuring effort.

- Improve coordination and cooperation among the functionally diverse components of the current system, including industry and federal regulatory agencies.
- Improve prioritization and scientific quality by developing an open and transparent process for the design and prioritization of clinical trials that are science-driven and meet the needs of patient care.
- Improve standardization of tools and procedures for trial design, data capture, data sharing, and administrative functions to minimize duplication of effort, and to facilitate development of a shared infrastructure to support an integrated national cancer clinical trials network.
- Improve operational efficiency by increasing the rate of patient accrual and reducing operational barriers so that trials can be initiated and executed in a timely, cost-effective manner.

The CTWG Report, published in June 2005, identified 22 initiatives intended to achieve these goals. A list of these initiatives is presented in Appendix A.

The CTWG also recommended that an evaluation structure be created in order to assess the impact of the recommended initiatives, if implemented, on the NCI-funded clinical trials enterprise. Three levels of evaluation were proposed.

- Program management to track and evaluate implementation of the initiatives
- System performance to evaluate the effect of the restructuring on the design, prioritization, and conduct of cancer clinical trials
- System outcomes to assess the effect of the restructuring on increasing the number of useful therapies for patients and improved targeting of therapies to the patients most likely to benefit from them

[4] National Cancer Institute, "Report of the Clinical Trials Working Group of the National Cancer Advisory Board: Restructuring the National Cancer Clinical Trials Enterprise", June 2005. Available at: http://transformingtrials.cancer.gov/files/ctwg-report.pdf. Last accessed March 1st, 2011.

The first level of evaluation, tracking and evaluating the process of initiative implementation, is the responsibility of the Director of the Coordinating Center for Clinical Trials (CCCT) which was established to implement the CTWG initiatives. The latter two levels of evaluation, assessing the impact of the initiatives on the performance and outcomes of the NCI clinical trials system, are the subject of the evaluation plan proposed in this report.

As a prelude to this proposed evaluation plan, a baseline feasibility analysis was conducted to determine the feasibility of data collection and also to report on certain measures of the state of the system before implementation of the CTWG initiatives (i.e., 2005-2006).[5] The baseline feasibility analysis report, which was completed in October 2008, also included a set of measures and methodologies for a proposed future evaluation plan.

B. Evaluation Working Group Process

In 2010, NCI constituted the CTWG Evaluation Working Group under the Clinical Trials and Translational Research Advisory Committee (CTAC) to advise on the proposed evaluation plan. The Working Group's charge was to "develop recommendations to CTAC for evaluating the impact of implementation of the recommendations of the Clinical Trials Working Group." Specifically, the Working Group was asked to:

- Refine the proposed plan for assessing implementation of the CTWG initiatives
- Establish a timeline for implementing components of the evaluation plan

The Working Group included 10 extramural participants and five NCI staff (see list of Working Group members at the beginning of this report). The extramural membership included individuals with the following perspectives.

- Six members affiliated with five different Disease Steering Committees, including four Steering Committee Chairs
- Three members of the Investigational Drug Steering Committee (IDSC)
- Two NCI-designated Cancer Center Directors
- Two Specialized Programs of Research Excellence (SPORE) Principal Investigators
- One Community Clinical Oncology Program (CCOP) Principal Investigator
- Members affiliated with six Cooperative Groups

NCI staff included representatives from the Cancer Therapy Evaluation Program (CTEP) of the Division of Cancer Treatment and Diagnosis (DCTD), the Division of Cancer Prevention (DCP), and CCCT. CTEP representatives included the program director and the branch chiefs of the

[5] While the baseline study is not a public document, a summary of the baseline study, and a link to a presentation of the results of the baseline, is available at http://transformingtrials.cancer.gov/initiatives/ctwg/evaluation, last accessed March 1st, 2011.

Investigational Drug Branch (IDB), which manages the CTEP early drug development program, and the Clinical Investigations Branch (CIB), which manages the Cooperative Group program.

The Working Group conducted the following activities.

- Orientation teleconferences (November-early December 2010)
- Face-to-face meetings to refine the proposed measures and methodologies (mid December 2010)
- DCTD and CCCT management review of meeting results to further refine the measures and methodologies (late December 2010)
- Working Group Co-Chair review and refinement of the measures and methodologies approved by DCTD and CCCT (January 2011)
- Teleconferences with Working Group members to review and refine the proposed evaluation plan based on the measures and methodologies approved by the Co-Chairs (late January and early February 2011)
- Presentation to CTAC of an interim report on the evaluation plan (March 2011)

C. Proposed Evaluation Plan Summary

The proposed evaluation plan includes four primary modules.

- System Outcomes
- Disease Steering Committees (includes Symptom Management and Health Related Quality of Life, Imaging, Pediatrics)
- Investigational Drug Steering Committee
- Collaboration

The first module is a set of system outcome measures designed to assess the effectiveness of the overall NCI-funded clinical trials system. The other three modules are directed at the impact of selected CTWG initiatives whose implementation is reasonably mature.

In addition to the specific evaluations proposed herein, evaluation of the implementation of several other CTWG initiatives (e.g. the informatics initiatives) is either complete or is recommended to be conducted as a separate, focused study (see Section 7). Section 7 also describes the status of the remaining CTWG initiatives which are judged not sufficiently mature to warrant evaluation at this time.

D. Context for Proposed Evaluation Plan

1. Scope of the Evaluation

The proposed evaluation plan covers those early-phase and late-phase trials[6] conducted by CTEP and certain programs within DCP which are tracked either via the CTEP Enterprise System or the DCP DESK clinical trials databases. This includes trials conducted by the Cooperative Groups and the CCOP program as well as CTEP's early drug development trials and DCP's N01 large chemoprevention and screening trials. Trials supported through other mechanisms (e.g., R01/P01, Cancer Center, SPORE awards) are not included. The evaluation process therefore covers approximately one-third of NCI's investment in clinical trials. This limitation is a practical one as the data required for evaluation is not routinely collected for these other trial categories at this time.

The proposed plan is also not intended to evaluate particular programs (e.g., SPOREs, Cancer Centers, Cooperative Groups) nor does it evaluate particular trial portfolios. For example, assessment of CTEP's early drug development program is limited to the impact of the IDSC. Finally, the plan does not assess the results of non-CTWG inspired changes. For example, evaluating the effect of NCI's response to the recommendations of the 2010 Institute of Medicine (IOM) report with regard to the Cooperative Groups[7] would require a separate evaluation.

2. Evaluation Challenges

The proposed evaluation plan faces two primary challenges. The first is the limited availability of relevant quantitative data. As is discussed in greater detail below, there are only a few quantitative measures that are valid and feasible to collect and some of those measures are not very powerful. The second challenge is the complex and dynamic character of the NCI clinical trials system, which will likely lead to difficulties in proper interpretation of the evaluation results. For example, definitive attribution of observed changes in the system to implementation of specific CTWG initiatives will be difficult if not impossible to establish. These changes may have been influenced by other perturbations (e.g., budgetary constraints, responses to the IOM report).

The complexity of the system also requires thoughtful data interpretation. Given the large number of System Outcome measures proposed for evaluation, it is likely that at any given point in time individual trials, and perhaps even the NCI-funded trials system as whole, may score "well" on some measures and "poorly" on others. Nevertheless, the Working Group decided that despite these challenges, proactive collection of both quantitative and qualitative information on the

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[6] In this document, the term "early-phase" is used to denote smaller, exploratory trials (e.g., nonrandomized Phase II treatment trials) and "late-phase" to denote larger, definitive trials (e.g., Phase III, large randomized Phase II treatment trials).

[7] Institute of Medicine, Board on Health Care Services, "A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program", April 15th, 2010. Available from: http://www.iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx, last accessed March 7th, 2011.

"state of the enterprise" is essential to progress. However, it is essential that NCI analyze and interpret all data generated by the evaluation carefully, and that single measures never be focused upon in isolation by decision-makers and other stakeholders.

E. Report Organization

Sections 3-6 of this report describe the four primary modules of the evaluation plan – System Outcomes, Disease Steering Committees, Investigational Drug Steering Committee, and Collaboration. Each section begins with background information on the relevant module as well as a description of the proposed evaluation approach. This is followed by a detailed discussion of the topic areas to be addressed and the measures proposed to evaluate performance within each area. The sections then conclude with a table that presents the individual measures as rows, with columns corresponding to the primary data collection methods employed (database analyses, expert panels, interviews with Steering Committee members, interviews with other trialists, interviews with NCI staff and document review).

The final section of the report, Section 7, describes the Working Group's recommended approach for evaluating implementation of the CTWG initiatives that are not included in this plan. The report also has one appendix that lists the 22 CTWG initiatives.

3. System Outcomes Evaluation

A. Background

The most important and meaningful outcome resulting from implementation of the CTWG initiatives is the degree to which the changes achieve the goals of enhanced clinical trial success and new treatments reaching patients more quickly. In order to operationalize achievement of this goal, the Working Group identified three specific outcomes that were judged suitable for the development of a set of measures to evaluate the direction and health of the NCI-funded clinical trials system.

- Clinical trials should be of high quality
- Clinical trial results should be scientifically important and clinically relevant
- Trials should be efficiently initiated and conducted

Not surprisingly, there is no single measure that adequately captures any of these three outcomes, nor even a consensus definition of what each entails. Therefore, for each outcome, the Working Group developed a set of measures which, in aggregate, were judged able to provide a valid and reliable indication as to whether the NCI-funded clinical trials system is achieving that particular outcome.

B. Proposed Evaluation Approach

The Working Group decided that, to the extent feasible, all the System Outcome measures should be quantitative. Moreover, the measures should rely upon either data already collected in NCI-funded data systems or data that could be added to these data systems without a great deal of effort. The Working Group generally rejected interviews or focus groups that would collect perceptions of key stakeholders concerning whether outcomes were being achieved. The majority of the proposed measures, therefore, are quantitative.

