

Investigational Drug Steering Committee Structure and SOPs

Introduction and General Overview

The Investigational Drug Steering Committee (IDSC) was established following recommendations from the Clinical Trials Working Group (CTWG) and Institute of Medicine (IOM) to collaborate with NCI to **design and prioritize early phase drug development trials with agents for which the Cancer Therapy Evaluation Program (CTEP) holds an Investigational New Drug Application (IND).**

The goals of the IDSC are to enhance strategic input, increase the transparency and openness of the trial design and prioritization process, achieve optimal phase I and phase II trial designs for the most promising agents and, ultimately, increase the predictive value of early phase trials, resulting in the design of more successful phase III trials.

1 Investigational Drug Steering Committee Structure

1.1 Membership

The IDSC should have the following expertise: drug development, clinical pharmacology, clinical immunology, clinical trial design, omics and biostatistics. Members are expected to actively participate in IDSC meetings and conference calls and may vote on motions brought before the IDSC. Members will include:

1.1.1 Principal Investigators (PIs) of all phase I UM1 grants (including pediatric oncology) and all phase II N01 contracts; this includes all PIs from multi-PI sites. The terms of the grant or contract will specify the time commitment required. Substitutes for PIs are not allowed because of the need for prior disclosure of potential conflicts of interest and confidential data agreements. PIs will serve as IDSC members while their grant or contract is active.

1.1.2 NCI DCTD Staff Liaisons including

- Chief, Investigational Drug Branch (IDB)
- Associate Branch Chief, IDB, Investigational Therapeutics Section I
- Associate Branch Chief, IDB, Investigational Therapeutics Section II
- Associate Branch Chief, IDB, Investigational Therapeutics Section III
- Associate Director, Cancer Therapy Evaluation Program (or designee)
- Associate Director, Developmental Therapeutics Program (or designee)
- Chief, Biometric Research Branch (or designee)
- Associate Director, Clinical Imaging Program (or designee). NCI Staff Liaisons are expected to actively participate in IDSC meetings and conference calls but may not vote.

- Associate Director, Radiation Research Program (or designee). NCI Staff Liaisons are expected to actively participate in IDSC meetings and conference calls but may not vote.

1.1.3 Subject Matter Experts in biostatistics, clinical trial methodology and drug development , preclinical evaluation, correlative science technologies, imaging, radiation oncology, structural biochemistry, and drug structure/function analysis, cancer genomics and preclinical animal cancer models. Ideally, some of these experts will have industry experience. However, current pharmaceutical employees would likely have potential conflicts of interest that would preclude their service on the IDSC. The IDSC Coordination Team (CT) will solicit names of experts from the IDSC, review them and recommend individuals for approval by the IDSC. Subject matter experts will be appointed for a term of 3 years and can be appointed to 2 consecutive terms.

1.1.4 Representatives from Cooperative Groups. Chairpersons of National Clinical Trial Network (NCTN) Groups that have an early therapeutics program (NRG, Alliance, ECOG-ACRIN, COG, NCIC and SWOG) will nominate a representative to the IDSC. The Chairman of NRG will nominate an expert in radiation therapy. Nominations will be reviewed and accepted by the IDSC (or the IDSC-CT on its behalf.) NCTN Group Representatives will be appointed for a term not to exceed 6 years.

1.1.5 A Patient Advocate with an interest in early phase clinical trials and drug development. Names of advocates will be obtained from IDSC members and from the NCI Consumer Advocates in Research and Related Activities (CARRA) program and the Coordinating Center for Clinical Trials (CCCT) Patient Advocate Steering Committee (PASC). After review by the IDSC-CT and ascertainment of interest, a recommendation will be made to the IDSC for approval. Patient advocates will be appointed for a term of 3 years and can be appointed to 2 consecutive terms.

1.1.6 Invited Observers. The Director, Division of Cancer Treatment and Diagnosis (DCTD), the Chief, Clinical Investigations Branch (CIB), and other federal staff or contractors may be invited to attend IDSC meetings and may receive copies of agendas and minutes.

1.1.7 A CCCT staff member, who will serve as the **IDSC Designated Federal Official (DFO)**. The role of the DFO is to ensure compliance with government policies and procedures.

1.2 Selection of IDSC co-Chairs

1.2.1 The IDSC will be led by two co-Chairs – a Phase 1 program PI and an a Phase 2 Program PI. The Phase 1 Program co-Chair will be nominated and elected by the IDSC (ETCTN) clinical investigators¹. Co-Chairs will serve for a period of two years. The co-Chairs will also chair the IDSC-CT.

1.2.2 Election of IDSC Co-Chairs. The Phase 1 Program PIs will be asked to volunteer or nominate a Phase 1 Program PI to serve as IDSC co-Chair. The Phase 2 Program PIs will be asked to volunteer or nominate Phase 2 Program PI to serve as IDSC co-Chair. Nominations will be emailed to all IDSC investigators. All IDSC PIs will participate in voting for the Phase 1 and 2

Program co-Chairs. Voting will be by confidential Survey Monkey ballot. The terms of the co-Chairs should be staggered to ensure continuity in leadership.

1.2.3 Co-Chairs may be from the same institution.

1.2.4 Co-Chairs may serve for a maximum of 4 consecutive years.

1.3 IDSC Responsibilities

Provide Strategic Input. The IDSC will discuss scientific and clinical strategic directions in drug development. The discussions will focus on critical new questions for early stage clinical trials, including but not limited to

- Agent portfolio review
- Emerging technologies,
- Gaps in the drug development pipeline,
- New therapeutic opportunities,
- Correlative science strategies
- Advanced clinical trial methodology.

Based on these discussions, the IDSC will provide input to CTEP regarding future scientific and clinical strategic directions.

1.3.1 Organization and Conduct of Strategic Scientific Symposia

The IDSC may organize scientific symposia addressing scientific and clinical strategic directions in drug development. This may be done by an IDSC Meeting Planning Working Group in conjunction with a Task Force (TF) if needed. The presentations and discussions will focus on critical new questions for early stage clinical trials, including emerging technologies, gaps in the drug development pipeline, new therapeutic opportunities, medicinal chemistry/drug discovery advances, correlative science strategies, advances in clinical trial methodology, etc.

