Data Safety and Monitoring Plan

Ensuring Patient Safety and the Integrity of Clinical Research

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FCCC RRC: GRANT088
Version Number: 2.0
Version Date: 15 March, 2012

FCCC IRB: 01868
## Amendment History:

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Summary of Changes</th>
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<tbody>
<tr>
<td>1.1</td>
<td>26-Jun-01</td>
<td>Initial version submitted to NCI and RRC.</td>
</tr>
<tr>
<td>1.1a</td>
<td>08-Oct-01</td>
<td>Initial version submitted to IRB following RRC approval. Corrected typographical errors Added table of amendment history</td>
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<tr>
<td>1.2</td>
<td>10-Jan-02</td>
<td>Expanded discussion of PMEC, Phase I-II Committee monitoring of investigator-initiated studies, special requirements for multi-center studies, QA audit program, and notification to NCI for suspension or termination of NCI-sponsored studies. Revision submitted to NCI and DSM plan approved 22-Jan-02.</td>
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<tr>
<td>1.3</td>
<td>10-Dec-02</td>
<td>Changed title page to reflect current RRC chair, version, RRC number, and IRB number</td>
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<tr>
<td>1.4</td>
<td>25-Sep-03</td>
<td>Incorporation of FCCC-CCOP Research Base</td>
</tr>
<tr>
<td>1.5</td>
<td>27-Jan-04</td>
<td>Supplemental material for FCCC-CCOP Research Base. Minor Updates: Phase I-II program, adoption of CTCAE v3, adverse event reporting, revised links to CTEP documents and templates, additional QA SOPs.</td>
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<tr>
<td>1.61</td>
<td>06-Apr-07</td>
<td>Annual update, incorporation of FER and Partners, revised phase I section</td>
</tr>
<tr>
<td>1.7</td>
<td>19-Jan-11</td>
<td>Update of Personnel, Removal of material relevant to the FCCC-CCOP Research Base</td>
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<tr>
<td>2.0</td>
<td>15-Mar-12</td>
<td>Revision of conflict of interest policies, implementation of safety or accrual study closure guidelines, addition of organizational chart, description of response to audit findings, change in name of facility, change in Facility Director, change in Associate Director, change in RRC review policy for cooperative group and NCI funded studies.</td>
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Data and Safety Monitoring Plan
Ensuring Patient Safety and the Integrity of Clinical Research

Summary

- Fox Chase Cancer Center (FCCC) places the highest priority on ensuring the safety of patients participating in clinical research.
- Principal Investigators at FCCC receive training and certification in human subjects research, and are ultimately responsible for monitoring the safety of their clinical trials.
- Every therapeutic interventional trial conducted at FCCC must include a data and safety monitoring plan. The adequacy of this plan is a mandatory review element considered by Research Review Committee (RRC) and the Institutional Review Board (IRB) during initial protocol submission and ongoing re-review.
- Specific plans may vary based on the degree of risk involved in participation and the size and complexity of the clinical trial. The development of protocol monitoring plans and reporting requirements are dependent upon the study sponsor, nature of the investigational agent, and phase of trial.
- NCI/CTEP-sponsored phase III studies will rely upon monitoring of the trial by the principal investigator with reporting to NCI/CTEP using the Clinical Trials Monitoring Service (CTMS), the Clinical Data Update System (CDUS), and/or the Adverse Event Expedited Reporting System (AdEERS).
- Clinical trials sponsored by the NCI Cooperative Group Program (ECOG, GOG, NSABP, ACOSOG, RTOG) will continue to be monitored by established centralized data and safety monitoring programs within each cooperative group. These studies are reviewed at RRC for programmatic fit and accrual feasibility and subsequently reviewed by central IRB (c-IRB). Local, investigator-initiated Phase I-II trials will be required to be continuously monitored by the principal investigator of the study and undergo ongoing review by RRC and IRB. More frequent (i.e. quarterly) safety and monitoring reports will be reviewed during regular meetings of the Phase I-II Committee. In essence, the Phase I-II Committee will provide independent data and safety monitoring for investigator-initiated studies that do not have a protocol-specific DSM Board.
- Local, investigator-initiated randomized Phase III clinical trials will be monitored by protocol-specific data safety and monitoring boards (DSMB). Each DSMB will consist of clinical investigators, biostatisticians, clinical trial experts, and lay patient advocates independent of investigators involved in the design and conduct of the trial. Data and safety monitoring will be specified in the protocol with reports being forwarded to RRC and IRB.
- Investigator-initiated clinical trials conducted through the Fox Chase Cancer Center Extramural Research Program will be monitored in accordance with approved standard operating procedures and these guidelines, with oversight provided by the Associate Director, Clinical Research, the Vice President, Extramural Programs, and the Extramural Data and Safety Monitoring Committee. Data safety and monitoring activities for each study will continue until all patients have completed their treatment and all patients are beyond the time point at which study-related adverse events would likely be encountered.
- Data safety and monitoring activities for each study will continue until all patients have completed their treatment and all patients are beyond the time point at which study-related adverse events would likely be encountered.
- Oversight of data safety and monitoring at FCCC will be the responsibility of the Associate Director, Clinical Research, Research Review Committee (RRC), Institutional Review Board (IRB), and the Protocol Management Executive Committee (PMEC).
- All data safety and monitoring plans, institutional as well as individual protocol-specific plans, must be reviewed and approved by the FCCC IRB prior to protocol initiation. The institutional master plan will be re-reviewed on an annual basis.

Acknowledgements

The authors of the Data and Safety Monitoring Plan for Fox Chase Cancer Center are greatly indebted to efforts of the National Institutes of Health, particularly the National Cancer Institute, whose data and safety monitoring policies and plans formed the basis of our plan. In addition, portions of this plan were adapted with permission from the Data
and Safety Monitoring Plan of the Ohio State University Comprehensive Cancer Center. Together with our principal investigators, we assume all responsibility for the integrated function of this plan and its implementation at Fox Chase Cancer Center.
Data and Safety Monitoring Plan

Introduction

As an NCI-designated comprehensive cancer center, the Fox Chase Cancer Center (FCCC) places the highest priority on ensuring the safety of patients participating in clinical trials. The ability to safely conduct high-priority clinical research is a mission-critical activity of the Center. Appropriately, we are entrusted to perform only those trials that meet all regulatory and ethical guidelines, as supported by a rigorous process of review and monitoring. Oversight for this process begins at the level of the principal investigator, but is reinforced through integrated scientific, technical, and ethical review, together with ongoing quality assurance monitoring, as embodied in this plan.

Active clinical research programs at FCCC include a range of interventional studies from single-center investigational phase I trials through participation in large-scale, multi-institutional randomized phase III studies. Although the majority of studies involve cancer treatment, other areas of clinical investigation include cancer prevention, behavioral research, collection and analysis of biosamples, and medical records review.

The extent of monitoring varies by the degree of risk encountered by patients on the study, the study sponsor, the type of agent or agents involved, and the phase of the clinical trial. Approximately 150 cancer therapy and prevention protocols are active at any one time. These include phase I trials, phase II studies, and randomized phase III trials. Sponsorship is divided among national cooperative groups (from ACOSOG, ECOG, GOG, RTOG), investigator-initiated trials with external peer-review, investigator-initiated trials with internal peer-review, pharmaceutical industry-sponsored trials, and studies in cancer prevention and control sponsored by the FCCC CCOP Research Base.

Currently, all FCCC clinical trials receive some form of data and safety monitoring. This includes ongoing review of toxicity with the principal investigator and clinical research team; timely adverse event reporting to the IRB, study sponsor, and appropriate regulatory agencies; preparation of ongoing review documents for RRC and IRB; periodic auditing of source documentation by external sponsors and regulatory agencies; and internal quality assurance auditing. Due to the complexity of clinical research and evolving regulatory guidelines, it is expected that this plan will require periodic amendments.

The FCCC Data and Safety Monitoring Plan has been developed to coordinate the oversight for data and safety monitoring for all therapeutic trials consistent with the following policy statements:

- National Institutes of Health Policy for Data and Safety Monitoring
  (05-Jun-00) http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

- National Cancer Institute policy for data and safety monitoring of all trials with special emphasis on utilization of Data and Safety Monitoring Boards for randomized phase III trials
  http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm

- Cancer Therapy Evaluation Program (CTEP) guidelines for monitoring of clinical trials for Cooperative
  Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU)

- Manual for Participants in Clinical Trials of Investigational Agents Sponsored by DCTD, NCI

- CTEP Common Terminology Criteria for Adverse Events (CTCAE)
  http://ctep.info.nih.gov/reporting/ctc.html

- Adverse Event Reporting Requirements for NCI Investigational Agents (Expedited and Routine)
  http://ctep.info.nih.gov/reporting/adeers.html
  http://ctep.info.nih.gov/guidelines/templates.html

- MEDWATCH - The FDA Medical Products Reporting Program
  https://www.accessdata.fda.gov/scripts/medwatch/

- Code Of Federal Regulations Title 45 Public Welfare Department Of Health And Human Services National
  Institutes Of Health Office For Protection From Research Risks, Part 46, Protection Of Human Subjects
  http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm
Key Components of Data and Safety Monitoring

Introduction

Although it is clear that the ultimate responsibility for data and safety monitoring rests with the principal investigator, it is equally clear that the institution must promote an environment that facilitates detailed ongoing review and safe conduct of high-priority clinical research studies. As such, truly effective data and safety monitoring is not the result of a single committee or individual, but is a shared responsibility within our protocol management infrastructure. Together, this cooperative and interactive process serves to maximize protection of our human subjects.