However, the Working Group could not identify meaningful and reliable quantitative methods to assess the scientific importance and clinical relevance of clinical trial results. The Working Group therefore concluded that expert judgment was required to determine whether this outcome is being achieved. In addition, the Working Group proposed that this expert judgment be supplemented by document analyses tracing the extent to which NCI-funded trials impact clinical practice by supporting:

- Food and Drug Administration (FDA) regulatory filings
- Insurance coverage determinations by the Centers for Medicare and Medicaid Services (CMS)
- Changes in national clinical practice guidelines

The Working Group recommended the following timeline for the System Outcomes portion of the evaluation.

- Database Analyses:
  - For measures already tracked in NCI databases (e.g. trial initiation timelines, amendments, accrual status), begin in 2011 and repeat annually.
  - For measures requiring database modifications, in 2011 perform analysis of the time and effort required, prioritize the measures for inclusion and set a timeline for implementation
- Expert Panel:
  - Methodology development and piloting of the expert panel qualitative evaluation of scientific importance and clinical relevance to begin in 2011 and complete in 2012
  - If expert panel process deemed feasible, implement annual evaluations in 2013
- Document Analyses:
  - Methodology development and piloting for measuring impact on practice complete in 2011
  - If process deemed feasible and results meaningful, implement annual analysis in 2012

C. Proposed Evaluation Measures

1. Trial Quality

There is no single parameter that defines trial "quality." Therefore, the Working Group identified four measures of quality as the basis for evaluating this outcome. Three of these measures are amenable to quantitative data collection while one relies on expert judgment. The following sections describe the rationale for, and implementation of, each of these measures.

Percentage of trials that complete accrual

One indicator of whether a trial is well-designed and "high-quality" is whether accrual is completed so that the results can be analyzed. If a trial's rationale is strong and the design is well constructed, there should be sufficient physician and patient interest to enroll the required subjects in a timely manner. However, meaningful application of this measure requires a more refined approach than determining a simple "yes" or "no" answer for each trial. The first refinement is a clear definition of what the term "complete accrual" means in different trial situations. For example, the Working Group noted that applying this measure to early phase trials with adaptive designs in which the accrual target may change over time will be more complicated than for a large Phase III trial where the target accrual is fixed by the statistical design.

It is also important to determine the reason that trials do not complete accrual as not all reasons reflect negatively on trial quality. To this end, the Working Group identified a range of reasons why trials may not complete accrual including:

- Sufficiently positive results at an interim analysis
- Sponsor withdraws from trial
- Loss of drug supply
- Safety concerns
- Negative results at an interim analysis
- Subjects accrue to competing trials
- Patients did not complete study
- Study not feasible/too complex
- Study loses relevance because of scientific advances

The first of these reasons reflects "positively" on trial quality. The intervention was so successful that conclusions became evident before the planned accrual was achieved. The next three reasons are "negative" events that are arguably beyond the control of the investigator or NCI. If a partner (e.g., industry) withdraws from a study or the investigator or NCI loses access to the drug, then the trial may need to be closed. Even the need to close a trial because of safety concerns may not reflect a poorly conceived trial as adverse effects cannot always be accurately predicted in advance. In contrast, the final five reasons are "negative" outcomes that potentially could have been averted and should be considered indications of inferior trial "quality". Their occurrence suggests that the trial design was flawed and that the review and prioritization processes were unable to detect the insufficiencies.

To implement this measure of trial quality, NCI would identify in its data systems trials that were closed before completing accrual, and code those trials with the reason for early closure. Although trials that do not complete accrual can currently be identified, a system for tagging those trials with a "reason code" would need to be developed. The Working Group concluded that the first four reasons above – which happen to be those that are not indicators of inferior trial "quality" – could be determined unambiguously by NCI staff and be coded into the data system without difficulty. However, determining which of the other four reasons (i.e., those that would be considered indicators of inferior trial quality) was responsible for early closure was judged much harder to establish unambiguously. Therefore, if this measure is to be implemented, NCI will need to collaborate with the extramural community in establishing criteria, and a process, for determining which of these reasons (or others identified in the future) was responsible for an early trial closure.

Clearly, the overall goal is a high percentage of trials that complete accrual. However, because of the complexity of events that can lead to trial closure, no *a priori* quantitative target for trial

quality by this measure should be set. In some cases trials that do not complete accrual may be as important as those that do. Moreover, it will be essential to not only report the percentage but also track the reasons for early trial closure. These data could provide valuable insights such as whether trial designs need to be improved or whether the focus should be on forging more stable relationships with drug company partners before initiating trials.

Percentage of trials that definitively answer primary question

The second measure proposed for evaluating trial quality was whether the results were unambiguous and definitively answered the primary question that drove the study design. The Working Group considered the definitive nature of the results more important than whether they proved or disproved the primary study hypothesis. Trials that are definitively positive, or negative, advance the science and clinical practice. Knowing that an intervention is unsuccessful means that research should shift in a different direction. In contrast, trials that provide ambiguous or uncertain results waste effort, resources, and time.

The Working Group concluded that a valid and reliable answer as to whether trial results were definitive could best be made by a proposed expert panel (described below), rather than the protocol chair or NCI staff. The "yes/no" conclusion of the expert panel, along with whether the result was positive or negative, could then be entered into the NCI data systems for use in quantitative analysis.

To evaluate trial quality, the Working Group recommended that the resulting data be analyzed in two ways. First of all, the percentage of trials that definitively answer the primary question should be determined and ideally would be as high as possible. Secondly, among that group of definitive trials, the ratio of positive versus negative results should be determined. However, the Working Group concluded that it is not possible to set *a priori* a specific ratio that is most indicative of high trial quality. Rather, consistent tracking of this ratio could provide valuable information for managing the trial portfolio. For example, if the percentage of trials that yielded negative results were consistently quite low, that could indicate the need to increase the percentage of the portfolio that was pursuing more novel, high risk ideas. Alternatively, in some diseases, one would simply expect a very low ratio of positive versus negative trials due to the underlying nature of the disease.

Percentage of trials published in peer reviewed journals

The third approach to trial quality identified by the Working Group is whether the primary results of the trial are published in a peer-reviewed journal. However, the Working Group concluded that peer reviewed journal publications regarding the trial design itself or correlative studies/secondary endpoints, while indicative of the scientific importance of the trial (see below), should not be considered indicators of overall trial quality. The Working Group considered including presentations at conferences, but concluded that as peer review standards for journal publication are on average higher than for conferences, only journal publications should be considered as a measure of trial quality. NCI already collects the publications associated with

clinical trials in its data systems, and clinicaltrials.gov identifies specifically those articles that present trial results.

The Working Group also recommended that the time between completion of a trial and publication be tracked. Inordinate delays between obtaining definitive trial results and their publication could thus be monitored and addressed. NCI data systems record the date accrual is complete but since data can be collected for varying periods of time depending on the trial, this is not an adequate date to use. The data systems also record a "trial completion" date but the operational definition of this date is unclear. Therefore, to operationalize this measure, a clear definition of "trial completion" will need to be determined and that date recorded in the data systems for every trial. The date of publication will also need to be added.

Finally, the Working Group recommended that the quality of the journal in which the results are published be tracked. Journal impact factor was considered an appropriate reflection of quality for this purpose. While NCI data systems do not now include journal impact factors, those data could be added or obtained from the NIH-wide Information for Management, Planning, Analysis, and Coordination (IMPAC) II data system, which already includes this information.

Publication in a peer reviewed journal is clearly required for a trial to be judged of high quality. However, the Working Group did not set specific targets for the time from trial completion to publication or journal impact factor. Rather they only specified that results should be published as quickly as possible in as high-quality journals as possible. Nevertheless, tracking and analysis of these data is likely to provide additional evidence bearing on the degree of overall trial quality.

Percentage of early-phase trials that influence the design of a late-phase trial

The fourth aspect of trial quality that the Working Group identified as being relevant and measurable is whether late phase trials conducted through the Cooperative Group and CCOP networks are based on results of NCI funded early phase trials. If an early-phase trial leads to the design and conduct of a late phase trial, the Working Group reasoned, that would be indicative of a high quality early phase trial. Such a linkage should be relatively straight forward to track as the design and results of the early phase trial would generally be referenced in the background section of the protocol for the NCI-funded Phase III trial. The early phase trials referenced in these protocols could be easily identified and the fact that they led to a late phase trial incorporated into NCI's clinical trials data systems.

The Working Group also recommended that NCI explore whether such linkages could also be determined for industry Phase III trials. One approach would be to identify industry Phase III trials from clinicaltrials.gov and contact the study chair (who is often listed in the clinicaltrials.gov record) in order to identify whether NCI-funded early-phase trials influenced the decision to conduct the trial and/or its design. Once the data on linkage is available, it would

be interesting to compare the relative influence on NCI-funded and industry funded late phase trials. [8]

The Working Group did not establish a target percentage of early phase trials leading to late phase trials that would be indicative of an overall high quality early phase trial portfolio. Furthermore, the Working Group cautioned that any such goals, if set, should be on a disease specific basis rather than at the overall portfolio level. There are some diseases where the state of the science dictates that a large number of exploratory Phase II trials must be conducted before the results will justify design of a Phase III trial. In other diseases, most successful Phase II trials should be expected to lead directly to a pivotal Phase III trial.

2. Scientific Importance and Clinical Relevance of Trial Results

After much deliberation, the Working Group settled upon "scientific importance and clinical relevance of trial results" as the second outcome to be evaluated. The Working Group also concluded that it would be difficult to identify meaningful and reliable quantitative measures for evaluating whether the results of a trial were valuable scientifically or relevant to clinicians.

Therefore, the Working Group recommended that the primary method for determining whether the results of a trial meet these criteria would be judgment by an expert panel. The Working Group further recommended that this expert judgment be supplemented with document analysis with regard to FDA approvals, CMS coverage decisions, and changes in clinical practice guidelines. Recognizing that these supplementary analyses are primarily relevant for therapeutics, the Working Group recommended that NCI attempt to identify additional measures of clinical relevance more applicable to diagnostics, symptom management approaches, and lifestyle alterations. The following sections describe the recommended expert panel process and the three document analyses.