1.3.1.1 Reports/Publications/Recommendations

When appropriate, organizers of Strategic Scientific Symposia may summarize their recommendations in a white paper, which could be submitted for publication in an appropriate journal. These recommendations should also be provided to the Clinical Trials Operations Committee (CTROC), the Clinical Trials Advisory Committee (CTAC), the National Cancer Advisory Board (NCAB) and the Board of Scientific Directors (BSA). Summaries should be posted on the IDSC public website. In addition, the Protocol and Information Office (PIO) should send important recommendations to investigators in the CTEP database.

1.3.2 Review Clinical Development Plans. New investigational agents for which CTEP holds an Investigational New Drug (IND) will be developed within the NCI's Experimental Therapeutics Clinical Trial Network (ETCTN). Prior to Letter of Intent (LOI) submittal by Drug "X" Project Teams, the IDSC will provide input during their quarterly meetings (WebEx and Face-2-Face) regarding Drug Development Projects (DDPs) prepared by Drug "X" Project Teams for all new agents and selected current agents. As CTEP Drug Development Plans evolve over time, the IDSC will provide continued input.

1.3.2.1 Background

NCI develops drugs from many sources including industry, academia and internal investigators. Regardless of the source, when an agent is developed under a CTEP-held IND by a Drug "X" Project Team, the full IDSC is responsible for providing guidance regarding the drug development plan.

1.3.2.2 Process and Timeline

Immediately after the NDeC (NCI Development Committee), when the internal NCI PT meeting is being scheduled to develop the **Project Team (PT) Member Application (PTMA)** from the NDeC-approved agent straw-man proposal, the IDSC CT will be notified that CTEP would like them to nominate up to 2 IDSC members who could participate in this internal NCI meeting. In addition to having expertise either with the agent or with some aspect of the agent straw-man proposal, the nominees would have to be available for the scheduled meeting. This may require that the CT identify more than 2 individuals. These IDSC members would be vetted for COI and sign a CDA. After the internal meeting CTEP would expect them to provide their comments/recommendations for PTMA development within a week.

CTEP will independently vet Drug "X" Project Team members for financial conflict of interest and confidential disclosure. The Financial Disclosure Questionnaire and Confidential Disclosure Agreement will be distributed to the Project Team members by the EMMES ETCTN PM (Project Manager). These documents will be returned to CTEP/RAB, tallied and screened by IDB/RAB/CCCT.

Prior to LOI submittal, Drug "X" Project Teams will present their draft Drug Development Plan (potentially as multiple projects) to the full IDSC during their quarterly meetings (WebEx and Face-2-Face), or sooner, if required, for all new agents and selected current agents. This will be followed by questions and discussion between the Project Team(s) and the IDSC. The goal of the process is for the IDSC to make recommendations to both the Drug "X" Project Team and CTEP regarding the Drug Development Project(s) developed and presented to them by the Drug "X" Project Team.

1.3.3 Drug "X" Project Team Coordination

1.3.3.1 Each Drug "X" Project Team will have two Team Leads and one Translational-Team Lead and one Clinical-Team Lead. The IDB drug monitor is a co-Team Lead by default.

- i. The co-Team Leads can be a Principal Investigator (PI) from either the Lead Project Organization (LPO) or Lead Academic Organization (LAO). CTEP personal will identify the Team Leads.
- ii. Co-Team and Translational Leads will oversee all of the project teams and sub-project teams for an agent.
- iii. EMMES ETCTN PM (Project Manager) will schedule meetings, distribute meeting materials, maintain the Drug “X” Project Team membership roster, and generate meeting minutes.
- iv. The Project Team will be asked as a regular order of business to address the following topics:
 - 1. Team-based authorship and how it will be handled throughout the project;
 - 2. Structure of Project Team presentation to IDSC and assignment of responsibilities;
 - 3. Identification of fit for purpose biomarkers and identification of appropriate reference laboratories (CAP/CLIA environment);
 - 4. Genomic analysis reference laboratories;
 - 5. SOPs for specimen collection and processing to be included in all LOIs and protocols;
 - 6. Other issues related to the unique development of specific agents.

2.3.3.1 A call will be scheduled with the Drug “X” Project Team, CCCT staff and IDB staff (IDB co-Team Lead, and available/interested senior IDB staff).

- i. Call schedule discussion:
 - 1. Weekly standard small group calls (staggered) will be scheduled.
 - 2. Potential days/times for a call ideal for Team members and Leadership will be determined. EMMES ETCTN PM will send out a doodle poll with potential dates/times.
 - 3. Calls will last up to 1.5 hours.
 - 4. *Ad hoc* calls may be scheduled. This may be required should small breakout sub-specialty project teams be required for highly specialized tasks and projects.
 - 5. Project Teams will be provided a presentation template to be used during IDSC meeting presentations. This template adheres to the principles established by the IDSC for introduction of investigational agents to the steering committee. The template is meant to serve as a guide designed to assure all topics related to the development of a new agent are adequately and appropriately covered.
- ii. WebEx format will be used on all conference calls. An overview of WebEx capabilities will be provided (*EMMES ETCTN PM will host and send all call-in and WebEx information.*)
- iii. IDSC WebEx/Meetings

1. Team and Translational Leads will attend the IDSC meeting. Project Team members can call-in by WebEx teleconference.
2. Winter and Summer IDSC meetings will be held by WebEx. Spring IDSC will be Face-2-Face (WebEx will be available) and held in conjunction with the ETCTN Annual Portfolio Presentation. The Fall IDSC meeting will be Face-2-Face and held in conjunction with the Annual CTEP EDD meeting (WebEx will be available).
3. If Project co-Team Lead is from a UM1 or N01 site, their grant or contract will cover their travel and lodging. If the Project co-Team Lead is from an Academic institution or not from a UM1 or N01 site, costs for travel and lodging will be covered by the CCCT. CCCT will also cover travel and lodging costs for the Project Translational Team Lead. If there are multiple PIs from LPO or LAO, these PIs may attend. All other team members will attend and present by WebEx.

3.3.3.1 Standing weekly calls will be scheduled by the EMMES ETCTN PM to summarize site team progress.

- i. There may be multiple sub-specialty projects proposed by the Drug “X” Project Team so as sub-specialty projects are developed there may be a need to stagger times on specified standing call date to discuss different projects.
 1. If co-Team Leads and Translational Team Lead are not available for the call, the co-Team Leads and Translational Team Lead will delegate call Leadership to another team member prior to call date and inform CCCT and EMME ETCTN PM.
 2. Appropriate NCI Project Team members will be included in these conference calls. EMMES ETCTN PM will send invitations to these individuals.
 3. All Project Teams members will meet for the last weekly call of the month (4th or 5th week of the month) to discuss data progress and any questions (IDB co-Team Lead will be on this call.)