Key elements and processes at Fox Chase Cancer Center that contribute to data and safety monitoring are summarized in this section.

Principal Investigator Qualifications

Every study submitted for review at Fox Chase Cancer Center must have a designated local principal investigator who is responsible for the safe conduct of the study at our Center. This rule applies to all clinical research studies, regardless of sponsor, including national cooperative group and FCCC-CCOP protocols. The principal investigator must be a member of the professional staff of the Center with an academic appointment in a clinical department. Staff with part-time appointments may serve as co-investigators, but cannot serve as a principal investigator without written departmental support. All principal investigators, co-investigators, and key study personnel must have certification in human subjects research and participate in research educational sessions, based on current NIH and local IRB guidelines.

Potential conflicts of interest must be declared prior to protocol review. An investigator will be deemed to have a potential conflict of interest if the individual (or the individual's spouse or dependent child) knowingly receives anything that when aggregated for the individual, the individual's spouse and dependent children equals or exceeds $5,000 for 12 months. This includes, but is not limited to, salary or other payments for service (e.g. consulting fees or honoraria); equity interests (e.g. stocks, stock options, or other equity interests); debt interests, capital holding or other remuneration or financial consideration, or thing of value for services as an employee, consultant, officer or board member in an entity which will reasonably appear to be directly and significantly affected by the protocol in question. Restrictions on a clinical trial investigator begin with the accrual of the first patient into the trial and extend through the first publication or presentation of trial results. Integrity will be protected by an independent oversight group for evaluation and monitoring of the research whenever a potential conflict exists. The IRB may request that the nature of the potential conflict be disclosed in the patient informed consent document, or an investigator may be barred from conducting or enrolling to a trial if the conflicted relationship continues. Conflict of interest reporting to the institution, RRC, IRB, and safety committees is required annually, but should a conflict arise during the course of the year, the investigator is required to report this to the IRB. In the case of failure to disclose or recuse, the President of FCCC shall be responsible for administering all matters.

FCCC Clinical Trials Operations (CTO)

Clinical Trials Operations (CTO) provides a centralized resource to facilitate the development, conduct, quality assurance monitoring, and evaluation of clinical trials at Fox Chase Cancer Center. As such, the Office coordinates the majority of clinical research studies in medical oncology, surgical oncology, radiation oncology, and population science (with the exception of genetic and epidemiology studies). Within the CTO, the Extramural Research Program provides support for clinical research activities within the community hospital systems affiliated through the Fox Chase Network program and other sites participating in research originating at Fox Chase Cancer Center.

The CTO participates at all levels in the activation and conduct of clinical trials, and is an important component of the overall data and safety monitoring plan. This effort includes attention to scientific, ethical, and regulatory issues, protocol compliance, as well as objective and verifiable data management for each study. Importantly, the CTO coordinates the flow of documents among internal bodies, such as RRC and IRB, as well as external agencies, to facilitate ongoing protocol review while adhering to local and federal guidelines to maximize protection of human subjects.

The CTO operates under the medical and scientific leadership of Margaret von Mehren, MD, Professor of Medical Oncology. In her capacity as Facility Director, Linda Kish serves as the Assistant Vice President of Clinical
Investigations, with direct responsibility for management of the CTO, reporting to the Facility Director. Specialized administrative support is provided by John Gricosi, Research Administration. High-quality clinical research requires the smooth integration of patient care, data management, regulatory procedures, quality assessment, and staff education. In this regard, the Office includes a Director of Regulatory Affairs and a Director of Quality Assurance, with their respective teams, all of whom report to the Coordinator of Clinical Investigations. The Regulatory Affairs team is responsible for reporting to the NCI Program Director responsible for funding a trial, as well as to other pertinent agencies, if that trial is suspended temporarily or permanently.

Fox Chase is committed to a strong centralized protocol operation. This provides a better opportunity for professional training and staff support, adherence to standardized procedures, and improved regulatory compliance. The clinical research staff are organized as disease- and modality-focused teams that generally include a nurse clinical research coordinator (CRC) and a clinical research associate (CRA) functioning as data manager. The disease-focused team structure facilitates interaction with physicians and patients and allows each team to develop expertise in their respective area, which improves routine monitoring and reporting of safety data, as well as actively providing support to the medical staff in identifying patients who are candidates for trial. This function is carried out via attendance at tumor boards, interaction in the clinics, and e-mail reminders and queries. There are currently 7 disease-specific teams and 3 modality teams (Phase-I, Radiation Oncology, and Cross Therapeutics, which includes prevention, imaging and sample collection trials). The Office also includes an Extramural Research Program dedicated to the coordination of multicenter studies operated within our Partners network of community hospital affiliates and other sites participating in Fox Chase Cancer Center Research.

Extramural Research Program (ERP)

The Extramural Research Program (ERP) was formerly known as the Office of Extramural Research (OER). OER was fully integrated with the Clinical Trials Operations (CTO, formerly the Protocol Management Office) March 2010. The Extramural Research Program was established to provide a centralized resource for research studies conducted at sites affiliated with Fox Chase Cancer Center. This program facilitates the development, conduct, quality assurance monitoring, and evaluation of investigator-initiated studies. The staff works with investigators on all levels of the study to include attention to ethical and regulatory issues, protocol compliance, quality assurance, and development of study-specific standard operating procedures, databases and case report forms. Regulatory staff manages the flow of documents to participating sites and external agencies to facilitate ongoing and timely review of the protocol and associated documents and events. ERP adheres to local and federal guidelines and regulations. The Extramural Research Program operates within Clinical Trials Operations (CTO) under the direction of the Facility Director and the Assistant Vice-president of Clinical Trials Operations and Extramural Research Program. The staff designated for the ERP consists of a regulatory coordinator, monitor, quality assurance coordinator and a project manager for Protocol Development. CTO staff supports data quality and data management for the ERP. All research conducted through this mechanism is prioritized and monitored by the FCCC RRC, IRB and the Extramural Data and Safety Monitoring Committee. The CTO facilitates the flow of these studies through the RRC and IRB and Extramural Data and Safety Monitoring Committee.

Research Review Committee (RRC)

The Research Review Committee (RRC) provides the primary mechanism for scientific evaluation of new and ongoing clinical research protocols, and has the authority to activate and close all clinical studies in conjunction with IRB. As such, RRC is a key component of the Fox Chase Protocol Scientific Review and Monitoring System (PSRMS), which received full approval from NCI in 1996. Administrative support is coordinated by Clinical Trials Operations, which facilitates team assignments and staff review of operational details for each new study. The process of scientific review is enhanced through formal and informal interactions with clinical departments, disease-specific clinical research programs, biostatistics, the Developmental Therapeutics program, investigational pharmacy, and laboratory research programs.

RRC is a Center-wide committee that reports directly to the Associate Director, Clinical Research. Hossein Borghaei, DO, a clinical and laboratory investigator who is an Associate Professor in the Department of Medical Oncology, has served as RRC Chair since September, 2011. Elizabeth Plimack, MD, Assistant Professor of Medical Oncology, serves as Associate Chair of the RRC. A prior chair of RRC, Gary Hudes, MD, Professor of Medical Oncology, continues to serve as a member of RRC. Membership spans a range of departments involved in clinical and laboratory research. In general, members are expected to serve for a minimum of three years, which provides a core of experienced reviewers. There is no maximum term limit, as there has generally been sufficient turnover to
accommodate two or three new members each year. In addition to the clinical departments, strong representation from Biostatistics, Pharmacology, Protocol Office, Pharmacy, Nursing, Behavioral Sciences, Prevention Research, and Laboratory Science is encouraged.

RRC is charged not only with ensuring that the studies activated at FCCC represent the best possible science, utilizing the most rigorous trial designs, but also with ensuring that the entire menu of trials which are activated at Fox Chase makes optimal use of the center’s resources, permitting accrual to novel and early phase studies. Prioritization of studies begins in the disease specific working groups, closely aligned with the clinical service lines. Medical Oncology departmental review discusses the majority of multi-disease and phase I studies. The RRC submission form collects data on competing studies, and the estimated accrual potential for the relevant target patient population. Studies are given highest priority when investigator-initiated, if the research question arose from primary research conducted at FCCC or by a FCCC investigator, if a novel drug or treatment assignment strategy is under investigation, or when a FCCC investigator played an integral role in trial design and development. However, there is also a strong commitment to cooperative group trials across the disease teams at Fox Chase.