Expert panel

The Working Group identified four preliminary measures for operationalizing the terms "scientific importance" and "clinical relevance" for the expert panel.

- Novelty of trial results
- Results sufficiently meaningful to warrant practice changes (e.g., two-week extension of survival likely not meaningful)

[8] If implemented, issues for further methodological consideration include:

- How to identify industry Phase III trials in clinicaltrials.gov
- If the clinicaltrials.gov record does not identify a study chair but only a corporate contact, would the corporate contact be approached
- Once the universe of potential trials to be analyzed has been determined, the nature of data collection (e.g., survey versus interview, whether all study chairs should be contacted or if a sampling approach should be used).

- Results led to real-world practice changes
- Results led to stand alone publication based on secondary aims

The Working Group recommended that NCI convene one or more expert panels involving clinical investigators, community oncologists, and patient advocates to make such determinations for completed trials. The eventual goal is to annually perform this evaluation for all NCI-funded trials completing data analysis during the previous year. Periodically, older trials would be reexamined with respect to whether the trial results influenced clinical practice. Once trial results were evaluated, the conclusions could be captured in the NCI clinical trials data systems.

The feasibility of convening a disinterested panel of experts was not discussed at length by the Working Group. However, because the function of the panel would be to assess the value of particular trials – rather than the quality of the Cooperative Group or Steering Committee under whose auspices those trials were conducted – the Working Group decided that it should be possible to convene the necessary panels without undue conflict of interest. Members of the panel who were directly involved with the design and implementation of a specific trial would need to recuse themselves but that should be required only infrequently.

The Working Group did not have sufficient time to design the expert panel methodology in detail. Rather they suggested that an initial expert panel be convened (which could include current Working Group members) to develop and pilot a methodology. This would involve the following activities.

- Expand and refine the preliminary scientific importance and clinical relevance measures listed above
- Establish a set of specific criteria for judging whether the measures had been achieved
- Pilot the proposed measures and criteria on all Phase III trials completed in a recent year (e.g., 2009 or 2010) in order to determine feasibility

If the results were considered meaningful by NCI staff and CTAC, and if the pilot were judged feasible with respect to level of effort and degree of difficulty, the initial expert panel would refine the measures and criteria based on the results of the pilot and establish a standard methodology. Each year thereafter, NCI would convene an expert panel to evaluate the results of trials completed in the previous year according to this standard methodology.

Support of FDA approvals

The Working Group identified FDA approvals based at least in part on the results of NCI funded trials as a definitive indicator of clinical relevance. The Working Group assumed that regulatory approval documents could be used to identify any NCI funded trials that were cited by industry in support of regulatory filings. To assess the feasibility and reliability of using publicly-available regulatory documents to identify NCI funded studies cited in drug company filings, a pilot study was conducted of FDA approvals in FY 2009 and FY 2010.

The pilot demonstrated that publically available New Drug Application (NDA) documents are sufficiently detailed to identify the specific trials that supported the regulatory filing. Cross-referencing those trials with clinicaltrials.gov readily identifies those trials that are NCI funded. For supplemental New Drug Applications (sNDAs) filed for approval of new indications, less (and less consistent) public information is available. Multiple avenues were explored for identifying the trials that supported the sNDA filings, but the procedure required a considerable effort and was more subject to uncertainty. Subject area expertise would be necessary for analysts to reliably and consistently obtain results and more methodological development is needed in this area. Therefore, a decision will need to be made as to the likely importance of NCI funded trials for sNDAs.

The Working Group recommended that the results of this analysis be captured by two different measures:

- Percentage of NDA/sNDA submissions and FDA approvals supported by one or more NCI-funded trials
- Percentage of NCI-funded trials that support NDA/sNDA submissions and FDA approvals

The first measure evaluates the role of NCI funded trials in the overall therapeutics development landscape. The second evaluates what percentage of NCI's clinical trial effort is directly supportive of therapeutics development. Understandably, the Working Group did not attempt to determine *a priori* what reasonable percentages should be for these two measures. Nevertheless, determining what they are would provide valuable information for assessing the impact of NCI funded clinical trials. Trials that contribute to regulatory filings could be coded in the NCI clinical trials databases for future longitudinal analysis of the types of trials that achieve this goal as well as trends over time.

Support of CMS coverage decisions

As cancer treatment is quite expensive, the decision by insurance companies as to whether to reimburse for particular treatments can strongly influence clinical use by physicians. The U.S. government, through the Medicare and Medicaid programs, is the largest health insurer in the United States. Because of the sheer number of Americans insured by Medicare and Medicaid, the Working Group concluded that if an NCI funded clinical trial was influential in making a positive CMS coverage decision, it would be a strong indicator of clinical relevance. Therefore, a pilot analysis was conducted to determine if CMS coverage decisions could be linked to specific clinical trials.

The pilot analysis first revealed that this information is only readily available for National Coverage Determinations (NCDs) for which CMS uses an "evidence-based approach" incorporating both clinical and socioeconomic data. Similar information on the data supporting regional CMS coverage decisions would be difficult if not impossible to obtain. Unfortunately,

the pilot analysis also determined that only a small percentage of oncology-related interventions (including both diagnostics and therapeutics) have gone through the full NCD process and most are ruled by regional coverage decisions. Therefore, operationalizing this measure of clinical relevance was judged not feasible.

Support of national clinical practice guidelines

An additional measure of clinical relevance discussed by the Working Group was the extent to which NCI-funded trials are referenced in clinical practice guidelines (e.g., NCCN, ASCO, ASTRO). Because of the long time often required for clinical trial results to appear in practice guidelines, the Working Group initially rejected this measure. However, in response to the interim report in March, 2011, CTAC members recommended that this measure be included in the evaluation plan. Based on a pilot analysis of the NCCN guidelines, such an evaluation appears feasible.

Each recommendation in the guidelines contains references to the publications that support the recommendation. Determining the percentage of recommendations that reference publications reporting NCI-funded trial results would be an indicator of the value of NCI-funded trials. For those recommendations referencing NCI trials, a second proxy would be the percentage of the total references the NCI citations represent. Both of these indicators provide only a rough measure of the value of NCI-supported trials, as they treat each individual recommendation equally. Nevertheless, if the identified trials were so coded in NCI data systems, the percentage of NCI-supported late-phase trials that are referenced in the guidelines could be calculated. Three measures are therefore recommended.

- Percentage of NCI-supported trials referenced in national guidelines
- Percentage of recommendations in national guidelines that reference NCI funded trial publications
- For recommendations in national guidelines with at least one NCI trial reference, percentage of total references represented by the NCI reference(s)

3. Efficiency of Trial Initiation and Conduct

Building on the CTWG report, the Working Group ratified efficiency of trial initiation and conduct as a third system outcome to be evaluated. For efficiency of trial initiation, the Working Group recommended two measures developed by the NCI Operational Efficiency Working Group (OEWG), whose report was released in March 2010.[9]

[9] National Cancer Institute, " Report of the Operational Efficiency Working Group Clinical Trials of the Clinical and Translational Research Advisory Committee: Compressing the Timeline for Cancer Clinical Trial Activation", March 2010. OEWG report available at: http://ccct.cancer.gov/files/OEWG-Report.pdf. Goals for late-phase trials can be found on pages 20-21; and goals for early-phase trials on pages 32-33. Last accessed March 2, 2011.

- Time from Letter of Intent (LOI) receipt by NCI to trial opening for accrual (CTEP early drug development trials)
- Time from concept submission to a Steering Committee to trial opening for accrual (CTEP late-phase and DCP symptom management trials)

As a consequence of the release of the OEWG report, NCI data systems now capture the data needed to track these measures.

The OEWG report recommended that early drug development trials be initiated in less than 210 days and late-phase trials in less than 300 days. The Working Group did not explicitly discuss accepting these targets for evaluation of trial initiation efficiency. However, given the general acceptance of the OEWG approach, these same timeline goals are recommended here.

With regard to the efficiency of trial conduct, there was substantial Working Group discussion about potentially quantifiable measures. The first challenge was that "efficiency" can have multiple potential meanings, including:

- NCI-funded trials accrue patients rapidly
- NCI-funded trials are completed at the lowest possible cost
- NCI-funded trials are completed with minimal administrative burden on investigators and NCI staff

The first measure seems straight forward, as it is certainly feasible to determine the rate at which patients accrue to trials. However, there is no absolute rate at which patients should accrue. Therefore, the only meaningful measure of "efficiency" would be the degree to which the actual accrual rate achieved the accrual rate projected for each trial. Moreover, Working Group members noted that original projections of both accrual rate and the number of patients required to complete the study are often modified during the course of a trial. Therefore, the projected accrual rate might need to be modified over the course of the trial. Nevertheless, tracking for each trial the original projected accrual rate, how the projected rate changed over time and the degree to which the actual accrual rate achieved the projected rate (either original or revised) would likely provide useful insights with regard to accrual efficiency.

Unfortunately, efficiency with respect to cost was considered impossible to quantify. There is no standard for what the per-patient cost of accrual should be in theory. There are also no standard systems for accurately capturing the cost of each individual accrual or the cost of each individual trial. Efficiency with respect to administrative burden is also difficult to measure. NCI does collect information regarding protocol amendments, and processing of amendments by sites does impose administrative burdens and delays trial conduct. However, the Working Group could not identify any other potential measures of administrative burden.

As a result, the Working Group finally settled on five relatively "soft indicators" of the efficiency of trial conduct as the only possible measures.