4.3.3.1 Project Team slide presentations for IDSC meetings/WebEx should be available 1-2 weeks in advance for distribution to IDB co-Team Lead and other IDB/CIB staff. Slides will also be distributed to all IDSC members.

5.3.3.1 During the IDSC meeting/WebEx Drug “X” Project Team members will present an agent’s Drug Development Plan (potentially as multiple sub-specialty projects.) When the presentation is completed the IDSC will have a question-answer session with the Project Team presenter(s). Following this discussion period the Project Team members both at the meeting and on WebEx will be informed that the meeting/WebEx is now closed and will be asked to recuse them-selves while the IDSC votes on approval or disapproval of the endorsement of the Project Team’s Drug Development Plan.

1.3.4 Assess LOIs The IDSC will periodically assess, from a strategic perspective, approved and unapproved Drug “X” Project Team LOIs and approved and unapproved unsolicited LOIs (from outside the ETCTN) to determine if the Drug Development Plan for an agent should be modified.

1.3.4.1 Appeals of LOI Decisions When requested by CTEP, the IDSC will assist in resolution of appeals of unsolicited LOIs by investigators. Coordination of the LOI resolution process will be carried out by the IDSC-CT. A lead IDSC-CT member, vetted for potential conflicts of interest, along with IDB Staff and CCCT Staff (and CCCT contractor) will assemble an appropriate IDSC LOI resolution Working Group (IDSC LOI WG). The IDSC LOI WG should be composed of at least 2 individuals with clinical and/or translational reviewers and 1 statistical reviewer with expertise in the focus of the LOI. Additional specialized expertise should be included on the IDSC LOI WG if needed. All IDSC LOI WG members will be vetted for potential conflict of interest. The IDSC LOI WG will be provided a CTEP consensus review (highlighting their concerns) as well as a written response by the LOI PI(s)/Study Team to the CTEP consensus review. Any additional information requested by the IDSC LOI WG will be obtained by CCCT staff. The IDSC LOI WG will provide written reviews of the disputed LOI to CCCT Staff (and their contractor). If the IDSC LOI WG requests a teleconference prior to providing their reviews the CCCT contractor will schedule this teleconference. IDSC LOI WG reviews will be compiled by the CCCT contractor and sent to the IDSC-CT and CTEP/IDB Leadership for comment. CTEP/IDB Leadership will send the final IDSC LOI WG review to the CTEP Protocol Information Office (PIO) for distribution to the LOI PI(s)/Study Team).

1.3.5 Provide Expert Opinion

When requested by CTEP, the IDSC will address specific scientific and/or clinical questions with regard to early stage clinical trials, provide input to the NCI Drug Development Group concerning a decision to move a specific agent into clinical development, and provide other input as needed.

1.3.6

1.3.7 Inform the Broad Oncology Community

To make the deliberations of the IDSC known to the broad oncology community, the following items should be provided to the Clinical Trials Operations Committee (CTROC), the Clinical Trials Advisory Committee (CTAC), the National Cancer Advisory Board (NCAB), the Board of Scientific Advisors (BSA), and the IDSC public website (<https://www.cancer.gov/about-nci/organization/ccct/steering-committees/investigational-drug>).

- Strategic directions identified by the IDSC
- New drugs approved for clinical development by CTEP
- Clinical Development Plans
- Guidelines or any other documents developed by the IDSC

1.4 Operating Procedures of IDSC

1.4.1 Meeting Frequency

There will be approximately four (quarterly) IDSC meetings per year. Winter and Summer IDSC meetings will be held by WebEx. The Spring IDSC meeting will be Face-2-Face (WebEx will be available) and held in conjunction with the ETCTN Annual Portfolio Presentation. The Fall IDSC meeting will be Face-2-Face and held in conjunction with the Annual CTEP EDD meeting (WebEx will be available).

Other meetings will be scheduled by the IDSC-CT at a mutually agreeable time and place. A teleconference may be scheduled between quarterly in-person meetings to provide information exchange, update action items and address new issues.

1.4.2 Role of CCCT Contractor

The **CCCT EMMES contractor** will work with the Co-chairs and CCCT staff to identify possible dates and times, poll the members, and schedule the meeting or teleconference. The meeting logistics, dial-in information and agenda will be emailed to the members.

1.4.3 Participation

IDSC members are expected to actively participate in IDSC meetings and conference calls and may vote on motions brought before the IDSC. IDSC members are expected to commit approximately 12 days per year to IDSC work. Alternates for members who are unable to attend calls or meetings are not allowed because of the need to screen for potential conflicts of interest and maintain confidentiality.

1.4.4 Quorum

A quorum (50% of the defined members of the group plus 1 member) is needed to schedule an IDSC call or meeting (currently 20 members). (This definition also applies to the IDSC-CT, TFs and WGs.)

1.4.5 Motions and Voting

Matters requiring a formal decision by the IDSC should be submitted as a motion to the IDSC-CT for placement on the next IDSC agenda. Voting at Face-to-Face meetings will be by anonymous paper ballot with a simple majority of the IDSC members present being required to pass. IDSC members that have called in to the Face-to-Face meeting will vote by email ballot. The EMMES coordinator will collect and tally all ballots. A voice vote may be sufficient for procedural matters not related to agent development. Voting during IDSC WebEx teleconference will be by a web-based anonymous Survey Monkey. Each of the N01 and UM1 sites will have a single vote (see below). Sites holding both a UM1 and N01 award will be able to cast one vote per grant or contract.

For voting on Drug "X" Project Team Drug Development Plan presentations during IDSC Face-2-Face/WebEx meetings, multi-PI UM1 sites will designate a single individual to be their representative voter. Ballots will be due by the COB on the day after the Drug "X" Project Team Drug Development Plan presentations in order for multi-PI UM1 sites to provide a consensus vote. All Drug "X" Project Team

members, including the designated voter, will be recused during the discussion and voting period of an IDSC meetings/WebEx for a particular agent.

1.4.6 Confidentiality

NCI will provide confidential information to IDSC members for the purpose of obtaining their input into drug development plans, LOI reviews, and other matters as required. IDSC members will be required to sign a confidential disclosure agreement to the effect that they will not disclose, reveal, or give the confidential information to anyone.