All studies are reviewed by the RRC. Cooperative group studies and other studies which have undergone peer-review at NIH are not reviewed for scientific content or study design, but only for programmatic priority and for the feasibility of accrual targets. RRC criteria are applied to all other studies in a consistent manner using a standardized written review form. All new protocols are reviewed by the full committee, which includes a mandatory review of biostatistics and the DSM plan. There is no process for expedited review of new studies. Individual comments are designated as either “mandatory” or “advisory”, and approximately 60% of new studies require a response from the investigator and/or revised protocol documents before the study can be approved for submission to IRB. Local investigators are familiar with the consistency of this review process, including the expectation that a written response and/or amendment is often required. If an RRC member contributed to the study design, either as principal investigator or co-investigator, that member is excluded from voting to avoid conflict of interest. In addition, if the biostatistician on RRC is also the study biostatistician, approval is contingent on review by another staff member from Biostatistics. All RRC members file conflict of interest reports annually. In addition, they are required to report new potential conflicts of interest within 30 days to the chair of the RRC. No reviewer with a potential conflict of interest may vote on the approval of a study with which said reviewer has a potential conflict. In the event that the RRC Chair has a potential conflict of interest with a given study, he shall recuse himself and the Associate Chair of the RRC, or another RRC member, shall chair the committee during discussion and voting on the trial in question, and prepare the written comments returned to the Principal Investigator. Failure to disclose or recuse when necessary shall be referred to the President of FCCC.

After initial review, the written comments are returned to the investigator within 48 hours after each weekly meeting (Appendix). Protocols that are not initially approved require a written response from the investigator with or without protocol amendments or supporting documentation. If the investigator resolves all mandatory comments in writing, the protocol can be approved by the Chairperson between meetings. If all mandatory comments are not clearly resolved, the protocol is referred back to the primary and secondary reviewers for formal discussion at the next full meeting.

Mandatory review elements include:

- **Documentation.** Confirmation of protocol completeness, status of preliminary review at the level of the department and sponsoring agency, and signatures.

- **Scientific and Clinical Rationale.** Is this an important question related to cancer biology and/or therapy? Is the overall approach justified by appropriate pre-clinical and clinical background material?

- **Study Design.** Is the design appropriate, including phase of study, treatment modalities, dose levels, randomization, dose modifications, and controls? Are the experimental methods for clinical and laboratory analysis adequately detailed and sound?

- **Feasibility.** Are there adequate numbers of potentially eligible patients to complete accrual in a timely fashion? To what extent does the proposed study compete with existing and planned studies? Are the forms and data monitoring procedures adequate? Is there evidence that the proposed clinical and laboratory analysis can actually be performed by the co-investigators? For CCOP Research Base protocols, is there evidence of interest by CCOP PI and need for CCOP participation in the research?
- **Biostatistics.** Is there a primary study hypothesis that can be tested through statistical analysis? Is the power and precision of the statistical analysis clearly stated with appropriate sample size justification? Is there an interim analysis of efficacy and/or provisions for early stopping in the event of excessive toxicity, if appropriate? If the study is investigator-initiated, has a statistician been included as co-investigator?

- **Data and Safety Monitoring.** Is the protocol-specific DSM plan appropriate based on the size, complexity, risk, phase, and sponsorship category? Is a study-specific DSM Board required? If the study will utilize a DSMB, have appropriate membership and organizational criteria been provided?

- **Race, Gender, and Age.** If a specific population is excluded, has this been adequately justified on the basis of tumor biology and/or access to clinical resources? If a substantial number of minority subjects are anticipated, how will the findings be interpreted in different populations?

*Not a reviewed element for cooperative group and other NIH funded studies.

Consonant with its responsibility for global oversight of the clinical trials portfolio and utilization of the center’s resources, the RRC is charged with identifying low-enrolling trials. Trials with accrual which is <50% of projected will be recommended for closure. Investigators will have the opportunity to provide a written plan to enhance accrual. This will be reviewed by the RRC Chair with or without full committee review. If the plan is accepted, the study will be reviewed again after 6 months. If substantial improvement is not demonstrated, the RRC Chair has authority to close the study. This decision will be communicated to the full committee as well as to the APCR, and the Regulatory Affairs team in the CTO. Regulatory Affairs will take responsibility for reporting study closure to the IRB as well as to any relevant external agencies or other clinical trials sites.

**Institutional Review Board (IRB)**

All activities involving human subjects, whether in research, development, demonstration or other activities, must be reviewed and approved by the Institutional Review Board (IRB) prior to implementation. The IRB functions as the human subjects review committee for all three divisions of FCCC and reports to the CCSG Associate Director for Academics and institutional Chief Academic Officer (J. R. Beck). The requirement for prior review of a protocol involving human subjects by the IRB is applicable regardless of the source of support for the research. Further, it is applicable whether the research is performed on the premises of FCCC or elsewhere, including collaborating sites, Network community affiliates, or other participating institutions. Cooperative group studies that have been reviewed by the Central IRB (CIRB) will not undergo review by the FCCC IRB; the CIRB will serve as the IRB for these trials.

The purpose of the IRB is to promote the continuance of research involving human subjects by assuring compliance with the Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) regulations and to assure protection of the rights and welfare of human subjects without interfering unduly in the conduct of a project. The IRB is responsible for the interpretation of governmental and institutional policy on human subjects and stands as our local authority in this area. As such, the IRB has the authority to disapprove, modify or approve each individual study based on its assessment of the adequacy of the protection of human subjects.

The IRB requests regular and ongoing progress reports from the investigators. The IRB may suspend, terminate or restrict studies as appropriate. The IRB submits all meeting minutes to the Executive Committee of Staff (ECOS) for review, and ECOS reports on IRB activities to the Board of Directors on a regular basis. In addition, the IRB Administrator and Coordinator report IRB activities to the Chief Academic Officer regularly. The IRB is composed of no fewer than ten (10) members who meet bi-monthly. Of the members, at least one will have primary concerns in scientific areas, one will have primary concerns in non-scientific areas and one will be unaffiliated with FCCC or any of its employees. Currently, the IRB has 32 active members, 24 have primary concerns in scientific areas, 8 have primary concerns in non-scientific areas, and 8 are unaffiliated with FCCC or its employees. The present IRB Co-Chairs are Adam Cohen, MD, Assistant Professor of Medical Oncology, and Clifford S. Perlis, MD, Assistant Professor of Medicine. There is no term limit to membership. IRB members are expected to objectively evaluate all protocols presented to the IRB to ensure adequate protection of human subjects, and must sign a conflict of interest statement annually. The members must excuse themselves from discussion or voting in the case of a trial where a conflict of interest exists. In addition, they are required to report new potential conflicts of interest within 30 days to the chair of the IRB. In the case that the potential conflict is held by one of the IRB Co-Chairs, new potential conflicts must be reported to the Chief Academic Officer within 30 days. In the event that the IRB Co-Chair has a potential conflict of interest with a given study, the study should be referred to a session chaired by the alternate Co-Chair. Failure to disclose or recuse when necessary shall be referred to the President of FCCC. Any member with a conflict
of interest must abstain from voting on a protocol with which he/she has a conflict. All IRB members are required to complete member orientation and educational programs, as well as supplemental education and training, as appropriate.

Protocol Management Executive Committee (PMEC)

A Protocol Management Executive Committee (PMEC) oversees CTO activities and interactions among the regulatory bodies (RRC and IRB), DSM boards, research programs, and other hospital departments. This committee provides a flexible multi-disciplinary platform to discuss and resolve a number of issues that impact the integrity of data collection and safety of study participants. Core membership on this Committee includes the Facility Directory (M. von Mehren), Coordinator of Clinical Investigations (L. Kish), and all Managers and Directors of the PMO. PMEC meets quarterly, or more often as needed, with invited participation from key areas and departments on a rotating basis, including outpatient nursing, inpatient nursing, pharmacy, phase I program, medical records, radiology, IRB, contracts and agreements, and clinical billing. Minutes of each meeting are maintained with an emphasis on data and safety monitoring, quality assurance, and operational functions.

Reports and recommendations from the Phase I-II Committee will be reviewed for action at every meeting to reinforce the monitoring of investigator-initiated phase I-II studies, which may include studies with NCI sponsorship. As such, PMEC has formal responsibility to enforce recommendations for study closure (or other actions) that may emanate from RRC and the Phase I-II Committee. If an NCI-sponsored study is suspended or terminated as a result of these recommendations, NCI will be notified within 48 hours of PMEC action.