- Percentage of trials meeting originally projected accrual rates
- Percentage of trials with revisions to the projected accrual rate
- Percentage of trials meeting a revised projected accrual rate
- Percentage of trials with substantive amendments not resulting from new safety information
- Average number of substantive amendments per trial not resulting from new safety information

The Working Group recognizes that these five measures, even taken together, may not constitute a strong indication of whether clinical trials are being conducted efficiently. The percentage of trials meeting the originally projected accrual rates assesses whether trial designers were correct in their estimates of the rate at which patients would accrue. This is therefore perhaps both a measure of the effectiveness of trial design as well as the efficiency of trial conduct.

Similarly, the percentage of trials requiring a revision of the projected accrual rate could also potentially reflect both the effectiveness of trial design and the efficiency of accrual. Moreover, changes in projected accrual rates could be either up or down, reflecting either positively or negatively on the efficiency of accrual. Finally, the percentage of trials that achieve a revised projected accrual rate could also be a measure of both accrual efficiency and the quality of the decision-making that led to the revision. The other two measures represent proxies for efficiency from the standpoint of administrative burden.

Even these simple measures would require the development of new tracking capabilities at NCI. NCI currently only tracks accrual rates for Phase III trials and then only for the first eight calendar quarters. Tracking would need to be extended for Phase III trials and instituted for early phase trials. NCI tracks amendments, differentiating between purely administrative amendments and substantive amendments. However, there is no current capacity for distinguishing substantive amendments resulting from safety issues. The Working Group recommends that when substantive amendments arise, the Cooperative Group or other trialists conducting the study identify whether the amendment involves a change due to safety concerns. Such safety issues could not be known in advance and therefore would not be considered a measure of the inefficiency of trial design and conduct. NCI could then track the number of substantive amendments not due to safety-related issues as a proxy measure of the efficiency of trial conduct. At this time, the Working Group could not recommend an *a priori* target for the number of substantive amendments that would be judged acceptable.

D. Methodological Development and Database Modifications

Several of the measures identified by the Working Group for evaluating the NCI-funded clinical trials system outcomes require future methodological development.

- Procedure for determining the reason that a trial does not complete accrual

- Expert panel procedure for determining that a trial definitively answered the primary question (positive or negative)
- Expert panel procedures for determining the scientific importance and clinical relevance of trial results
- More robust procedures for linking NCI-funded trials to FDA approvals
- Development of clinical relevance measures for interventions that do not require FDA approval or generally appear in practice guidelines (e.g., lifestyle alterations)
- Approaches for identifying NCI-funded early-phase studies that contributed to the development of industry late-phase trials

In addition, the measures recommended by the Working Group would require the incorporation of at least 15 new data fields in NCI data systems for each clinical trial.

- Reason(s) why trial did not complete accrual
- Whether trial definitively answered primary question (either positively or negatively)
- Impact factor of journals publishing clinical trial results
- Linkage between NCI-supported early-stage trial and Cooperative Group Phase III trial
- Linkage between NCI-supported early-stage trial and industry Phase III trial
- Whether trial results were novel when trial was completed
- Whether trial results warrant practice changes
- Whether trial results led to real-world practice changes
- Whether trial results met important secondary aims
- Trial referenced in FDA regulatory submission
- Trial referenced in regulatory submission that led to FDA approval
- Trials referenced in support of a recommendation in the NCCN guidelines
- Accrual rates for trials
- Changes in projected accrual rates
- Number of substantive protocol amendments (exclusive of those resulting from new drug safety information)

NCI has not yet determined the difficulty of incorporating each of these new data fields into their clinical trial databases or the effort and expense required to collect and code these data. Should the effort prove substantial, it may be necessary to prioritize the new fields.

E. Summary of Measures

TRIAL QUALITY						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Percentage of trials that complete accrual	Yes	No	No	No	No	No
Reason(s) trials do not complete accrual	Yes	No	No	No	No	No
Percentage of trials that definitively answer the primary question (positive or negative)	Yes	Yes (to make determination)	No	No	No	No
Percentage of trials that answer the primary question positively	Yes	Yes (to make determination)	No	No	No	No
Percentage of trials published in peer-reviewed journals	Yes	No	No	No	No	No
Time between trial completion and date of publication	Yes	No	No	No	No	No
Journal impact factor of publications	Yes	No	No	No	No	No
Percentage of early-phase trials that contribute to the design of an NCI-funded late-phase trial.	Yes	No	No	No	No	Background section of trial protocols
Percentage of early-phase trials that contribute to the design of an industry-funded Phase III trial	Yes	No	No	Industry trial study chairs	No	No

SCIENTIFIC IMPORTANCE AND CLINICAL RELEVANCE OF TRIAL RESULTS						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Percentage of trials whose results were novel	Yes	Yes (to make determination)	No	No	No	No
Percentage of trials whose results warrant practice changes	Yes	Yes (to make determination)	No	No	No	No
Percentage of trials whose results led to real-world practice changes	Yes	Yes (to make determination)	No	No	No	No
Percentage of trials with publications based on secondary aims	Yes	Yes (to make determination)	No	No	No	No
Percentage of trials that support FDA submissions and approvals	Yes	No	No	No	No	FDA regulatory documents
Percentage of FDA submissions and approvals supported by NCI trials	Yes	No	No	No	No	FDA regulatory documents
Percentage of late-phase trials referenced in national guidelines	Yes	No	No	No	No	National Guidelines
Percentage of national guideline recommendations that reference an NCI trial	No	No	No	No	No	National Guidelines
Percentage of references to national guidelines recommendation the NCI trial represents	Yes	No	No	No	No	National Guidelines

EFFICIENCY OF TRIAL INITIATION AND CONDUCT						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Time from LOI receipt to trial opened for accrual	Yes	No	No	No	No	No
Time from concept submission to Steering Committee to trial opened for accrual	Yes	No	No	No	No	No
Percentage of trials meeting originally projected accrual rates	Yes	No	No	No	No	No
Percentage of trials with revisions to projected accrual rate	Yes	No	No	No	No	No
Percentage of trials meeting revised projected rate	Yes	No	No	No	No	No
Percentage of trials with substantive amendments not resulting from new safety information	Yes	No	No	No	No	No
Average number of substantive amendments per trial not resulting from new safety information	Yes	No	No	No	No	No

4. Disease Steering Committee Evaluation

A. Background

The CTWG recommended that NCI "Establish a network of Scientific Steering Committees to address design and prioritization of phase III trials that leverages current Intergroup, Cooperative Group, SPORE, and Cancer Center structures and involves the broad oncology community." [10] The rationale for these Steering Committees was as follows.

- Promote an open, collaborative process for setting clinical trial priorities and reducing trial duplication and overlap
- Ensure a well-informed evaluation of strategic directions
- Coordinate and integrate the best ideas arising from Cooperative Groups, Cancer Centers, SPOREs, P01s, R01s, CCOPs, and NCI intramural investigators
- Stimulate greater involvement by practicing oncologists, patient advocates, and NCI staff early in the process of trial design and prioritization

The implementation plan proposed by the CTWG involved the creation of Scientific Steering Committees for each major disease area as well as for pediatric oncology and symptom management/quality of life.

In response to the CTWG Report, NCI initiated the Steering Committees in 2006. Since then, 12 Steering Committees have been established according to the following timeline.[11]

- 2006: Gastrointestinal and Gynecological
- 2007: Head and Neck and Symptom Management/Health Related Quality of Life
- 2008: Genito-Urinary, Breast and Thoracic
- 2009: Lymphoma, Myeloma and Leukemia
- 2010: Brain and Clinical Imaging

The high-level goal of the Steering Committees is to ensure that NCI supports the best-designed trials, addressing the most important questions and leveraging the most significant scientific advances. To achieve that goal, the Steering Committees have three specific areas of responsibility:

- Evaluate and prioritize concepts for Phase III clinical trials with consideration of Phase II trial concepts as deemed appropriate by the Steering Committee

[10] CTWG report, page 26.

[11] http://transformingtrials.cancer.gov/steering/overview, last accessed February 23rd, 2011

- Develop or refine trial concepts utilizing Task Forces and/or Working Groups
- Convene Clinical Trials Planning Meetings to identify critical questions and prioritize key strategies and concepts for NCI supported clinical trials

Steering Committee membership includes Cooperative Group disease committee chairs, leaders of other relevant clinical trials networks[12], SPORE, Cancer Center and R01/P01 investigators, community oncologists, biostatisticians, patient advocates and NCI staff. Steering Committees may form Task Forces or Working Groups that focus on specific scientific topics or on clinical trial concepts in particular disease areas. For example, the Gastrointestinal Steering Committee has seven disease-focused Task Forces[13]:

- Colon Cancer
- Esophago-Gastric Cancer
- Gastrointestinal Stromal Tumors
- Hepatobiliary Cancer
- Neuroendocrine Cancer
- Pancreatic Cancer
- Rectal/Anal Cancer

As a second example, the Head and Neck Steering Committee has four Task Forces[14]:

- Metastatic/Recurrent Disease
- Previously untreated Locally Advanced Disease
- Rare Tumors
- Tumor Biology and Imaging

B. Proposed Evaluation Approach

The recommended Disease Steering Committee evaluation plan addresses the extent to which the first years of implementation have met the expectations of extramural late-phase clinical trialists

[12] For example, the Lymphoma Steering Committee includes representatives from the Blood and Marrow Transplant Clinical Trials Network (BMTCTN) and the AIDS Malignancy Consortium (AMC). Source: http://transformingtrials.cancer.gov/steering/lymphoma, last accessed February 23rd, 2011

[13] List of Task Forces taken from: http://transformingtrials.cancer.gov/steering-committees/gastrointestinal, last accessed February 23rd, 2011

[14] List of Task Forces taken from: http://transformingtrials.cancer.gov/steering-committees/head-neck, last accessed February 23rd, 2011

(both Committee members and other trialists) and NCI staff. The proposed measures are designed to assess the Committees along five dimensions:[15]

- Timeliness of Concept Review
- Quality of Concept Review
- Influence on Concept Development
- Portfolio Management
- Collaboration

In addition, the performance of trials approved by each Steering Committee on the System Outcomes of Trial Quality and the Scientific Importance and Clinical Relevance of Trial Results (see Section 3) will be included in the evaluation.