1.4.7 Potential Conflicts of Interest

The IDSC developed a conflict of interest (COI) policy and management guidelines to ensure the integrity of the IDSC regarding disclosure, assessment, and management of conflict of interest (See Appendix 1). The policy specifies the information needed to determine if a member has a real or perceived conflict of interest with the agent or class of agents under discussion and if so, what remedy should be applied. Categories of interests that must be disclosed include stock, employment, consulting agreements, grants, contracts, patents, royalties, trademarks, testimony as an expert witness, teaching, speaking, writing or any other activity that could pose a potential conflict of interest. Members must disclose this information prior to participating in discussions of LOIs or Drug Development Plans. NCI staff will determine which IDSC members should be recused from voting on and/or discussing a specific agent. Recusals should be reviewed periodically by the COI Working Group.

1.4.8 Meeting Minutes

A summary of the meeting will be prepared by CCCT staff and the EMMES contractor within one week of the meeting. Draft minutes will be submitted to CCCT staff, IDSC Co-chairs and the IDSC-Coordination Team for review. The draft minutes will be distributed to IDSC members for review at least three weeks prior to teleconferences and at least six weeks prior to in-person meetings. The minutes should be approved at the next IDSC meeting. The minutes will identify the action items that resulted from the meeting.

1.4.9 Website

The CCCT and its EMMES contractor will maintain a secure private website for the IDSC. IDSC members and designated NCI staff will be given user names and passwords. The website will house the IDSC, TF and WG rosters, member contact information, upcoming meeting materials, final copies of meeting minutes and other materials as appropriate. Each Task Force will have a linked web page. Pages with confidential information should be protected such that it is only available to users authorized by NCI.

2 IDSC Coordination Team

A Coordination Team will manage operations of the IDSC, including resolution of disputes and stalemates and will ensure that IDSC deliberations do not delay the NCI-supported drug development process.

2.1 Membership and Selection

The Coordination Team (CT) will include the two Phase 1 and Phase 2 IDSC co-Chairs, one NCTN representative and one Phase 1 and Phase 2 representative (in addition to the Phase 1 and Phase 2 IDSC/CT co-Chairs). CT members will serve for a period of two years, with staggered terms to maintain continuity. CT members may serve for a maximum of 4 consecutive years. There may be 2 members from the same institution. Ex officio, non-voting members include the CTEP Associate Director, IDB Branch and Section Chiefs, and CCCT staff and contractors.

2.2 Operating Procedures of IDSC-CT

The IDSC-CT will coordinate activities of the IDSC. It is charged with the following responsibilities: to organize meetings, plan agendas, receive correspondence and other input for the IDSC, set and analyze milestones, and ensure the smooth operation of the IDSC.

Although the IDSC retains the formal authority to appoint all TFs, it is anticipated that the IDSC-CT will make recommendations to the IDSC regarding potential co-chairs and key members. To facilitate progress, the IDSC delegates to the IDSC-CT the authority to appoint additional members to the current IDSC TFs: Biomarker TF, Clinical Trial Design TF, Pharmacology TF and Immunotherapy TF. However, the TF co-Chairs must concur with the addition of these members. The IDSC shall be notified of all TF appointments. The IDSC-CT may also appoint administrative Working Groups (WG) to assist in the executive responsibilities of the IDSC.

2.2.1 Meeting Frequency

The IDSC-CT will meet approximately monthly or as needed in person or by conference call. A standing day and time should be selected for teleconferences based on the general availability of the IDSC-CT members. The CCCT contractor will work with the co-chairs to identify available meeting times, and then poll the other members to determine the best time.

2.2.2 Meeting Minutes

CCCT staff and their EMMES contractor will prepare a summary within one week of the IDSC-CT teleconference or meeting. The draft minutes will be submitted to the IDSC Co-chairs and IDSC-Coordination Team for review and approval. Approved minutes should be distributed to the IDSC and posted on the IDSC private website.

2.2.3 Participation

The IDSC Co-chairs will be expected to devote 20-28 days total to IDSC work.

3 IDSC Task Forces

Task Forces (TFs) will carry out IDSC activities for specific clinical areas (e.g., Pharmacology, Clinical Trial Design, Biomarkers and Immunotherapy). Working groups might also be formed to address specific

Clinical Development Plans or other issues.

3.1 TF Co-chairs and Members

Task Forces will be comprised of IDSC members plus additional members of the broad oncology community as needed. The IDSC-CT will make recommendations to the IDSC regarding potential co-Chairs and key members. Each TF will have 2 co-Chairs. One co-Chair must be an IDSC member and the other may or may not be an IDSC member. The co-chairs should be from different institutions. co-Chairs will serve 3 year terms and may serve for a maximum of 6 consecutive years. Ad hoc experts should be included in the task force as needed. An NCI staff member will serve as the NCI Lead TF member. The TF chair and co-chair will conduct the meetings, assign tasks, assure that tasks are completed and present the products of the work. The NCI Lead will assist in the agenda-setting process with the chair and co-chair and participate in the TF's activities. TF rosters will be maintained by the CCCT or its contractor and posted on the IDSC website.

3.2 Operating Procedures of Task Forces

3.2.1 Meeting Frequency

Task forces will meet face to face or by teleconference as needed. They will suggest new agents for CTEP to pursue, consider clinical trial design, and discuss correlative studies or other topics related to early phase drug development, biomarkers, clinical trial design, pharmacology and immunotherapy. The CCCT EMMES contractor will work with the co-chairs to identify available meeting times, and then poll the other members to determine the best time.

3.2.2 Voting

Given the advisory nature of TFs, the need for a formal procedure is not anticipated. When feasible, TFs will conduct reviews electronically, for example using ePanel.

3.2.3 Confidentiality and Potential Conflict of Interest

The confidentiality and conflict of interest policies and procedures of the IDSC apply to TFs.

3.2.4 Meeting Minutes

CCCT and its EMMES contractor will prepare a summary within one week of the meeting. The summary will be emailed to the TF co-chairs for review prior to distribution to the TF members within two weeks of the meeting. TF co-chairs will determine when summaries are ready to be emailed to IDSC members and posted on the private IDSC website.