Phase I - II Program and Committee

Fox Chase investigators have consistently demonstrated a strong commitment toward the design and activation of phase I-II studies with investigational agents. Together, these account for more than 50% of the average annual protocol accrual among cancer treatment studies. Many of these studies are investigator-initiated or developed in collaboration with cooperative groups or the pharmaceutical industry. Each study has individualized requirements for data and safety monitoring, reflecting the diverse nature of agents under evaluation. In support of these unique and usually complex studies, a dedicated phase I team has been established in the Protocol Office and a centralized biospecimen facility (the Protocol Support Laboratory) has been created for collection, processing, analysis, and shipping of patient samples.

The overall process of data and safety monitoring has been facilitated through regular meetings convened by the director of the phase I program (A. Olszanski, MD) to review toxicity, dose escalation and laboratory correlates for all of our phase I and investigator-initiated phase II studies. Objective review of toxicity is essential to support the designation of dose-limiting toxicity (DLT), determination of the maximal tolerated dose (MTD), assignment of dose levels, and to provide overall guidance for active studies. The Phase I team meets weekly to review the enrollment and progress of every patient enrolled to a phase I trial. In addition, the Phase I-II Committee (see below) constitutes a Data Safety and Monitoring Board to review formally the progress of all investigator-initiated phase I and II trials. These meetings have been coordinated with the ongoing scientific review process (RRC) to facilitate the objective assessment of accrual goals and scientific prioritization, which can quickly change based on emerging preclinical and clinical data.

The Phase I-II Committee is chaired by B. Burtness. Committee members include the Coordinator of Clinical Investigations (L. Kish), A. Olszanski, J. Stein, S. Roethke, R. Mehra, M. Buyyounouski, and C. McAlleer. Ad hoc members include the RRC Chair (H. Borghaei), Director of the Protocol Management Facility (M. von Mehren, MD), Manager of the Protocol Support Laboratory (K. Alpaugh, PhD), Director of the Biospecimen Repository (D. Connelly, PhD), Chair of Biostatistics (E. Ross, PhD) and Chair of Medical Oncology (M. Cristofanilli, MD).

On a quarterly basis (or more often if indicated based on rapid accrual, AE frequency, achievement of pre-defined endpoints or need for an interim analysis, or problems identified during QA audits) the Committee will review the general progress of all ongoing investigator-initiated phase I and II studies, including those sponsored by NCI. Most of these studies will not otherwise be externally monitored and/or audited, and the Committee will therefore have primary responsibility in this area. In this regard, the Committee will function similar to a DSM Board for these studies, unless an individual protocol already has an independent study-specific DSM Board, which is not generally required for phase I-II studies.

Prior to the meeting, a summary is prepared of all active phase I trials, including accrual status (open, enrolling, on-hold, or suspended), current dose level, cumulative record of patients accrued on-study, cumulative record of
observed toxicities (with an emphasis on unexpected toxicities of any grade, dose-limiting toxicities, and adverse events), together with recent and planned protocol amendments. The biostatistical and analytic plan for each study is also reviewed to ensure that boundaries for early-stopping and/or interim analysis are respected. This will therefore constitute a "real-time" review. As appropriate, operational elements of the review will include items such as patient eligibility (including any waivers or exceptions to the eligibility criteria), bottlenecks in screening and accrual to protocols, and a review of any technical challenges such as biosample procurement and processing.

While the focus of the Committee is on phase I studies, this Committee will also review similar data on investigator-initiated phase II studies that are not otherwise externally monitored and/or audited, including any studies with NCI sponsorship. Review of selected phase II studies by this committee is appropriate to maintain a heightened awareness of the potential for unexpected and serious toxicity. As the Committee chair is primarily a phase I investigator and is not expected to serve as PI for phase II studies, this process minimizes the potential for conflict of interest in the review of phase II trials. In the event of a conflict of interest for a Phase I protocol run by the Chair, another committee member will chair the discussion and voting, and the Chair will recuse herself.

Meeting minutes will be prepared within 2 working days by the Committee Chair (Burtness, MD) and distributed to the principal investigators, protocol staff, and PMEC. The Committee will have the power to recommend study suspension, closure, or amendment in response to toxicity, adverse events, or significant operational issues. These recommendations will be communicated to the Associate Director, Clinical Research, who will decide on study closure. In the event of a conflict of interest arising for the APCR with respect to the study to be closed, the matter will be referred to the PMEC for rapid resolution.

In addition to written minutes and reporting as noted, written documentation of Committee findings on individual studies will be incorporated in the study-specific material submitted for ongoing (annual) review through RRC and IRB. Finally, in the event of suspension or termination of an NCI-sponsored study, NCI will be notified within 48 hours of APCR or PMEC action in response to the Committee recommendation.

**Extramural Data and Safety Monitoring Committee**

The Extramural Data and Safety Monitoring Committee (EDMSC) was established as an oversight committee for research conducted at Fox Chase Affiliate sites. The Committee is chaired by Michael Millenson, MD. The Committee meets at least semi-annually to review all proposed extramural investigator-initiated research, or FCCC investigator-initiated trials which are activated as multicenter studies. The committee evaluates the proposed data and safety monitoring plan. The Committee will vote to approve the plan and their support as the oversight committee as applicable. The Committee will review each active supported study according to their approved policies. The OER will prepare study data. The review will consist of no less then a cumulative list of all reported toxicities, all grade 3, 4, and 5 adverse events, a summary of any pertinent finding from monitoring and auditing and a description of all known or suspected protocol deviations, demographic information, protocol amendments and other pertinent regulatory history. Meeting minutes are prepared and all recommendations are submitted to the Associate Director, Clinical Research, as well as the Vice President of Extramural Programs. The APCR will be responsible for implementing decisions respecting study closure. In the event of a conflict of interest for the APCR, the matter will be referred to the PMEC. Regulatory Affairs and the ERP staff will ensure that IRB, all external sites, and appropriate granting agencies and/or FDA are alerted as necessary.

**Fox Chase Quality Assurance (QA) Program**

Development of a robust departmental Quality Assurance (QA) Program has been a high priority, and this contributes substantially to our overall data and safety monitoring plan. Our protocol QA program is directed by a full-time quality assurance team, who report to the Director of Quality Assurance (C Jerome), with assistance from key CTO staff. Responsibilities include technical review of protocol documents, internal auditing of cases enrolled on investigator-initiated studies, development of written standard operating procedures (SOPs), and facilitation of external cooperative group audits at Network hospital sites. Written summaries of internal QA protocol and data audits are reviewed by the clinical research team and local principal investigator, and a written report is then submitted to the PMEC, and/or the Phase I-II Committee as appropriate. Through this process, these committees provide oversight for QA activities on investigator-initiated studies.

In view of the increased complexity associated with our ongoing studies, a working group has been established to develop and revise written SOPs, which then receive formal review, approval, and structured implementation. All existing SOPs are reviewed yearly and updated as needed, and numerous new SOPs have been developed to
address changes in the research environment and to improve the quality of research and data management. These processes can have a direct impact on patient safety and regulatory compliance. For example, our ongoing review and verification of patient eligibility has demonstrated a positive impact on the confirmed eligibility rate for recent accruals while promoting amendments to clarify ambiguous eligibility requirements in the protocol text. Accurate determination of eligibility helps to protect human subjects from receiving inappropriate and potentially toxic therapy. Representative SOPs that will have a direct impact on data and safety monitoring are summarized below:

Q009 QA Review Process for Investigator-Initiated Draft Protocols. Describes a formal process for early review of draft study documents by the clinical research coordinator, clinical research associate (data manager), and QA coordinator to verify feasibility, eligibility criteria, and other protocol documentation. A written report is prepared for review with the principal investigator in conjunction with reviews performed by RRC and IRB.

C021 Eligibility Review and Confirmation Process. Includes review of signed informed consent document, collection and review of source documentation, and independent review of eligibility documentation by a second party, central registration, and entry of accrual in protocol database.

Q002 Preparation for Phase II Data Safety Monitoring Committee (DSMC) Meeting. Addresses required elements for PIs to submit for review to the DSMC for ongoing review of these issues at their regular meetings.

Q0006 FCCC Internal Auditing Policy for FCCC Investigator-Initiated Studies. Audits will be conducted in accordance with Good Clinical Practice (GCP) guidelines. For active studies, cases will be selected at random. Cases will also be audited following protocol closure, or if required for cause. The first case accrued on a newly activated study will be audited as soon as practical to confirm eligibility, informed consent, available treatment data, and applicability of protocol requirements to avert potential deficiencies in subsequent cases. Cases from all participating sites will be included in the audit process. A minimum of 20% or six cases, whichever is greater, will be randomly selected for audit. In addition, all cases with a reported partial or complete response will be audited and the responses will be confirmed by the Response Verification Committee. Regulatory compliance, including IRB documentation and content of the informed consent document will be reviewed. Pharmacy records will be reviewed, as appropriate for investigational agents. A written audit report will be generated, reviewed with appropriate staff, and an opportunity will be provided to respond to cited deficiencies.