Each Steering Committee is to be evaluated five years from inception and every five years thereafter. The evaluation process, therefore, will begin with the Gastrointestinal and Gynecologic Steering Committees, which were initiated in 2006. As Steering Committees were initiated in each year between 2006 and 2010, an annual evaluation process would be required, with assessments of different Steering Committees occurring each year. As additional Steering Committees are established, they will be added to the evaluation cycle.

Measures for the evaluation were developed for each of the five evaluation categories. With the exception of the Timeliness of Concept Review, the data required for the evaluation is largely qualitative, collected through interviews. The Working Group rejected an expert panel as a means for assessing the effectiveness of the Steering Committees. The reason for this decision was that Steering Committees are intended to constitute the best clinical research expertise in a particular disease area. Therefore, it was considered not feasible to identify an outside group of objective experts with sufficient knowledge to reliably assess the Steering Committee. Data collection for each Steering Committee evaluation therefore includes the following.

- Database analysis with respect to the time required for concept review
- Interviews with Steering Committee and Task Force members
- Interviews with NCI staff involved in Steering Committee operations
- Interviews with Cooperative Group leadership and investigators who submitted concepts

[15] As the evaluation will encompass the various Disease-Specific Steering Committees as well as the Symptom Management and Imaging Steering Committees, the proposed measures may require slight modifications for specific committees.

C. Proposed Evaluation Measures

1. Timeliness of Concept Evaluation

The only quantitative indicator of Steering Committee performance identified by the Working Group was the timeliness of concept evaluation which is captured by the following measure.

- Time from initial concept receipt to final decision by the Steering Committee

NCI currently collects these data and could report out performance by each Steering Committee over time.

2. Quality of Concept Evaluation

The Working Group decided that quantitative assessment of the "quality" of Steering Committee concept evaluation was not feasible as there was no objective measure of "quality" that could be identified. As a result, evaluation must depend primarily on judgments by stakeholders as to whether Steering Committee processes are effective. The Working Group agreed that such judgments could best be collected through stakeholder interviews addressing the following measures with regard to the evaluation of concepts. These interviews would include all stakeholder groups listed above.

- Transparency and whether there has been improvement since implementation of the Steering Committee
- Fairness and whether there has been improvement since implementation of the Steering Committee
- Efficiency and whether there has been improvement since implementation of the Steering Committee
- Roles played by patient advocates, community oncologists, translational researchers, clinical researchers and NCI staff
- Procedures for ensuring accountability
- Procedures for conflict resolution
- Potential for double jeopardy due to Task Force and then Steering Committee review
- Whether concepts rejected by Task Forces or the Steering Committee have been implemented by others and led to scientifically important/clinically relevant results

Objective analysis of whether rejected concepts were taken forward by others is theoretically possible but would be labor intensive and unlikely to be definitive. Therefore, stakeholder interviews seemed a more reasonable approach for this measure as well.

3. Influence on Concept Development

The Working Group decided that it was not feasible to include a quantitative – or even an objective – assessment of Steering Committee influence on the "quality" of approved concepts.

First, there is no objective measure of the "quality" of a concept. Furthermore, the heterogeneity of Steering Committee processes in this regard renders meaningless any attempt to set a common standard across Committees. Moreover, the Cooperative Groups differ in the degree of internal review before a trial idea or concept is brought before a Task Force or Steering Committee for discussion. It therefore would not be meaningful to compare the influence of a Steering Committee on concepts even within a single Steering Committee.

As a result, this aspect of the evaluation is also based primarily on interviews with all stakeholder groups listed above to address the following measures with regard to influence on concept development.

- Role and value of Task Force deliberations
- Role and value of Steering Committee deliberations
- Responsibilities of Groups versus Task Forces/Steering Committee
- Value of translational science and correlative studies proposed by Task Forces/Steering Committees
- Role played by patient advocates, community oncologists, translational researchers, clinical researchers and NCI staff

4. Portfolio Management

The primary Steering Committee activity related to portfolio management is the convening of Clinical Trials Planning Meetings to identify critical questions and prioritize key strategies and concepts for NCI supported clinical trials. However, during Working Group discussions, two additional themes emerged. The first was the degree to which Steering Committee and Task Force deliberations themselves provided strategic guidance for future trials. One example is the role of the Steering Committee in directing trials in pancreatic cancer away from Phase III and into a range of Phase II trials to better inform Phase III trial development. The second theme was to gather information on the quality of the overall portfolio of concepts approved by the Steering Committee.

Again, no quantitative measures were identified for evaluating Steering Committee performance in these three aspects of portfolio management. Therefore, the evaluation will again rely on interviews with regard to the following measures.

- Influence of Clinical Trials Planning Meetings on trial priorities and strategic directions
- Role of Steering Committee in identifying new trial priorities and strategic directions
- Extent to which trial portfolio reflects state of science with regard to biological basis of disease
- Extent to which trials are based on new innovative scientific hypotheses rather than more standard, previously studied hypotheses

- Extent to which trials are designed to identify practice changing improvements rather than incremental improvements
- Value of Steering Committee in reducing competition for patient populations among NCI-funded trials and trials supported by others

These interviews would not include Cooperative Group leadership or investigators who submitted concepts but only Steering Committee/Task Force members and NCI staff.

5. Collaboration

While facilitating collaboration is not identified as a high-level goal of the Steering Committees, it is considered by NCI to be an important Steering Committee function. Three types of collaboration were identified as being relevant.

- Collaboration in the design of trials fostered by Steering Committee activities
- Collaborations between Steering Committees, including between Disease Steering Committees and modality-based Steering Committees (e.g., Symptom Management/Health Related Quality of Life)
- Collaborations between Steering Committees and the IDSC

As each Steering Committee's approach to collaboration likely would vary somewhat, the Working Group recommended interview-based data collection rather than trying to develop objective measures. Stakeholder interviews would thus address the following measures.

- Incentives and disincentives for collaboration in the design of trials and whether there has been improvement since implementation of the Steering Committee
- Collaborations between Steering Committees, including between modality Steering Committees and Disease Steering Committees
- Collaborations between Steering Committee and the IDSC
- Influence of IDSC reports and guidelines on design of Phase III trials with CTEP agents

These interviews would include all stakeholders on the first measure but only Steering Committee/Task Force members and NCI staff on the other three measures. Interviews with regard to the final two measures would include individuals serving as Steering Committee/IDSC liaisons.

D. Summary of Measures

TIMELINESS OF CONCEPT EVALUATION						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Time from initial concept receipt to final Steering Committee decision	Yes	No	No	No	No	No

QUALITY OF CONCEPT EVALUATION						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Transparency and whether there has been improvement since implementation of the Steering Committee	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Fairness and whether there has been improvement since implementation of the Steering Committee	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Efficiency and whether there has been improvement since implementation of the Steering Committee	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Roles played by patient advocates, community oncologists, translational researchers, clinical researchers and NCI staff	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Procedures for ensuring accountability	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Procedures for conflict resolution	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Potential for double jeopardy due to Task Force and then Steering Committee review	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Whether concepts rejected by Task Forces or Steering Committee have been implemented by others and led to scientifically important/ clinically relevant results	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No

CONCEPT DEVELOPMENT						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Role and value of Task Force deliberations in influencing trial design	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Role and value of Steering Committee deliberations in influencing trial design	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Responsibilities of Groups versus Task Forces/Steering Committee	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Value of translational science and correlative studies proposed by Task Forces/Steering Committees	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Role played by patient advocates, community oncologists, translational researchers, clinical researchers and NCI staff	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No

PORTFOLIO MANAGEMENT						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Influence of Clinical Trials Planning Meetings on trial priorities and strategic directions	No	No	Yes	No	Relevant staff from DCTD, DCP, CCCT	No
Role of Steering Committee in identifying potential new trial priorities and strategic directions	No	No	Yes	No	Relevant staff from DCTD, DCP, CCCT	No
Extent to which trial portfolio reflects state of science with regard to biological basis of disease	No	No	Yes	No	Relevant staff from DCTD, DCP, CCCT	No
Extent to which trials are based on new innovative scientific hypotheses rather than more standard previously studied hypotheses	No	No	Yes	No	Relevant staff from DCTD, DCP, CCCT	No
Extent to which trials are designed to identify practice changing improvements rather than incremental improvements	No	No	Yes	No	Relevant staff from DCTD, DCP, CCCT	No
Value of Steering Committee in reducing competition for patient populations among NCI-funded trials and trials supported by others	No	No	Yes	No	Relevant staff from DCTD, DCP, CCCT	No

COLLABORATION						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**Steering Committee/ Task Force Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Incentives and disincentives for collaboration in the design of trials and whether there has been improvement since implementation of Steering Committee	No	No	Yes	Cooperative Group leadership, investigators submitting concepts	Relevant staff from DCTD, DCP, CCCT	No
Collaborations between Steering Committees	No	No	Yes	No	Relevant staff from DCTD, DCP, CCCT	No
Collaborations between Steering Committee and the IDSC	No	No	Yes	Steering Committee/IDSC liaisons	Relevant staff from DCTD, DCP, CCCT	No
Influence of IDSC reports and guidelines on design of Phase III trials with CTEP agents	No	No	Yes	Steering Committee/IDSC liaisons	Relevant staff from DCTD, DCP, CCCT	No

5. Investigational Drug Steering Committee Evaluation

A. Background

The CTWG recommended that NCI "Establish an Investigational Drug Steering Committee to collaborate with NCI in the design and prioritization of early phase drug development trials for which CTEP holds an IND."[16] In response to this recommendation, NCI established the IDSC in late 2005.

As intended, the IDSC provides NCI with broad external scientific and clinical input with regard to the CTEP early drug development program. The goal is to increase the predictive value of these early phase trials, resulting in the design of more successful Phase III trials. To realize this goal, the IDSC provides four core functions.