3.2.5 Communication Flow

CCCT staff or their EMMES contractor will arrange TF meetings and conference calls in conjunction with the TF co-chairs. TF co-chairs should communicate with the IDSC-CT and CCCT staff regarding their charge, progress, need for additional expertise and other matters that arise. Co-chairs will report TF deliberations to the IDSC-CT and IDSC at regular intervals.

Information requests from TFs that will take the contractor more than two hours to complete will be reviewed by IDB and CCCT staff to determine what information is needed, who should obtain the information, how much effort is required, and the relative cost/benefit ratio. If contractor support is requested, a task request form should be submitted to the project officer. Liaisons between related TFs should be designated to promote communication.

3.2.6 Need

The need for a given TF should be reevaluated annually by the IDSC-CT and a recommendation made to the IDSC.

3.2.7 Participation

TF co-Chairs are expected to devote 10-14 days per year, depending on workload.

4 IDSC Working Groups

The IDSC Coordination Team will form Working Groups to assist it in discharging its administrative and executive responsibilities (e.g., management of confidentiality and conflict of interest, meeting planning, etc.)

4.1 WG co-Chairs and Members

Working Groups (WGs) will be comprised of IDSC members plus additional *ad hoc* members of the broad oncology community as needed. WGs will be formed to address a specific issue or task and then be dissolved. The IDSC-CT may appoint WG co-Chairs and key members. Each WG will have one IDSC member as co-Chair and may have one DCTD staff member as a co-Chair. *Ad hoc* experts should be included as needed. WG rosters will be maintained by the CCCT or its contractor and posted on the IDSC website.

4.2 Operating Procedures of Working Groups

4.2.1 Meeting Frequency

Working groups will meet face to face or by teleconference as needed. The CCCT contractor will work with the co-Chairs to identify available meeting times, and then poll the other members to determine the best time. Given the administrative nature of working groups, the need for a formal voting or review procedure is not anticipated.

4.2.2 Confidentiality and Potential Conflict of Interest

The confidentiality and conflict of interest policies and procedures of the IDSC apply to working groups.

4.2.3 Meeting Minutes

CCCT and its contractor will prepare a summary within one week of the meeting. The summary will be emailed to the WG co-Chairs for review prior to distribution to the WG members within two weeks of the meeting. WG co-Chairs will determine when summaries are ready to be emailed to the IDSC-CT.

4.2.4 Communication Flow

CCCT staff or their contractor will arrange meetings and conference calls in conjunction with the WG co-chairs. WG co-chairs should communicate with the IDSC-CT and CCCT staff regarding their charge, progress, need for additional expertise and other matters that arise. WG co-Chairs will report deliberations to the IDSC-CT. The IDSC-CT will determine when reports should be made to the IDSC.

4.2.5 Participation

WG members are expected to devote 3 – 10 days per year, depending on workload.

5 Coordinating Center for Clinical Trials

5.1.1 The Coordinating Center for Clinical Trials (CCCT), located in the Office of the Director, NCI, is charged with implementing the Clinical Trials Working Group Initiatives. CCCT staff will work with DCTD staff, contractors, and IDSC and TF members to ensure that the IDSC achieves its goals of providing strategic input and increasing transparency in the design and prioritization of NCI's early phase clinical trials.

Appendices

Appendix 1 IDSC Conflict of Interest Policy

Appendix 2 IDSC Conflict of Interest, Confidentiality and Non-Disclosure Rules: Information for Reviewers of CTEP Letters of Intent (LOI)

Appendix 3 IDSC SOP Change Control Process *(to be added)*

Appendix 4 IDSC NCI Interaction Diagram *(to be added)*

Appendix 1

Investigational Drug Steering Committee

A. Policy on Financial Conflict of Interest

I. BACKGROUND

The National Cancer Institute (NCI) has played an important role in the discovery and development of new anticancer agents. The justification for such intensive involvement of a government agency in research and development is clear: significant improvement of cancer treatment is in the public interest. NCI is a major sponsor of clinical trials with investigational anti-cancer agents; currently, well over 100 INDs are held by the Division of Cancer Treatment and Diagnosis, NCI.

Most of the anticancer agents in clinical development by NCI are being co-developed by a pharmaceutical company. Compounds of mutual interest may be submitted by a company for antitumor screening, preclinical toxicology, or clinical testing. Conversely, if a compound is discovered by NCI, the involvement of a collaborator is sought as early in development as possible because NCI does not commercialize new agents. The early involvement of a pharmaceutical company permits substantial cost-sharing between the public and private sectors, and can hasten the availability of new agents by several years.

In this joint effort, NCI and the private sector share the goal of defining the contribution of a new agent to cancer treatment as precisely and expeditiously as possible. The three-way relationship among clinical investigators, the NCI, and private industry involves complex issues in coordination, priority-setting, and allocation of limited resources.

II. INVESTIGATIONAL DRUG STEERING COMMITTEE

The Investigational Drug Steering Committee (IDSC) was formed at the recommendation of the Clinical Trials Working Group to design and prioritize early phase drug development trials for investigational treatments being developed by the NCI. The IDSC is comprised of the Principal Investigators of cooperative agreements and contracts funded by NCI to conduct phase 1 and phase 2 clinical trials respectively, additional subject matter experts, NCTN Group representatives, DCTD supported disease-specific Consortia Representatives and Patient Advocates. Task Forces (TF) and Working Groups (WG) will be constituted by the IDSC to comment on NCI's development plans for specific agents or classes of agents and provide input into the prioritization of NCI resource use in the development of new agents.

While NCI has a great need for scientific input from the extramural community, it is critical that the advice be untainted by financial conflict of interest. Financial conflict of interest (COI) may exist when an investigator has a financial interest in the investigational agent under consideration that may potentially influence the review, evaluation, and/or recommendations regarding that agent. Independence from financial conflict of interest allows the investigator to rely on professional judgment in the review and clinical trial process and ensures the highest quality design, conduct, publication, and protection of human subjects.

The outside experts who serve on the IDSC, TFs and WGs are typically active clinical researchers on the cutting edge of science. As such, they and their organizations are often sought out by the pharmaceutical industry to assist in product development. Academic biomedical research in the United States increasingly is supported by industry. This situation can give rise to potential financial conflicts of interest or appearances of a lack of impartiality. It is important that real or perceived conflicts of interest are identified and addressed.