Q0007 Internal Auditing Policy for ECOG cooperative group studies (FCCC and affiliated institutions). Provides a process for education and internal review of documentation and procedures independent of routine ECOG audits. A minimum of 20% or three cases are randomly selected for on-site audit on an annual basis using standard cooperative group procedures. New affiliates will be audited after the first two patients have been entered on ECOG trials. In addition, the first case entered on a newly opened study will be audited as practical to confirm eligibility, informed consent, available treatment data, and applicability of protocol requirements to avert potential deficiencies in subsequent cases. In addition, all audited cases with a reported partial or complete response will be confirmed by the Response Verification Committee. A written audit report will be generated, reviewed with appropriate staff, and an opportunity will be provided to respond to cited deficiencies.

Q010 FCCC Procedures for Reporting Protocol Deviation. Provides a standardized mechanism and form to document and report major protocol deviations, defined as a failure to adhere to protocol-specific requirements pertaining to the consent process, eligibility, treatment, and/or toxicity management.

Q011 Corrective Action Plan for Deficiencies Identified in the Medical Record Chart. Provides a means to notify medical records regarding deficiencies and/or documentation errors detected during routine data monitoring or audits.

CO47 Adverse Event and Serious Adverse Event Reporting. Provides general guidelines for identification and classification of adverse events together with detailed instructions and contact information for prompt reporting of adverse events to supplement protocol-specific guidelines.

N005 Regulatory Files for Affiliates Participating in Fox Chase Cancer Center (FCCC) Investigator-Initiated Protocols - Contents, Organization, Maintenance and Access. Guidance for joint maintenance of all regulatory documents for each affiliate institution participating in FCCC investigator-initiated protocols in accordance with Federal Regulations and ICH Good Clinical Practice Guidelines.

N007 Clinical Trials Operations (CTO) Multi-Center Team (MCT)/QA Scheduling and Conducting Monitoring Visits at Affiliate Sites. To establish a standard process for scheduling and conducting
monitoring visits of Affiliate Sites by the MCT. On-site monitoring visits are performed to ensure that the rights and well-being of human subjects are protected; reported trial data are accurate, complete and verifiable; and the conduct of the trial is in compliance with the currently approved protocol and in accordance with Good Clinical Practices Guidelines (GCP). The MCT will utilize the monitoring visits as an educational vehicle for the Clinical Research Coordinator/Associate (CRC/CRA) at Affiliate Sites.

N008 Registration of Patients from Affiliate Institutions for Fox Chase Cancer Center Investigator-Initiated Studies. Standardized process by which patients from affiliate institutions can be registered on Fox Chase Cancer Center Investigator-Initiated studies.

R016 Preparation and Distribution of protocol Amendments, Addendums, Revisions, and/or Updates to the FCCC Research Review Committee and the FCCC Institutional Review Board. Process by which updates are distributed to inform the RRC, IRB and participating investigators about changes to a research trial.

Key Processes that Support Data and Safety Monitoring

Review of New Studies

Review of a new study begins with submitting a collated set of complete protocol documents. Information on required elements, forms, contacts, and procedures is available through the local protocol website [https://www.protonet.fccc.edu/fccc/pims], including a sample protocol and standardized informed consent language.

Each new submission must include:

- A completed "Request for Protocol Review Form" (Appendix), which includes a study synopsis, signatures of approval from co-investigators and participating departments, identification of resources and funding, description of biosample requirements, and attestation regarding potential conflict of interest.
- A fully developed and complete protocol document with informed consent, appendices, and supplemental materials.
- A protocol-specific data and safety monitoring plan should be appended, or fully described within the protocol text.
- If an investigational agent is being utilized, a copy of the full investigational brochure should be provided.
- Actual survey tools and/or data management forms should be appended, or a description of standardized forms that will be utilized should be described in the protocol text.
- Evidence of compliance with institutional requirements for investigator-initiated research studies, including the identification of a biostatistician (either internal or external) to serve as a co-investigator.

Following receipt of a complete study, primary and secondary reviewers are designated to lead discussion at the next RRC meeting. Investigator-initiated studies are concurrently assigned to a team in the Clinical Trials Operations for review of operational issues. The IRB will not review new protocols until they have been approved by RRC, with the exception of preliminary review of grant applications. To allow time for response to RRC comments, and to avoid delays in IRB review, RRC meets three times per month or weekly. The majority of studies are reviewed within one week of initial submission and structured written comments are returned to investigators within 48 hours (Appendix).

In summary, protocols cannot be activated for patient accrual until they have met the following specific criteria:

- Full-Board approval by both RRC and IRB, which includes review of prioritization and feasibility, approval of the proposed DSM plan, and finalization of the informed consent document.
- Establishment of a protocol-specific DSM Board, if required by an individual study.
- Availability and IRB-approval of current complete sponsor-approved protocol documents.
- Confirmation of study review, approval, and activation by the sponsoring agency.
- Completion of a study initiation meeting with the principal investigator, protocol management team, and pertinent support facilities. Pharmaceutical industry-sponsored studies generally require separate site initiation meetings with the sponsor and/or designated contract research organization (CRO).
Ongoing (Annual) Review of Research

Ongoing RRC and IRB review is a mandatory process for all active studies. At a minimum, a formal review is performed at least once every 364 days. Protocols that are closed to patient accrual, but still collecting data from surviving patients, receive an abbreviated review. In total, approximately 300 ongoing reviews are performed on a yearly basis. To initiate the ongoing review process, a draft annual report is generated from the protocol management database and distributed to the responsible Clinical Trials Operations team (Clinical Research Coordinator and Clinical Research Associate) for verification of accrual, survival, adverse events, and protocol status. After updating, the report is reviewed with the principal investigator, who indicates by signature whether to request renewal or closure. The annual review includes a tabular summary of all adverse event reports (AERs) extracted from the protocol database for each study. Prior to the ongoing review, individual AERs will have already been submitted in detailed format to IRB, in accordance with the reporting requirements for each study. If appropriate, supplemental reports, protocol amendments, significant literature, and/or changes in the informed consent document can be appended to the annual review. Completed ongoing reports are submitted initially to RRC for review of actual and targeted accrual within the context of stated scientific goals and objectives. Following review by RRC, the signed and annotated reports are forwarded to IRB for primary review of safety, ethics, and the informed consent process. The IRB may approve the study without change, request additional information, propose modifications or amendments, or initiate immediate suspension and closure based on unacceptable risk to participants.

RRC Criteria for Ongoing Review

- **Full Approval for 12 months.** Full approval is generally granted if actual accrual is within 50% of target for the preceding 12 months and the scientific objectives remain valid. Approval is also granted for national cooperative group studies with low accrual at our institution, provided that the study objectives remain valid in accordance with ongoing review at the cooperative group.

- **Approval for 6 months with a warning to the investigator.** This category requires mandatory interim review within 6 months together with a response from the investigator. In general, a 6 month approval is granted if accrual is below 50% of target for the preceding 12 months or if there are concerns regarding the validity of scientific objectives. In the case of a national cooperative group study, a warning may be issued if it appears that eligible patients are not being enrolled due to investigator bias, lack of prioritization, or other factors.

- **Recommended for closure and tabled without approval.** This action is generally reserved for protocols without any accrual during the preceding 12 months, or for protocols that have not improved accrual or been appropriately amended after a previous 6 month warning. This category is also used for protocols that have exceeded targeted accrual without amendment or justification.

IRB Criteria for Ongoing Review

- **Full approval.** Full approval is granted for protocols if actual accrual is within 50% of the target for the preceding 12 months, the scientific objectives remain valid and the measures to ensure the protection of human subjects continue to be appropriate. Approval is also granted for national cooperative group studies with low accrual at our institution, provided that the study objectives remain valid in accordance with ongoing review within the cooperative group. Ongoing review must occur in less than 1 year from the previous review date, initial review or ongoing review and must be in accordance with Title 45 Code of Federal Regulations Part 46 Protection of Human Subjects.

- **Approval for 6 months with a warning to the investigator.** This category requires mandatory interim review within 6 months. Part of that early re-review is a response from the investigator to the concerns raised by the IRB. In general, a 6 month approval is granted if accrual is below 50% of target for the preceding 12 months, if there are concerns regarding the validity of the scientific objectives, or if there are factors that may cause undue risk to human subjects. In the case of a national cooperative group study, a warning may be issued if it appears that eligible patients are not being enrolled due to investigator bias, lack of prioritization, or other factors.

- **Not approved.** Those studies which may jeopardize the rights and welfare of human subjects or those that have had insufficient accrual for some period of time will not be approved for continuation.

- **Immediate suspension or closure.** Those studies that may jeopardize the rights and welfare of human subjects will be suspended or closed. Suspensions and closures will occur if protocol related adverse
events occur, the protocol or consent form fail to include necessary information, or the investigator is not in compliance with IRB requirements.