- Strategic input to NCI's early drug development priorities
- External input into Clinical Development Plans for CTEP investigational agents
- Open forum for interaction among extramural early drug development investigators and NCI staff
- Reports and guidelines that address key issues in early drug development trial design.

IDSC membership includes the Principal Investigators of all CTEP Phase I U01 grants and Phase II N01 contracts, representatives from the Cooperative Groups, liaisons from the Disease Steering Committees, a patient advocate, biostatisticians, and NCI staff. As of spring 2011, the IDSC had established ten Task Forces, with some covering particular disease mechanisms (e.g., the PI3K, AKT, mTOR Task Force and the Angiogenesis Task Force), others covering particular disciplines or research approaches (e.g., Immunotherapy Task Force, Pharmacology Task Force), and some covering operational issues (e.g., Gap Analysis Task Force). The IDSC also has three Working Groups covering operational issues – Conflict of Interest and Confidentiality, Metrics, and Scientific Meeting Planning.[17]

B. Proposed Evaluation Approach

The recommended evaluation plan addresses the extent to which IDSC implementation has met the expectations of the extramural community and NCI by assessing IDSC performance with regards to its four core functions. The plan further recommends that data relevant to each of these functional areas be collected from a combination of the following sources.

- Independent review by an expert panel

[16] CTWG report, page 25.

[17] List of Task Forces and Working Groups available from: http://transformingtrials.cancer.gov/steering-committees/investigational-drug, last accessed February 28th, 2011.

- Interviews with IDSC members and NCI staff involved in IDSC operations
- Interviews with non-IDSC extramural early drug development investigators
- Interviews with Disease Steering Committee liaisons to the IDSC
- Interviews with industry early drug development investigators
- Database queries with respect to collaboration in accrual
- Bibliometric analysis of IDSC reports and guidelines
- Review of IDSC reports and guidelines

As the IDSC has been in operation since 2006, the evaluation should be conducted in 2011 or 2012 and every five years thereafter.

C. Proposed Evaluation Measures

1. Strategic Input

One core function of the IDSC is to provide strategic input to NCI regarding priorities for CTEP investigational agents. The Working Group identified expert panel review as the most appropriate mechanism for evaluating IDSC effectiveness in providing this strategic input.

Three specific measures are recommended for consideration by the expert panel, which would include non-IDSC early drug development experts.

- Value of IDSC recommendations regarding targets
- Degree to which trials address biological opportunities and/or patient populations identified by a Disease Steering Committee as needing early phase trials
- Degree to which trials are designed to expand knowledge around particular agents in response to IDSC recommendations

In addition, the Working Group concluded that interviews with IDSC members, NCI staff, and non-IDSC extramural early drug development investigators be conducted to assess the transparency and quality of early drug development trial prioritization before and after implementation of the IDSC.

2. Clinical Development Plans

A second core function of the IDSC is to provide external input regarding draft Clinical Development Plans (CDPs) prepared by NCI staff for CTEP investigational agents. The Working Group identified two strategies for assessing IDSC performance relative to this function.

The first is to utilize the same expert panel convened to evaluate IDSC effectiveness with regard to strategic input. The expert panel would compare CDP documents before submission to the IDSC and after incorporation of IDSC input. Review comments and minutes from IDSC meetings would be used- to aid in assessing IDSC influence on each individual CDP. The expert

panel would also evaluate the overall quality of the final CDPs. As there have been 19 new CDPs for which the IDSC provided input[18], such an expert panel review was considered feasible.

Three specific measures are therefore proposed for this facet of the evaluation.

- IDSC role in improving CDP quality with regard to:
  - Enhanced innovation in therapeutic approaches
  - Enhanced incorporation of biomarker studies
  - Enhanced clarity and specificity
- Degree to which trials based on the CDP, if successful, are likely to lead to a Phase III trial
- Degree to which trials based on the CDP address gaps in knowledge about the tested agent

The second strategy is to conduct interviews with IDSC members and NCI staff involved with IDSC operations to determine their views on the following measures.

- IDSC role in improving CDP quality with regard to:
  - Enhanced innovation in therapeutic approaches
  - Enhanced incorporation of biomarker studies
  - Enhanced clarity and specificity
- Quality of the process by which NCI develops, and IDSC reviews, CDPs

3. Collaboration

A third function of the IDSC is to promote collaboration with respect to early drug development trials. The Working Group judged that interviews with IDSC members and NCI staff involved in IDSC operations would be most valuable in assessing the extent to which the IDSC has been successful in promoting collaboration. It is recommended that these interviews address the following measures.

- Degree to which the IDSC process has improved incentives for collaboration among IDSC participants
- Degree to which the IDSC process has increased involvement of new investigators (e.g., SPORE investigators) in CTEP early drug development trials[19]
- Role, activities and effectiveness of the IDSC/Disease Steering Committee liaisons[20]

[18] Personal communication with Deborah Jaffe, NCI/CCCT, June 2011.

[19] Non-IDSC extramural early drug development investigators would also be interviewed with regard to this measure.

[20] IDSC/Disease Steering Committee liaisons would also be interviewed with regard to this measure.

In addition, the Working Group recommended database analyses to evaluate whether there has been increased collaboration in accrual to CTEP early drug development trials since the founding of the IDSC. To that end, the following measure should be assessed for 2005-2011 and then tracked annually.

- Percentage of CTEP early drug development trials (and patients on trials) that involve collaboration in accrual across multiple institutions

4. Reports and Guidelines

The fourth key IDSC function is development and publication of documents offering guidance on the conduct of early drug development trials. The IDSC lists such publications on its Internet site[21] along with reports from IDSC workshops and planning meetings.[22] Given the range of IDSC generated reports and guidelines, and the multiplicity of potential users, the Working Group identified three approaches to assessing the value of these documents.

The first approach is bibliometric. If IDSC generated documents are highly relevant to the scientific community, then their publications should be broadly cited. However, because most IDSC publications are 2009 or later, bibliometric analyses conducted in 2011 may not be a strong indicator of their value. However, repeated bibliometric analysis should show citation trends. The second approach is to interview NCI early drug development program staff and early drug development investigators from both academia and industry to assess the influence of IDSC documents on the design and conduct of trials. The third recommended approach is document review to determine whether any NCI guidance documents on trial design and conduct reflect IDSC recommendations.

These three approaches combined will assess the following measures.

- Number of citations to published IDSC reports and guidelines
- Impact of IDSC reports and guidelines on the design of NCI supported early drug development trials
- Impact of IDSC reports and guidelines on the design of industry early drug development trials
- Extent to which NCI early drug development guidance documents reflect elements of IDSC reports and guidelines

D. Methodological Development

There are two elements of the proposed evaluation plan that will require further methodological development. The first is the expert panel process. Although the Working Group concluded that

[21] http://transformingtrials.cancer.gov/files/IDSC_Pubs_Listing_6%2021%2010.pdf, last accessed March 1st, 2011

[22] http://transformingtrials.cancer.gov/steering-committees/investigational-drug, last accessed March 1st, 2011

an expert panel process would be feasible to conduct, they did not specify from which stakeholder populations an unbiased group of experts would be drawn or how large the panel should be. Moreover, although the Working Group identified the specific questions that the expert panel should address, additional effort is required to more fully develop the expert panel approach and procedures.

A second area where methodological development will be required is assessing the impact of IDSC reports and guidelines on NCI early drug development guidance documents. Specifically, it may not be possible from review of documents alone to determine any influence from IDSC reports or guidelines. If that is the case, this aspect could be added to the interviews.

E. Summary of Measures

STRATEGIC INPUT						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**IDSC Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Value of IDSC's recommendations regarding targets	No	Yes	No	No	No	No
Degree to which trials address biological opportunities and/or patient populations identified by a Disease Steering Committee as needing early phase trials	No	Yes	No	No	No	No
Degree to which trials are designed to expand knowledge around particular agents in response to IDSC recommendations	No	Yes	No	No	No	No
Change in transparency of early drug development trial prioritization since IDSC implementation	No	No	Yes	Non-IDSC early drug development extramural investigators	CTEP and CCCT staff involved in IDSC operations	No
Change in quality of early drug development trial prioritization since IDSC implementation	No	No	Yes	Non-IDSC early drug development extramural investigators	CTEP and CCCT staff involved in IDSC operations	No

CLINICAL DEVELOPMENT PLANS						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**IDSC Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
IDSC role in enhanced innovation in therapeutic approaches	No	Yes	Yes	No	CTEP and CCCT staff involved in IDSC operations	No
IDSC role in enhanced incorporation of biomarker studies	No	Yes	Yes	No	CTEP and CCCT staff involved in IDSC operations	No
IDSC role in enhanced clarity and specificity	No	Yes	Yes	No	CTEP and CCCT staff involved in IDSC operations	No
Degree to which trials based on CDP, if successful, are likely to lead to a Phase III trial	No	Yes	No	No	No	No
Degree to which trials based on the CDP address gaps in knowledge about the tested agent	No	Yes	No	No	No	No
Quality of process by which NCI develops, and IDSC reviews, CDPs	No	No	Yes	No	CTEP and CCCT staff involved in IDSC operations	No

COLLABORATION						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**IDSC Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Degree to which the IDSC process improved incentives for collaboration among IDSC participants	No	No	Yes	No	CTEP and CCCT staff involved in IDSC operations	No
Degree to which the IDSC process increased involvement of new investigators (e.g., SPORE investigators) in CTEP early drug development trials	No	No	Yes	Non-IDSC early drug development extramural investigators	CTEP and CCCT staff involved in IDSC operations	No
Role, activities and effectiveness of IDSC Disease Steering Committee liaisons	No	No	Yes	IDSC Disease Steering Committee liaisons	CTEP and CCCT staff involved in IDSC operations	No
Percentage of CTEP early drug development trials (and patients on trials) that involve collaboration in accrual across multiple institutions	Yes	No	No	No	No	No