III. FINANCIAL CONFLICT OF INTEREST POLICY

This document provides a financial conflict of interest policy and guidelines for management of COI that will ensure the integrity of the IDSC and its Task Forces and Working Groups. These policies will apply to all IDSC participants as well as participants in Task Forces and Working Groups. All are referred to as participants in this document. Consideration must be given to disclosure, assessment, and management of financial conflicts of interest. The document specifies the type and amount of information that will be collected to determine if an IDSC, TF or WG member has a real or perceived financial conflict of interest with the agent or class of agents under discussion and if so, what remedy should be applied.

Information relating to the nature and magnitude of the financial conflicts of interest must be noted and reviewed prior to an IDSC, TF or WG meeting. This information will allow a reasonable person to understand the nature of the potential financial conflict and the degree to which it could be expected to influence the recommendations the participant will make. The table below shows the types of information that should be disclosed. The information will be reviewed by NCI (as described below) with input from the IDSC Conflict of Interest Working Group as needed.

In formulating this policy, conflict of interest (COI) guidelines were reviewed from the following sources: the National Institutes of Health (“Conflict of Interest Rules for Reviewers of Grants and Contracts” and “Conflict of Interest Workshop Summary – 2002”), the Food and Drug Administration (“Policies and Procedures for Handling COI with FDA Advisory Committee Members, Consultants, and Experts” and “Disclosure of COI for Special Government Employees Participating in FDA Advisory Committees”), and the American Society of Clinical Oncology (“Conflict of Interest Policy – 2005”). Those sources were clear and consistent on many issues, especially financial conflicts of interest.

The information contained in Table 1 should be disclosed by the participant as it relates to his/her relationship **with companies developing the agent or a related agent or class of agents under discussion by the IDSC, Task Forces or Working Groups**. A list of relevant companies will be provided for each discussion topic. Potential participants should also disclose information regarding their involvement with competing agents, even if not on the provided list. The disclosure should identify whether the interest is related to the company or competitor that markets a competing agent and whether the member worked on the competing agent or not.

Table 1. Information to be Disclosed Concerning Conflicts of Interest

Type of Interest	Magnitude
<p>Stock</p>	<p>Identify whether stock (excluding stock options) is valued at:</p> <ul style="list-style-type: none"> a. from \$5,001 to \$25,000; b. from \$25,001 to \$50,000; c. from \$50,001 to \$100,000; or d. greater than \$100,000. <p>Identify if individual owns stock options (vested or unvested).</p>
<p>Employment of Participant or Spouse</p>	<p>Identify whether employment involves the company's agent, a competing agent or an unrelated agent.</p>
<p>Consulting</p>	<p>Identify whether consulting fees earned within the last year are:</p> <ul style="list-style-type: none"> a. from \$5,001 to \$25,000; b. from \$25,001 to \$50,000; c. from \$50,001 to \$100,000; d. or greater than \$100,000. <p>Identify whether consulting is related or unrelated to agent, and whether consulting is ongoing or completed</p>
<p>Contracts and Grants</p> <p>(This includes contracts and grants imputed to the Participant through his/her employer)</p>	<p>Identify whether contract or grant is:</p> <ul style="list-style-type: none"> a. less than \$100,000 per year; b. between \$100,001 and \$300,000 per year; or c. greater than \$300,000 per year. <p>Identify whether individual is the PI or a coinvestigator, whether contract/grant is related or unrelated to the agent, and whether funded research is ongoing or completed. Only those contracts and grants on which an individual is the PI or has a major scientific role as coinvestigator require disclosure. (This does not include studies on which an individual is simply enrolling patients.)</p>
<p>Patents/Royalties Trademarks</p>	<p>Identify if royalties received within the past year (related to specific company) are:</p> <ul style="list-style-type: none"> a. from \$5,001 to \$25,000; b. from \$25,001 to \$50,000; c. from \$50,001 to \$100,000; d. or greater than \$100,000 <p>Identify whether patents/royalties are related or unrelated to agent.</p>

Expert Witness	<p>Identify whether fees earned within the last year are:</p> <ol style="list-style-type: none"> from \$5,001 to \$25,000; from \$25,001 to \$50,000; from \$50,001 to \$100,000; or greater than \$100,000 <p>Identify whether testimony is related or unrelated to agent, whether matter is ongoing or resolved, and whether testimony was on behalf of or against company.</p>
Teaching, Speaking or Writing	<p>Identify whether fees earned within the last year are:</p> <ol style="list-style-type: none"> from \$5,001 to \$25,000; from \$25,001 to \$50,000; from \$50,001 to \$100,000; or greater than \$100,000 <p>Identify whether topic is related or unrelated to agent and whether activity is ongoing or completed. Is the source of fees academic or from a company?</p>

Other Involvements

- Identify situations not covered above including (but not limited to):
- planning a competing study for which remuneration described above is expected
 - receiving funds from a communications company to speak about the agent, a competing agent or class of agents at a CME session
 - chairman of a department or division receiving sizeable funds from collaborating or competing company

Potential participants will be asked to provide this information for review by designated NCI staff and the IDSC Conflict of Interest Working Group. Participation will be contingent upon disclosure. This information will not be disclosed to other NCI staff, IDSC members, or the public.

IV. PROCEDURE FOR FINANCIAL CONFLICT OF INTEREST CLEARANCE

The process for determining the eligibility of outside experts to participate in IDSC, TF and WG deliberations involves multiple levels of review.

Review of Assignment to Assess the Potential for Conflicting Financial Interests

The first step is to determine the topic of the IDSC, TF or WG deliberation. If a specific agent is being considered, all entities with a financial interest in the agent are identified to the extent feasible by NCI staff or contractors in conjunction with the IDSC COI WG. These entities will include the collaborating company and firms who will manufacture or market (1) the agent being discussed and (2) agents of the same class or that affect the same molecular target and could plausibly compete with the one being discussed. This information is provided to the potential participant along with the topic of the deliberation. **Any individual may choose to be recused from a particular discussion in lieu of disclosure.**

Completion of Confidential Financial Disclosure Questionnaire

Potential participants are asked to complete a confidential financial disclosure questionnaire. The questionnaire covers the potential participant, their spouse, minor children, and general partners, and organizations in which the potential participant serves as an officer, director, trustee, general partner or employee or is negotiating for employment. In preparation, NCI staff sends each potential participant instructions and a summary of previously reported financial interests to assist them in updating their relevant information. Forms should be sent to potential participants at least 2 weeks prior to the discussion and should be returned within one week. Participants whose forms have not been received prior to the deadline will not be able to participate in the discussion.