Adverse Event Reporting and Monitoring

Serious adverse events (SAE) experienced by a patient on a clinical trial must be reported according to standard requirements for investigational agents, commercial non-investigational agents, as well as non-pharmaceutical interventions, including radiation therapy, invasive biosample collection, and behavioral interventions. Specific reporting procedures are included in all cancer treatment studies, and are reviewed during protocol submission by RRC, IRB, and the Protocol Office. Ultimately, it is the responsibility of the principal investigator to monitor all adverse event reports and verify that appropriate procedures are being followed.

By federal regulatory guidelines, an AE is defined as “serious” according to the following criteria:

- Fatal or life-threatening (i.e., results in an immediate risk of death), with exceptions for expected reversible hematologic toxicity.
- Permanently or substantially disabling
- Requires or prolongs hospitalization (only if related to an unexpected complication)
- Gives rise to a congenital anomaly, new (secondary) cancer, or medication overdose
- Any other event the investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect or precaution.

Routine toxicity assessments and reporting of adverse events are graded according to the most recent version (currently v3.0) of the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute.

Adverse events which do not meet the definition of an SAE also require timely reporting dependent upon grade, attribution, and whether the event is expected or unexpected.

Part of the decision process for expedited reporting is based on the assignment of attribution, which reflects the determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories are:

- **Definite** - The adverse event is clearly related to the investigational agent(s).
- **Probable** - The adverse event is likely related to the investigational agent(s).
- **Possible** - The adverse event may be related to the investigational agent(s).
- **Unlikely** - The adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s).

As a minimum standard, it is expected that FCCC investigator-initiated phase I-II trials that employ investigational agents will utilize the CTEP paradigm for adverse event reporting. Representative guidelines from CTEP templates for investigational treatment studies are summarized in Tables 1 and 2. Prevention trials with investigational agents are generally coordinated through the Division of Cancer Prevention (DCP), and DCP guidelines for reporting will be followed for those studies. It is also recognized that individual sponsors may incorporate supplemental reporting requirements. If investigational agents are supplied through the CTEP Investigational Drug Branch (IDB), it is expected that the on-line Adverse Expedited Event Reporting System (AdEERS) and Clinical Data Update System (CDUS) will be utilized, as appropriate, and this should be reflected in the protocol documentation.

Phase I, II, and III studies with commercial (non-investigational) agents have a modified paradigm. For any study with toxicity attributable to a commercial (non-investigational) agent, the MedWatch 3500 form should be used to file a report with FDA. This requirement would apply to any unexpected (not listed in the package label), life-threatening (Grade 4) or unexpected, fatal (Grade 5) adverse event with an attribution of possible, probably or definite should be reported in 10 working days. The AE should be reported on FDA Form 3500 MedWatch (http://www.fda.gov/medwatch.) The completed form should be forwarded to the FDA by mail, completed electronically on-line, or FAXed. A copy should be provided to the local IRB and sponsor, as appropriate.

All protocol AERs at FCCC are logged in the protocol management database in summary form and tabulated as a routine component of the mandatory ongoing review process involving RRC and IRB. For treatment protocols managed by the Protocol Office, the initial draft AER is prepared by the Protocol Office team in consultation with clinical staff, reviewed by the local principal investigator, and submitted to the local IRB and other regulatory agencies with copies retained in the master protocol file.

All adverse events must be reported promptly to the IRB. These reports are reviewed by the IRB Chairman, discussed by the IRB as necessary, and filed in the individual protocol folders in the IRB Office. All serious protocol
related adverse events are recorded in the monthly meeting agendas and reviewed by the IRB with the subsequent action recorded in the minutes of the meeting. The IRB may require continuing review at more frequent intervals if it is determined the degree of risk is more significant due to unforeseen problems or accidents experienced by study participants.

Prompt review of AERs on an ongoing basis is the direct responsibility of the local principal investigator, who should ensure that reports are promptly submitted as per guidelines.

**Investigator Responsibilities for Data and Safety Monitoring**

The principal investigator (PI) of each study is ultimately responsible for every aspect of the design, conduct, and final analysis of their protocol. As such the study PI is responsible to ensure that all protocols must include a data and safety monitoring plan (DSMP) together with procedures to support its implementation. In certain cases, a study-specific data and safety monitoring board (DSMB) will also be utilized.

**General Study Requirements**

- Investigators must be trained and certified in human subjects research and should be aware of HHS, NIH, and FDA policy as referenced in the introduction to this plan.
- All studies must have an explicit structure for adverse event determination, monitoring and reporting to the local IRB, FDA and, if applicable, NIH, the study sponsor, or other agencies. Standard Clinical Trials Operations policies and procedures can be cited, if appropriate.
- The proposed schedule for reporting adverse events to the DSMB must be described. The proposed schedule should include a system for sending DSMB reports regarding safety issues to the study PI. In multi-site studies, the study PI is responsible for sending these DSMB reports to individual site PIs, who in turn are required to distribute these reports to their local IRBs. ERP and Regulatory Affairs assist with this function.
- It should be stipulated that all investigators will be notified following the reporting of an adverse event or study modification.
- Protocols must include the proposed human subjects consent form and describe procedures for protection of human subjects.
- A brief description of specific quality assurance procedures should be included, such as random chart audits and verification of eligibility. Alternatively, if the study is managed by the Clinical Trials Operations, include a statement that standard Clinical Trials Operations policies and procedures will be employed.
- All masked studies should describe a randomization scheme, and specific criteria and procedures for unmasking. If a DSMB is not proposed, the application should also designate individuals with access to unmasked data.

**Utilization of a Data and Safety Monitoring Board (DSMB)**

The DSMP must explicitly address whether or not a study-specific data and safety monitoring board (DSMB) will be utilized, which is generally required if the proposed study meets any of the following criteria:

- The study is a randomized Phase III clinical trial
- The study is a multi-site clinical trial
- The study includes a high risk intervention (such as allogeneic hematopoietic stem cell transplantation or gene therapy)
- The study proposes to include over one hundred participants
- The principal investigator feels that a study-specific DSMB would enhance the quality of data and safety monitoring, even if a DSMB is not explicitly required in accordance with the above criteria.

*Note:* In these circumstances, an investigator may request RRC-IRB approval for alternate data and safety monitoring programs that do not include a formal DSMB, but this will require strong justification, such as utilization of well-established or minimal-risk interventions.
If the PI believes that an independent DSMB is required for adequate subject safety, the protocol (or supplemental documents) should address the following items:

- Proposed frequency of DSMB meetings
- List of data items to be provided to the DSMB
- Nomination of prospective DSMB members, including pertinent information for each prospective member, such as a *curriculum vitae*, list of current affiliations with pharmaceutical and biotechnology organizations including the name of the company and the type of affiliation (e.g., stockholder, consultant), as well as any other relationship that could be perceived as a conflict of interest related to the proposed study.

*Note:* Nominations are subject to approval by RRC and IRB as part of their review of the DSM plan. DSMB members should have no direct involvement with the study or conflict of interest with investigators conducting the study.

### DSMB Requirements

An independent DSMB must be established prior to trial initiation. At a minimum, a DSMB requires three clinicians/investigators experienced in the treatment modalities and disease under study, a clinical biostatistician, an individual with expertise in the regulatory aspects of clinical trials, and a layperson patient advocate. No members of a DSMB will be associated with the trial.

For non-cooperative group, limited-institution phase III studies without NCI/NIH monitoring, the PI at the lead institution will be responsible for monitoring the study and establishing the independent DSMB. RRC and IRB will be required to review and approve data and safety monitoring plans and verify the existence of an appropriate DSMB prior to study activation.

Phase III protocols must include:

- Plans for establishment of an independent DSMB (or utilization of a standing DSMB).
- Plans for securing support, resources, and funding appropriate for the DSMB to meet its requirements as listed below.
- A data processing and analysis unit administered by a designated individual other than the PI(s) of the trial. This individual may report to the PI. In all cases, all data from this unit must be directly available to the DSMB, RRC, IRB, and PMEC upon request.
- Procedures for quality assurance/quality control, data management, and analysis.
- Plans for notifying subjects of trial results after the conclusion of the trial and providing the subjects' health providers with the appropriate information from the trial, as needed, concerning the individual subject (e.g., cessation of drugs, changes in dosage, etc.).

Once a DSMB is established, its initial tasks are to review the entire study protocol, the Manual of Procedures (if appropriate), and the informed consent form with regard to recruitment, randomization, intervention, subject safety, data management, plans for auditing of primary subject records, quality control and analysis, and to identify needed modifications. The DSMB shall then identify the relevant data parameters and the format of the information to be regularly reported. If the need for modifications to the protocol, Manual of Procedures, consent form, etc., is indicated, the DSMB shall postpone its recommendation for the initiation of subject recruitment until after the receipt of a satisfactory revised protocol.