IDSC REPORTS AND GUIDELINES						
Evaluation Measure	**Database Analysis**	**Expert Panel**	**IDSC Interviews**	**Other Trialist Interviews**	**NCI Staff Interviews**	**Document Review**
Number of citations to published IDSC reports and guidelines	No	No	No	No	No	Bibliometric analysis
Impact of IDSC reports and guidelines on the design of NCI supported early drug development trials	No	No	No	Non-IDSC early drug development extramural investigators	NCI early drug development program staff	No
Impact of IDSC reports and guidelines on the design of industry early drug development trials	No	No	No	Industry trialists	No	No
Extent to which NCI early drug development guidance documents reflect elements of reports/guidelines	No	No	No	No	NCI early drug development program staff	NCI program documents

6. Evaluation of Clinical Trial Collaboration

A. Background

The CTWG report included five initiatives related to coordination, both within the NCI-funded clinical trials system and with external parties.[23]

- Establish a comprehensive database containing regularly-updated information on all NCI-funded clinical trials.
- Realign NCI funding, academic recognition, and other incentives to promote collaborative team science and clinical trial cooperation.
- Develop guidelines and procedures for joint participation of FDA and NCI in meetings, including those with industry, concerning new agents and diagnostics.
- Increase awareness of the NCI-FDA expedited concept/protocol approval process, including use of the FDA Special Protocol Assessment.
- In collaboration with CMS and other payers and stakeholders, establish a robust and transparent process for identifying clinical studies that might have routine and clinical costs supported using traditional reimbursement mechanisms

Of these five initiatives, the evaluation plan proposed by the Working Group addresses only the second. As recommended by the CTWG, this initiative included a range of proposed changes both in NCI funding practices and in academic recognition and incentive practices in order to facilitate greater collaboration in the design and conduct of clinical trials. Of those changes, the realignment of NCI funding practices to promote collaborative team science and clinical trial cooperation is reasonably mature and therefore included in the evaluation system. However, realignment of academic recognition practices is not included.

The first initiative listed above – the clinical trials database – will be part of the future evaluation of NCI's informatics initiatives related to clinical research (see Section 7). For the remaining initiatives, the Working Group concluded that NCI's implementation was not sufficiently mature to warrant evaluation at this time.

B. Description of Approach

As shown in Figure 1, "collaboration" in clinical trial design and conduct can involve both industry and academic investigators, and can have a variety of specific meanings.

[23] CTWG Report, pages 16-23.

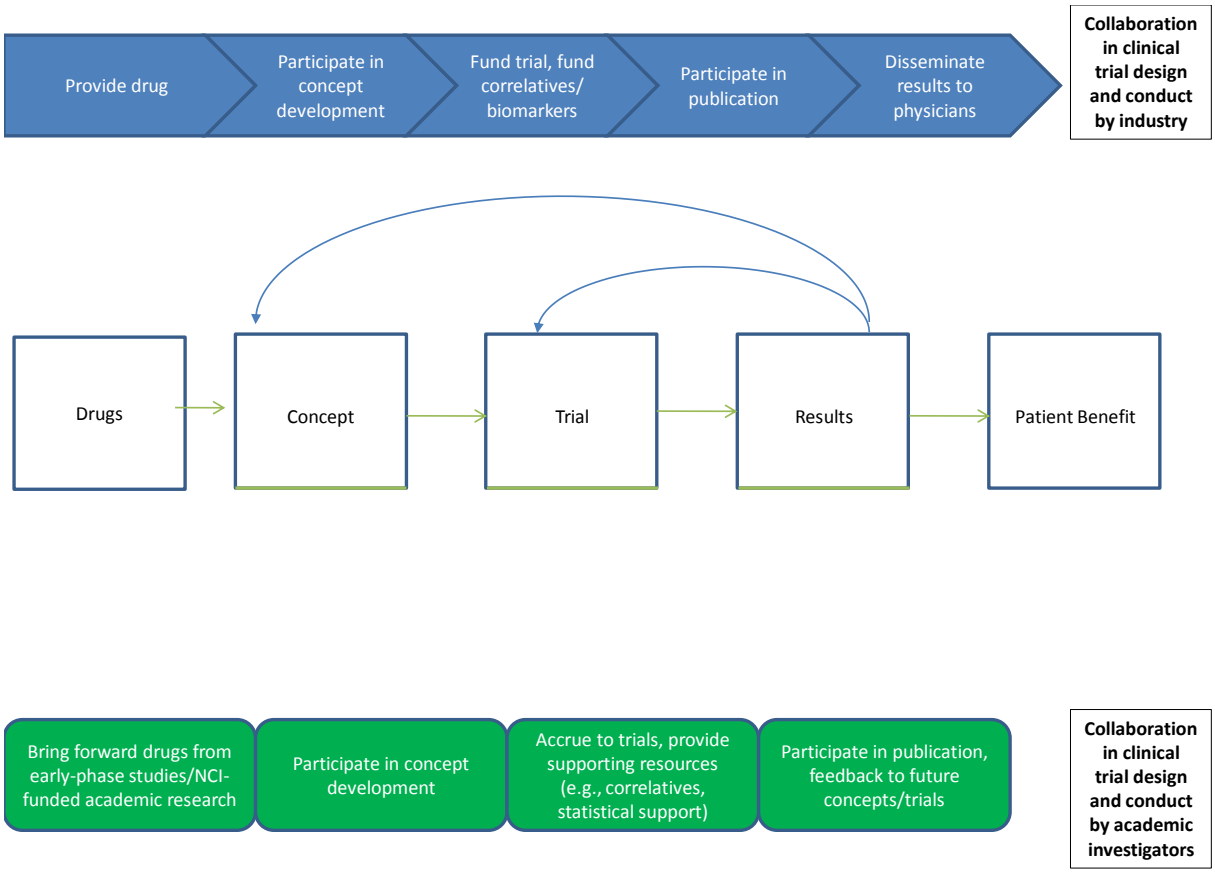

Figure 1: Collaboration in the Design and Conduct of Clinical Trials

While the Working Group actively discussed a range of definitions of "collaboration" that could be included in the evaluation, several limitations emerged. First, most forms of collaboration among academic researchers (and many of the forms of collaboration between academia and industry) are hard to capture in quantifiable fashion. Who participates in the design of a clinical trial, or what funding mechanisms and other resources support a clinical trial, are not easy to identify in a comprehensive and reliable fashion. Furthermore, some measures of collaboration (e.g., bringing forward a drug from earlier stage development) are included under System Outcomes in Section 3.

As a result, only three aspects of "collaboration" are addressed in this section of the evaluation plan. The first is assessment of the revisions made to NCI translational and clinical research program documents to promote collaboration. The second is collaboration in clinical trial accrual and the third is collaboration between NCI/CTEP and industry. Data collection includes two elements.

- Analysis of NCI program documents
- Database analyses for accrual and industry/NCI interactions

Analyses of collaboration in accrual and interactions with industry rely on currently available data and could begin at any time and could be repeated annually or every 2-3 years. The Working Group recommended that analysis of NCI program documents not begin until the current planned revision of the Cooperative Group guidelines is completed.

C. Proposed Evaluation Measures

1. Funding Incentives for Collaboration

The CTWG recommended three specific ways in which NCI could reward collaboration in clinical research.

- Reward collaborations among Cancer Centers, SPOREs, P01s, R01s, early clinical trials networks, Cooperative Groups and other NCI-supported multisite clinical trials networks that advance concepts from pilot studies to Phase III trials and provide correlative science services for large, multisite studies.
- Reward Cooperative Groups and other NCI-funded clinical trials networks for broad participation in multisite trials conducted throughout the NCI-supported clinical trials system.
- Reward efforts to move innovation forward through the most effective and expeditious means, including handoffs between various NCI-funded programs.

Analysis would begin by agreeing upon a comprehensive list of desired forms of collaboration, building on the efforts of the Guidelines Harmonization Working Group of the CTAC (Coordination Subcommittee. Once that list was formulated and approved, it would guide analysis of the Cancer Center, SPORE, and Cooperative Group Guidelines, Funding Opportunity Announcements and written instructions provided to reviewers, if any. The goal would be to assess potential incentives and disincentives for collaboration explicitly required by the document language. Examples might include the following.

- Scored review criteria associated with an aspect of collaboration
- Availability of award funds to conduct or promote collaborative activities
- Availability of supplemental funds for collaborative activities

The analysis will include a detailed comparison of corresponding documents prior to the revisions inspired by the CTWG to assess the degree and scope of the changes. The analysis would also consider the November 2010 program entitled “CTSU Support for Collaborative Multi-Center Phase 2 Trials Led by NCI Designated Cancer Centers and SPORES.”

2. Collaboration in Clinical Trial Accrual

The Working Group identified two measures of collaboration in clinical trial accrual that would be both meaningful to assess and feasible to analyze given currently available data.

- Percentage of CTEP funded Phase II clinical trials (and patients on trials) involving collaboration in accrual across multiple institutions
- Percentage of Phase III clinical trials (and patients on trials) involving collaboration in accrual across multiple Cooperative Groups[24]

3. Industry/CTEP Collaboration

Rather than assess industry collaboration on a trial-by-trial basis, the Working Group suggested several measures of overall industry collaboration with CTEP in regard to clinical trials.

- Total number of investigational agents provided to CTEP by industry
- Year-over-year change in the number of agents
- Total number of companies collaborating with CTEP
- Year-over-year change in the number of companies collaborating with CTEP

The Working Group recognized that there are many other industry collaborations associated with NCI-funded trials, but that it would be overly difficult at this point in time to capture those collaborations in a systematic manner.

[24] The Working Group discussed the likely effect of changes to the Cooperative Group system on the meaningfulness of this particular measure. Even should the number of adult Cooperative Groups decline from the current nine to the proposed (as of March, 2011) four, it would still be expected that collaboration in accrual across Groups would continue to occur, and that the extent to which accrual to trials occurs at institutions affiliated with multiple Cooperative Groups is still worth measuring.