If such disclosure would violate a confidentiality agreement, the participant may note a conflict without disclosing the name of the company. If disclosure of any of the details of that relationship were also covered under such an agreement, then the participant should be recused from the IDSC, TF or WG discussion.

There is no general requirement that potential participants seek out additional information about interests of their employing institutions beyond their own personal knowledge. The exception is that department heads are expected to be knowledgeable about all research within their department and to obtain additional details on the research if needed.

Review of Questionnaire and Initial Determination

The NCI staff reviews the potential participant's response to the questionnaire and determines whether a conflict of interest exists. Based solely on the reported information, a preliminary categorization will be made: (1) there is no financial conflict of interest, (2) there is a financial conflict of interest that is minimal and a waiver can easily be justified by NCI, (3) there is a financial conflict of interest that requires additional review or (4) there is a financial conflict of interest that is so significant that recusal is the only course of action. When clarification is needed, NCI staff may ask the potential participant to respond to additional questions and/or seek input from a subcommittee of the IDSC COI Working Group. If a financial conflict of interest exists, the details of the conflict will be documented.

The Director of the Coordinating Center for Clinical Trials or designee is notified of significant financial conflicts of interest and determines the extent to which the potential participant's expertise is important to the meeting. If the reported interest is significant and the need for the participant's services is not great, recusal would be appropriate. If the participant's services are important to the meeting because no one else with the expertise can attend the meeting, a waiver may be appropriate. Where the financial interest is relatively large it is essential that the justification be particularly strong.

Final Approval by Director, Division of Cancer Treatment and Diagnosis

A proposed waiver and justification for the waiver receives multiple levels of review including consultation with staff of the Cancer Therapy Evaluation Program before reaching the Director of the Division of Cancer Treatment and Diagnosis for final approval. Possible actions include recusal, approval of a waiver, modification of the agenda for the meeting, or another appropriate action. Every effort should be made to resolve the issue expeditiously.

V. SOME EXAMPLES OF POSSIBLE FINANCIAL CONFLICTS OF INTEREST

Interactions between industry, individual investigators, academic medical centers, and government are inherent in the cancer drug development process. These interactions are often mutually beneficial, facilitate the comprehensive evaluation of a new agent, and speed the drug development and approval process. These interactions are not intrinsically unacceptable or undesirable. The following examples represent potential financial conflicts of interest and should be noted in Section 3 (Other Involvements) of the Confidential Financial Disclosure Questionnaire if not already noted in Section 2 (Current Financial Interests):

- A direct **financial** relationship exists between a potential participant and the pharmaceutical company. This relationship may range from being quite limited (e.g., holding a use patent for a particular indication or method of drug administration) to being quite broad (e.g., having an ownership position within the company or rights to royalties from sale of the agent). The relationship may be directly with the potential participant or with the potential participant's academic institution. In the case of a direct financial relationship between the company and the potential participant, where financial gain to the potential participant may result from the decisions made by the IDSC, TF or WG, the potential participant should generally recuse himself/herself from the review process, especially if the potential participant has significant stock holdings or options in such company. When the relationship exists between the company and the potential participant's institution, decisions regarding the presence of a conflict of interest should be made on a case-by-case basis and should take into account the size of the financial and academic benefit that may accrue to the potential participant from the institution and the participant's control over the funds.
- An **indirect relationship** exists between the potential participant and the pharmaceutical company. For example, the participant has been invited by a communications company to speak at a session on a certain class of agents, for which the attendees will receive CME credit. Although the pharmaceutical company is not supporting the speaker directly, the funds originated from the company. This kind of interaction poses a potential conflict of interest and should be noted in the appropriate section of the questionnaire—consulting, speaking or other involvement.

In some situations, disclosure may be all that is needed and the potential participant may participate fully in all discussions and decisions regarding a particular new agent. In others, the potential participant may be asked to recuse himself from some of the discussions and/or decisions. In others, the potential participant may be asked to refrain from participation in any discussion or decisions regarding that particular new agent.

In the rare instance in which special knowledge or expertise essential to the review and/or decisions regarding an agent resides only with a potential participant with a conflict of interest, the NCI in consultation with the IDSC COI WG may grant a waiver and allow that individual to participate in the review and planning meetings for that agent.

B. POLICY ON NON-FINANCIAL CONFLICT OF INTEREST

Conflict of interest (COI) may also exist when an investigator has an intellectual or academic interest in the investigational agent under consideration that may potentially influence the review, evaluation, and/or recommendations regarding that agent. Financial COIs are relatively straightforward to define, identify, and establish criteria for recusal from the review and evaluation process. For non-financial matters, it may be difficult to distinguish between subject matter expertise that would facilitate a well informed and objective recommendation from that which could influence an individual's recommendation to be less than completely objective in a manner that would serve his/her intellectual or academic interests.

It is essential that the IDSC review process is as transparent as possible, requiring that non-financial COIs be disclosed. The process of disclosing such information, and managing conflicts when indicated, is described herein:

- Information regarding potential non-financial COIs will also be collected from IDSC members at the same time as financial COI information is being collected by NCI staff. IDSC members may request recusal from voting (or participation and voting) in a specific meeting if they believe that the non-financial interests will impair their ability to offer an objective recommendation.
- Non-financial COI information will be reviewed by the COI Committee prior to each meeting. The committee may elect to recommend recusal of an individual from voting (or participation and voting) if the members believe that the conflict is significant. In circumstances where time does not permit review by the entire COI committee, review by the COI committee chair or vice-chair is adequate. If circumstances do not permit review by the COI committee, chair, or co-chair, the information will be disclosed at the time of the IDSC meeting.
- Non-financial COI information will be disclosed to all IDSC members at the beginning of IDSC meeting in which a specific agent is being discussed, and will also be recorded as an appendix to the meeting minutes. IDSC members will also be informed of recommendations of the COI committee regarding recusal from voting (or participation and voting) for specific individuals.
- IDSC members may make a motion to request recusal of an individual from a voting (or participation and voting) that has not been made the COI committee, although it is anticipated that this would occur only in unusual circumstances. If such a motion is made, the specific individual for whom recusal is requested may voluntarily agree; if the member does not agree, a majority vote of voting IDSC members will be required to result in recusal of that member (with the member in question recused from discussion and voting).