### DSMB Responsibilities

The DSMB must meet on a regular schedule, of not less than twice per year, over the course of study to:

- Review data (including masked data) over the course of the trial relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trials operating procedures, form completion, intervention effects, gender and minority inclusion and subject safety.
- Identify problems relating to safety over the course of the study. Inform study PI via written report, who in turn will ensure that all clinical site PIs receive this report.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety and endpoints.
- At each meeting, consider the rationale for continuation of the study, with respect to recruitment, progress of randomization, retention, protocol adherence and compliance, data management, safety issues, and outcome data, if relevant, and make a recommendation for or against continuation of the trial.
- Provide the PI, PMEC, Senior Vice President of the Extramural Research Program (as applicable) and Chairs of RRC and IRB with written reports following each DSMB meeting.
- Review manuscripts of trial results prior to submission for publication.
- If there is more than one clinical site, the study PI is responsible for sending the reports to individual site PIs, who in turn are required to distribute the report to their local IRBs, as detailed in the NIH "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999).

**DSMB Meetings**

DSMB meetings will be divided into three parts. First, an open session in which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. Issues discussed may include accrual, protocol compliance, and general toxicity. Outcome results must not be discussed during this session. Following the open session, a closed session involving the DSMB and study statistical staff will be held. The statistician[s] should present and discuss the outcome results with the DSMB. A final executive session involving only DSMB members should be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

**DSMB Recommendations**

DSMB recommendations should be based on results for the trial being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the PI to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of DSMB recommendation(s) will be given to the trial principal investigator, PMEC, chairs of RRC and IRB and the Associate Director, Clinical Research. If the DSMB recommends a study change for patient safety or efficacy reasons, or that a study be closed early due to slow accrual, the trial principal investigator must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator does not concur with the DSMB, then the Associate Cancer Center Director for Clinical Research must be informed of the reason for disagreement. The ACDR will make the final determination. In the event of a conflict of interest on the part of the ACDR, the matter will be referred to the Chair, RRC, Chair, IRB or the PMEC. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision.

**Release of Outcome Data**

In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment. At this time, the DSMB may approve the release of outcome data on a confidential basis to the trial principal investigator for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

**Confidentiality Procedures**

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB, except as indicated above in the Recommendations section, until the recommendation to release the results are accepted and implemented. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.
Conflict of Interest

DSMB members are subject to FCCC policies regarding standards of conduct. Individuals may not serve on an independent DSMB if a conflict of interest exists. Conflict of interest must be declared at the initiation of the DSMB and annually thereafter. If a conflict of interest arises during the course of the year, prior to a DSMB interim review, this must be declared and the principal investigator will be required to replace the DSMB member who has a new conflict of interest. Failure to disclose this information, or to withdraw from the DSMB, will be referred to the President of Fox Chase, who will resolve the matter. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page Il-12, and 45 CFR Part 94. Potential conflicts which develop during a member’s tenure on a DSMB must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSMB will be made in accordance with the institution’s policies.

Sponsorship of Clinical Trials and Monitoring Required

The extent of the monitoring and reporting period varies by the degree of risk encountered by patients on the study, the study sponsor, the type of agent or agents involved, and the phase of the clinical trial. Given the diversity of clinical trials at FCCC, our Data and Safety Monitoring Plan is tailored to 1) ensure monitoring of all clinical trials, 2) meet the reporting requirements of individual trial sponsors, and 3) minimize redundant monitoring and reporting, while retaining a degree of cross-verification among systems.

Several features apply to all studies, regardless of sponsor:

- All studies require a local principal investigator trained and certified in human subjects research.
- All studies require an explicit data and safety monitoring plan that is approved by RRC and IRB prior to activation of accrual. Adequacy of the plan will be reviewed on a yearly basis.
- All SAEs at FCCC and at affiliate sites are required to be reported to the local IRB regardless of sponsor.
- All internal and external SAEs are tabulated as a required component of the RRC and IRB ongoing review process.
- Based on internal or external SAEs, the local IRB retains authority to close any active study to further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

National Cooperative Oncology Groups

FCCC participates in clinical trials sponsored by the Eastern Cooperative Oncology Group (ECOG), the Gynecologic Oncology Group (GOG), the American College of Surgeons Oncology Group (ACOSOG), the National Surgical Adjuvant Breast and Bowel Project (NSABP), the South West Oncology Group (SWOG), the Radiation Therapy Oncology Group (RTOG) and the NCI Clinical Trials Support Unit (CTSU).

Each of these national groups conducts a range of therapeutic (phase I, II, and III) and non-therapeutic clinical trials. Each group maintains a contract with a local principal investigator (who are all members of the FCCC full-time professional staff) and this contract clearly specifies overall data and safety monitoring requirements, including audit and quality assurance procedures. Individual trials also must contain specific language related to adverse event reporting, as well as data and safety monitoring. In addition, Fox Chase requires that each individual trial have a local principal investigator who is responsible for all communications with RRC, IRB, and the CTO. All national cooperative group trials are submitted to RRC and IRB for ongoing review. In general, we will not place additional reporting requirements on staff supporting these trials, but will rely on mandated centralized reporting mechanisms to monitor patients on these studies.

Pharmaceutical Industry-Sponsored

All pharmaceutical industry-sponsored clinical trials with FCCC participation will require data and safety monitoring plans that have been reviewed and approved by both the RRC and IRB. These protocol-specific plans will adhere to industry and FDA-specified guidelines. In addition, local reporting of SAEs to the IRB is required using either industry-specified report formats or the FDA MedWatch form. Similar to national cooperative group studies, Fox Chase requires that each individual trial have a local principal investigator who is responsible for all communications
with RRC, IRB, and the Protocol Office. All pharmaceutical industry-sponsored trials are submitted to RRC and IRB for ongoing review, which includes a tabulation of internal and external SAEs.

Investigator-Initiated, Cancer Treatment

Investigator-initiated studies are categorized as either "external peer-reviewed", which includes grant funding through NIH, ACS, DOD or other agencies, or "internal peer-reviewed", which includes local funding, primarily through the Cancer Center Support Grant, or limited support from the pharmaceutical industry. In general, these trials are not externally audited and/or monitored, and will not have an external DSM Board. As such, these studies receive the highest priority for local monitoring through the Phase I-II Committee as previously described.

Each such study will be initially reviewed by RRC and IRB to determine if data and safety monitoring plans are complete and appropriate, including establishment of a study-specific DSMB, if required. The majority of these trials will be phase I-II studies with investigational agents or new combinations, including agents supplied by CTEP/NCI. It is expected that SAE reporting will follow established CTEP/NCI paradigms, as included elsewhere in this document. It is our general policy that approximately 20% of charts will be subject to internal audit verification of source documentation for eligibility, treatment, and toxicity reporting through our Quality Assurance Program. In addition, summaries of routine toxicity and SAEs for phase I trials will be reviewed at least quarterly during regular meetings of the Phase I Program and summarized annually for RRC and IRB review. In the event that an NCI sponsored study is suspended or terminated, notification will be provided to NCI within 48 hours of Committee action. Regulatory Affairs will take responsibility for this notification.

In general, investigator-initiated phase III clinical treatment studies are uncommon at our Center, as they require large patient populations with lengthy follow-up. If a DSMB is required for an individual study, regardless of study phase, the composition and function of the DSMB will be as stipulated in this plan.

Investigator-Initiated Chemoprevention Trials

One of the major goals of FCCC is the development of phase I and phase II investigator-initiated protocols for chemoprevention research. Therefore, it is anticipated that multi-institutional phase II chemoprevention research protocols will be activated. Each study will be reviewed by the RRC and IRB to determine if data and safety monitoring plans are complete and appropriate. It is anticipated that the majority of investigational agents will be supplied by the Cancer Prevention Branch, NCI. In addition, all of the chemoprevention trials will require concept review and protocol approval by the Cancer Prevention Branch/DCP PIO. It is expected that serious adverse event reporting will follow established DCP guidelines for prevention trials using investigational agents. It is our general policy that approximately 20% of Fox Chase charts will be subject to internal audit verification of source documentation for eligibility, treatment and toxicity reporting through our Quality Assurance Program. In addition, as a Research Base, Fox Chase will be responsible for auditing a proportion of cases at participating affiliated institutions, in compliance with NCI guidelines for monitoring multicenter trials (http://ctep.info.nih.gov/monitoring/guidelines.html).

Investigator Initiated Epidemiologic, Behavioral, and Nutritional Research

FCCC has an active social science and epidemiology research program within the Division of Population Science. A number of investigator-initiated studies have been conducted following external peer-review (with grant funding) and/or internal peer-review. These studies include small pilot protocols to develop research tools (such as questionnaires, surveys, or focus groups), non-randomized studies to validate survey tools and/or interventions, as well as larger randomized studies to evaluate outcomes associated with different behavioral interventions.