D. Summary of Measures

Evaluation Measure	Database Analysis	Expert Panel	Steering Committee/ Task Force Interviews	Other Trialist Interviews	NCI Staff Interviews	Document Review
Funding incentives for collaboration	No	No	No	No	No	Cancer Center, SPORE, Cooperative Group program documents
Percentage of CTEP funded Phase II clinical trials (and patients on trials) involving collaboration in accrual across multiple institutions	Yes	No	No	No	No	No
Percentage of Phase III clinical trials (and patients on trials) involving collaboration in accrual across multiple Cooperative Groups	Yes	No	No	No	No	No
Total number of investigational agents provided to CTEP by industry	Yes	No	No	No	No	No
Year-over-year change in the number of these agents	Yes	No	No	No	No	No
Total number of companies collaborating with CTEP	Yes	No	No	No	No	No
Year-over-year change in the number of companies collaborating with CTEP	Yes	No	No	No	No	No

7. Other CTWG Initiatives

A. Initiatives Recommended for Separate Evaluation Studies

1. Informatics Initiatives

- Establish a comprehensive database containing regularly updated information on all NCI-funded clinical trials
- Promote establishment of national clinical trial information technology infrastructures that are fully interoperable with NCI's Cancer Biomedical Informatics Grid (caBIG).
- Achieve industry and FDA concurrence on standard Case Report Forms incorporating common data elements.
- Develop a credentialing system for investigators and sites that is recognized and accepted by NCI, industry sponsors, clinical investigators, and clinical trial sites.

A separate group convened under the auspices of the Center for Biomedical Informatics and Information Technology (CBITT) and CCCT should be charged with responsibility for developing an evaluation plan for these initiatives.

2. Biomarker, Imaging, and Quality of Life Initiatives

- Establish a funding mechanism and prioritization process to ensure that the most important correlative science and quality of life studies can be initiated in a timely manner in association with clinical trials.
- Establish a process for ensuring that correlative science studies conducted in association with clinical trials are performed according to standard protocols and standardized laboratory practices.

NCI implemented the first initiative by creating the Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP). The second initiative has been implemented through the Program for the Assessment of Clinical Cancer Tests (PACCT) and its Strategy Group. These two initiatives should be included in a future study to be conducted approximately five years after initiation of BIQSFP and PACCT's addressing of this initiative (i.e., in 2014).

3. Clinical Trial Agreement Standardization Initiative

- Establish commonly accepted clauses for clinical trial contracts

In 2008, NCI conducted a project that resulted in the development of the Standard Terms of Agreement for Research Trials (START) clauses for clinical trial agreements between Cancer Centers and industry.[25] In 2010, NCI conducted an evaluation of the status of implementation of

[25] http://transformingtrials.cancer.gov/initiatives/standardization/highlights/start

the START clauses by Cancer Centers and industry which was reported to CTAC in December, 2010.[26]

4. Increase Minority Accrual Initiative

- Expand current outreach programs to increase the recruitment of minority populations to cancer clinical trials.

In 2007 NCI implemented an initiative regarding minority supplements, which will be evaluated separately.

B. Initiatives Considered Premature for Evaluation

There are nine initiatives for which the recommendations of the CTWG have been implemented, but for various reasons are not yet ready for evaluation.

1. Restructure the funding model for Phase III efficacy trials to incentivize more rapid rates of patient accrual.

NCI has conducted a financial, organizational and management analysis of the NCI-funded Cooperative Groups. NCI is currently using the results of this analysis as input to the overall restructuring of the Cooperative Groups.

2. Identify the institutional barriers that prolong the time from concept approval to accrual of the first patient, and develop solutions for overcoming these barriers.

The Operational Efficiency Working Group (OEWG) was established in late 2008 to address this initiative. The OEWG Report, issued in March, 2010, made specific recommendations for reducing the time for trial initiation. NCI, Cancer Centers and Cooperative Groups are currently implementing these recommendations. The effect on trial initiation times will be reflected in the System Outcome measure of the efficiency of trial initiation.

3. Develop approaches for enhancing adoption of centralized Institutional Review Board (CIRB) processes.

In 2008, NCI conducted an analysis of the barriers to acceptance of the CIRB process which resulted in recommendations for enhanced adoption. Several of these recommendations have been or are being implemented by NCI. Evaluation of their effect on the acceptance of CIRB review should be evaluated 3-5 years after implementation is complete. The impact of increased acceptance may also be reflected in the Systems Outcome measure of the efficiency of trial initiation.

4. Enhance patient advocate and community oncologist involvement in clinical trial design and prioritization.

The Patient Advocate Steering Committee (PASC) was initiated in 2008. The Working Group recommends that this Steering Committee, like the Disease Steering Committees, should be

[26] http://deainfo.nci.nih.gov/advisory/ctac/1210/presentations/STARTclauses.pdf

evaluated five years from its inception. As the role and function of the PASC is quite different from that of the Disease Steering Committees, a separate study would need to be designed. The role of patient advocates and community oncologists in Disease Steering Committees is evaluated as part of the Disease Steering Committee evaluation described in Section 4 above.

5. Realign academic recognition incentives to promote collaborative team science and clinical trial cooperation.

NCI initiated the Clinical Team Investigator Award (CTIA) in 2009. The awards provide recognition and $50,000 in funding to investigators who make substantial contributions to cancer research efforts and clinical trials at NCI-designated Cancer Centers. The Working Group recommends that this award program should be assessed five years from its inception; as the CTIA is a distinct program, a separate study would need to be designed.

6. Develop guidelines and procedures for joint participation of FDA and NCI in meetings, including those with industry, concerning new agents and diagnostics.

CTEP has standing meetings with FDA and facilitates industry discussions as appropriate. Additional discussion with CTEP is required concerning how to best evaluate the results of this initiative and when such an evaluation should be conducted.

7. Increase awareness of the NCI-FDA expedited concept/protocol approval process, including use of the FDA Special Protocol Assessment.

NCI has worked to promote the NCI-FDA expedited concept/protocol approval process. Additional discussion with CTEP is required concerning how to best evaluate the results of this initiative and when such an evaluation should be conducted.

8. In collaboration with CMS and other payors and stakeholders, establish a robust and transparent process for identifying clinical studies that might have routine and clinical costs supported using traditional reimbursement mechanisms.

NCI has conducted pilot activities with CMS on this initiative, focusing on gastrointestinal cancer studies. Additional discussion with CTEP is required concerning how to best evaluate the results of this initiative and when such an evaluation should be conducted.

9. Promote patient and public awareness and understanding of clinical trials.

The CTWG Operational Efficiency Enhancement Initiative #1 (“Promote patient and public awareness and understanding of clinical trials.”) intended that NCI’s Office of Communication and Education (OCE) play an enhanced role in assisting other NCI Divisions, Offices, and Centers in efforts to recruit patients to clinical trials. Currently, these efforts are not ready for evaluation.

Appendix A: CTWG Initiatives

A. Coordination Initiatives

- Create a comprehensive database containing information on all NCI-funded clinical trials to facilitate better planning and management across clinical trial venues.
- Realign NCI and academic incentives to promote collaborative team science.
- Increase cooperation between NCI, FDA, and industry to enhance the focus and efficiency of oncology drug development.
- Expand awareness of the NCI-FDA expedited approval process to speed trial initiation.
- Work with CMS to identify clinical studies that address both NCI and CMS objectives, and for which CMS may be able to reimburse some routine and investigational costs.

B. Prioritization/Scientific Quality Initiatives

- Create an Investigational Drug Steering Committee to work with NCI to enhance the design and prioritization of early phase drug development trials.
- Create a network of Scientific Steering Committees, which leverage current Intergroup, Cooperative Group, Specialized Programs of Research Excellence (SPORE), and Cancer Center structures, to work with NCI in the design and prioritization of phase III trials to better allocate scarce resources, improve scientific quality, and reduce duplication.
- Increase community oncologist and patient advocate involvement in clinical trial design and prioritization to improve the rate of patient accrual, and better address practical and quality of life concerns in the design of trials.
- Develop a funding and prioritization process to ensure that critical correlative science and quality of life studies can be conducted in a timely manner in association with clinical trials.
- Develop a standards-setting process for the measurement, analysis, and reporting of biomarker data in association with clinical trials to enhance data comparisons, reduce duplication, and facilitate data submission for regulatory approval.
- Investigate integration of phase II trials into the overall prioritization process to further coordinate the national clinical trials system.

C. Standardization Initiatives

- Create, in partnership with the extramural cancer research community, a national cancer clinical trials information technology infrastructure fully interoperable with NCI's cancer Bioinformatics Grid to improve cost effectiveness and comparability of results across trials and sites.
- In consultation with industry and FDA, develop standard Case Report Forms incorporating Common Data Elements to improve information sharing among cancer researchers and optimize data requirements.
- Build a credentialing system for investigators and sites recognized by NCI and industry to allow faster trial initiation and keep the investigative community abreast of legal, safety, and regulatory changes.
- Develop commonly accepted clauses for clinical trial contracts with industry to reduce the lead-time needed to open trials.

D. Operational Efficiency Initiatives

- Restructure the phase III funding model to promote rapid patient accrual rates and cost-effectiveness.
- Reduce institutional barriers to timely trial initiation.
- Increase patient and public awareness and understanding of clinical trials.
- Increase minority patient access to clinical trials to improve the participation of underserved and underrepresented populations.
- Promote adoption of the NCI Central Institutional Review Board facilitated review process to reduce the time and resources needed to open trials at individual sites.

E. Enterprise-Wide Initiatives

- Create a Clinical Trials Oversight Subcommittee of the NCAB to advise the NCI Director on conduct of clinical trials across the Institute.
- Develop a coordinated NCI organizational structure to manage the entire clinical trials enterprise supported by the Institute.