An **intellectual/academic** conflict exists between the pharmaceutical company, the government and the potential participant that does not involve a financial relationship. Several potential examples are described herein:

- The individual is a first author on an abstract, presentation or manuscript that emanates from a study of an agent that is at a similar point in development and is thought to act through the same mechanism as the agent under discussion.
- The individual is the principal investigator of a trial involving an agent that is at a similar point in development and is thought to act through the same mechanism as the agent under discussion.
- The individual is a department chair, committee chair, or other leadership position in which he/she directs the principal investigator of a trial involving an agent that is at a similar point in development and is thought to act through the same mechanism as the agent under discussion.

Appendix 2

IDSC Conflict of Interest, Confidentiality and Non-Disclosure Rules: Information for Reviewers of CTEP Letters of Intent (LOI)

This document applies to the strategic review of approved and/or disapproved CTEP Letters of Intent (LOIs) by the Investigational Drug Steering Committee (IDSC), IDSC Task Forces, or other IDSC-constituted groups.

As reviewers themselves are most familiar with their own situations, it is their personal responsibility: (1) to alert the CCCT and NCI staff to any possible conflict of interest situation, whether real or apparent, that may impact on the review, and (2) to identify and certify on the Conflict of Interest Certification Forms associated with this information sheet, (a) any letter of intent (LOI) where they have a conflict of interest, and (b) that they will not be, and have not been, involved in the review of any LOI where their participation constitutes a conflict of interest. Reviewers must also certify that they will maintain the confidentiality of the proceedings and associated materials and that they will not disclose to another individual any matter or information related to the review proceedings. In addition, the NCI may determine that a particular situation involves a conflict of interest and require that the potential reviewer not be involved in the review of the LOI(s) in question.

There are several bases for a conflict of interest: employment, financial benefit, personal relationships, professional relationships or other interests. If applicable, any one condition may serve to disqualify a reviewer from participating in the review of a letter of intent. A **conflict of interest may be real or apparent.**

The following guidance and definitions, derived from federal regulations governing the Scientific Peer Review of Research Grant Applications and Research and Development Contract Projects (42 CFR Part 52h), will assist reviewers in determining whether they are faced with a real or apparent conflict of interest. The guidance is not all-inclusive, due to the variety of possible conflicts of interest. Therefore, it is important that reviewers consult NCI staff when there is any question about their participation in a review.

GUIDANCE AND DEFINITIONS

A **Conflict of Interest** in LOI review exists when a reviewer has an interest in an LOI that is likely to bias his or her evaluation of it. A reviewer who has a real conflict of interest with an LOI may not participate in its review.

Real Conflict of Interest means a reviewer or a close relative or professional associate of the reviewer has a financial or other interest in a proposal that is known to the reviewer and is likely to bias the reviewer's evaluation of that LOI as determined by the NCI staff managing the review, as acknowledged by the reviewer, or as prescribed by 42 CFR 52h as follows:

A reviewer shall have a real conflict of interest if he/she or a close relative or professional associate of the reviewer: (1) has received or could receive a direct financial benefit of any amount deriving from an LOI under review; (2) has received or could receive a financial benefit from the applicant institution, or principal investigator that in the aggregate exceeds >\$5,001 per year; this amount includes honoraria, fees, stock or other financial benefit, and additionally includes the current value of the reviewer's already existing stock holdings, apart from any direct financial benefit deriving from an LOI under review: or (3) has any other interest in the proposal that is likely to bias the reviewer's evaluation of

that LOI.

Regardless of the level of financial involvement or other interest, if the reviewer feels unable to provide objective advice, he/she must recuse him/herself from the review of the LOI at issue. The LOI review system relies on the professionalism of each reviewer to identify to NCI staff any real or apparent conflicts of interest that are likely to bias the reviewer's evaluation of an LOI.

Employment: A reviewer who is a salaried employee, whether full-time or part-time, of the LOI institution or principal investigator, or is negotiating for employment, shall be considered to have a real conflict of interest with regard to an LOI from that organization or principal investigator. The Director of NIH or designee may determine whether there is no real conflict of interest or an appearance of a conflict of interest where the components of a large or multi-component organization are sufficiently independent to constitute, in effect, separate organizations, provided that the reviewer has no responsibilities at the institution that would significantly affect the other component.

Financial Benefit: See definition of Real Conflict of Interest above.

Personal Relationships (Relatives): A close relative means a parent, spouse, sibling, son or daughter or domestic partner. A conflict of interest exists if a close relative of a reviewer submits an LOI, or receives or could receive financial benefits from or provides financial benefits to the LOI PI. In such case, it will be treated as the reviewer's financial benefit.

Professional Associates: Professional associate means any colleague, scientific mentor, or student with whom the LOI reviewer is currently conducting research or other significant professional activities or with whom the member has conducted such activities within one year of the date of the review.

Longstanding Disagreements: A conflict of interest may exist where a potential reviewer has had longstanding scientific or personal differences with an applicant.

Appearance of A Conflict Of Interest means that a reviewer or close relative or professional associate of the reviewer has a financial or other interest in an LOI that is known to the reviewer or the NCI staff managing the review and would cause a reasonable person to question the reviewer's impartiality if he or she were to participate in the review. NCI staff will evaluate the appearance of a conflict of interest and determine whether or not the interest would likely bias the reviewer's evaluation of the LOI.

CONFIDENTIALITY AND NON-DISCLOSURE OF MATERIALS AND PROCEEDINGS

The LOIs and associated materials made available to reviewers, as well as the discussions that take place during review meetings are strictly confidential and must not be disclosed to or discussed with anyone who has not been officially designated to participate in the review process.

CERTIFICATION

All reviewers must certify that they have read these instructions on "IDSC Conflict of Interest, Confidentiality, and Non-Disclosure Rules and Information for Reviewers of CTEP LOIs." Under penalty of perjury (US Code Title 18 chapter 47 section 1001), the reviewer must certify that, to the best of his/her knowledge, he/she has disclosed all conflicts of interest that he/she may have with the LOIs and he/she fully understands the confidential nature of the review process and agrees: (1) to destroy or return all materials related to it; (2) not to disclose or discuss the materials associated with the review, their evaluation, or the review meeting with any other individual except as authorized by the NCI staff; and (3) to refer all inquiries concerning the review to the NCI staff. This will be included in the CDA sent to

reviewers prior to receiving the LOIs.