In general, the risk associated with behavioral or epidemiological interventions is lower than the acute and chronic risk associated with cancer treatment studies, and this decreased risk is reflected by a markedly reduced frequency of adverse event reporting associated with behavioral and social science studies. However, some of these studies may include the transfer of potentially stressful information to non-cancer subjects, such as genetic testing results in relatives of cancer patients. As such, it is appropriate to require that each of these studies also include a tailored data and safety monitoring plan that will be reviewed and approved by RRC and IRB. In general, the same requirements would be applied to behavioral intervention studies as would be applied to treatment intervention studies. However, in view of the reduced overall risk, a study-specific DSMB would only be required in unusual circumstances.
Investigator-Initiated Multicenter Trials

By their nature, investigator-initiated multicenter trials require specialized procedures for study coordination, regulatory compliance, communication among investigators, adverse event reporting, data storage, and data auditing. Each trial must clearly designate, in writing, a specific coordinating center that is responsible for development and distribution of protocol documents and amendments, maintenance of regulatory files, coordination of adverse event reporting and communication to co-investigators, and interactions with sponsoring agencies. In addition, the coordinating center must provide secure and confidential storage of protocol data and follow an accepted plan for routine auditing of protocol compliance, eligibility verification, data management, response assessment, and drug accountability. Multicenter phase I and phase II studies will require regular conference calls or other methods to keep all investigators aware of toxicity reports and decisions on dose escalation. In general, these studies will be monitored by the Phase I-II Committee or Extramural Data Safety and Monitoring Committee as previously described. However, larger multicenter phase II trials may require an independent DSMB, depending on review of the protocol document and study-specific DSM plan. These activities are supported by ERP.

Review and Approval of Data and Safety Monitoring Plans

According to NIH policy, the master Fox Chase Cancer Center Data and Safety Monitoring Plan (this document) and individual protocol data and safety monitoring plans require review and approval by RRC and IRB. In addition, this master plan will be re-reviewed on an annual basis by the Chairs of RRC and IRB, the Chief Academic Officer and the Associate Cancer Center Director for Clinical Research.

This plan is available in its entirety on the Fox Chase protocol website at the following URL:

https://www.protonet.fccc.edu/fccc/pims/rrc
Appendix

1. Sample Form "Request for New Protocol Review"
2. Sample Form "Research Review Committee - New Protocol Review"
## Study Synopsis:
(Provide a concise typed study description, rationale, primary and secondary objectives, feasibility, disease specific service line prioritization, known competition with existing studies, potential risks and benefits. To be completed by local PI.) Incomplete information will result in return of the protocol without review.

InsertStudySynopsis
Rationale:
Objectives
Feasibility
Disease site priority
Competing trials

## Originating Sponsor for this Protocol (Check One):
- NCI-Sponsored Cooperative Group  
- Cooperative Group Protocol ID: InsertStudyID#  
- Industry Sponsor  
- Sponsor Protocol ID: InsertStudyID#  
- Investigator Initiated (FCCC-Grant/Industry Support)  
- Investigator Initiated (FCCC Investigator national study chair-NCI-Sponsored Cooperative Group)  
- Investigator Initiated (FCCC Investigator a major contributor to the scientific design of study-Industry Sponsored)  
- Investigator Initiated (Non-FCCC)  

## Trial Category/Type (Check One):
- Cancer Therapeutic  
- Cancer Prevention  
- Data Collection Only  
- Blood/Sample Collection  
- Imaging  
- Behavioral (Intervention)  
- Behavioral (non-Intervention)  
- Nursing  
- Supportive Care  
- Other(specify): InsertOtherType

## Study Phase (Check One):
- Pilot (non-treatment)  
- I  
- I/II  
- II  
- II/III  
- III  
- N/A

## Does this trial have therapeutic intent?  
_i.e. Not exclusively designed to test toxicity and/or pathophysiology?_  
- Yes, this trial has therapeutic intent  
- No, this trial does not have therapeutic intent

## For Therapeutic Trials only: (Check all treatment modalities which apply to this study):
- Surgery  
- Radiation  
- Chemo  
- Hormone  
- Biologic  
- Other
**Study Site Locations** *(Note: Protocol document must contain a complete site listing):*

- [ ] FCCC only
- [ ] FCCC & Multicenter sites: # Sites: InsertNumber
- [ ] Temple University Only
- [ ] Fox Chase Partners Participation (All Sites)
- [ ] Fox Chase Partners Selected Sites: InsertPartnerSites

**Projected Accrual and Study Duration for Intervenational Studies:**

- Total Overall Accrual (All Sites): 999
- Total Accrual (Fox Chase): 999
- Annual Accrual (Fox Chase): 999
- Anticipated Activation Date: 1/1/2001
- Study Duration (Years): 9.9

**If NCI Cooperative Group Study:**

- Actual Activation Date:
- Current Overall Accrual:
- Accrual Goals Not Applicable (Registry Study, etc.)

**Feasibility for Proposed Study:**

- Estimated pool of potentially eligible participants for this study at Fox Chase: 999 (Per Year)
- Methods used to determine the estimated pool: [ ] Tumor Registry  [ ] Clinical Database  [ ] Other: InsertCategory

**Potentially Competing Studies (Excluding Phase I):**

- [ ] There are no competing studies for this patient population at Fox Chase
- [ ] Competing studies exist: InsertCategory

**Note:** If competing studies exist, justification for activation of the proposed study must be provided.

**Data Access, Management, Monitoring will be completed by:**

- [ ] Study Sponsor
- [ ] FCCC Research Staff: InsertCategory

**Responsibility for Statistical Analysis:**

- [ ] Study Sponsor
- [ ] FCCC Statistician

**Data Safety Monitoring Plan (Please review current FCCC Policy and Procedures before responding):**

- All protocols require a study-specific plan to explain how the data and study progress will be monitored.

  - DSM Board for this Study: [ ] Not Required
  - DSM Board Chair (If Utilized): InsertDSMBChair&Address

**Note:** If a study-specific DSM Board is required, the PI is responsible for creating the board and complying with policy.

**Investigator-Initiated Phase I/II Studies:**

- DSM Monitoring to be Provided by Fox Chase Phase I/II Committee: [ ] Yes  [ ] No

**Investigational New Drug (IND) and Investigational Device Exception (IDE):**

- Does this study include agents or devices manufactured or produced at FCCC? [ ] Yes  [ ] No
- Does this study require an IND? [ ] Yes  [ ] No
- Does this study require an IDE? [ ] Yes  [ ] No
- If the study requires an IND or IDE, who will file with FDA? [ ] PI*  [ ] Sponsor

**Note:** If a new study-specific IND or IDE is required, attach supporting documentation

*Requires letter from sponsor to be attached with protocol explaining reason for filing of an investigator-sponsored IND.

- Name of Drug(s) requiring IND filing: InsertCategory
- Name of Device requiring IDE filing: InsertCategory

**Note:** For investigational agents acquired for special exception (compassionate use) for an individual patient, please review policy and procedure located on RRC website.
### Informed Consent

<table>
<thead>
<tr>
<th>Informed Consent</th>
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<tbody>
<tr>
<td>Informed consent document:</td>
<td></td>
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<tr>
<td></td>
<td>□ Attached</td>
<td>□ Waiver Requested</td>
</tr>
<tr>
<td>Consent obtained by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ PI and/or Research Nurse</td>
<td></td>
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<tr>
<td>Consent presented via:</td>
<td></td>
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<tr>
<td></td>
<td>□ In-Person</td>
<td>□ Telephone</td>
</tr>
<tr>
<td>Is the process by which informed consent is obtained described in the protocol?</td>
<td></td>
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<tr>
<td></td>
<td>□ Yes</td>
<td>No InsertReason</td>
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<tr>
<td>Source of Research Subjects:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>□ Clinic Patients</td>
<td>□ Volunteers</td>
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### Confidentiality of Collected Data

<table>
<thead>
<tr>
<th>Confidentiality of Collected Data</th>
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<tbody>
<tr>
<td>Will data be de-identified?</td>
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<td></td>
<td>□ Yes</td>
<td>□ No</td>
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<tr>
<td>If not, will data be coded?</td>
<td></td>
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<td></td>
<td>□ Yes</td>
<td>□ No</td>
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<tr>
<td>Will electronic databases be password-protected?</td>
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<td></td>
<td>□ Yes</td>
<td>□ No</td>
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</table>

**Note:** Protocol should describe how access to hard copies of data will be protected.

### Privacy of Participants

<table>
<thead>
<tr>
<th>Privacy of Participants</th>
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<tbody>
<tr>
<td>Are procedures to protect privacy of participants included in the protocol?</td>
<td></td>
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<tr>
<td></td>
<td>□ Yes</td>
<td>No InsertReason</td>
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### Committee Review and Approval

<table>
<thead>
<tr>
<th>Committee Review and Approval</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Does study require approval by Institutional Biosafety Committee?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.e. involves recombinant DNA, involves organisms that are infectious to humans, involves stem cells</td>
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<tr>
<td></td>
<td>□ Yes</td>
<td>□ No</td>
</tr>
<tr>
<td>(Contact IBC Chairperson at x2462 for forms and guidelines.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does study required approval by Infection Control Committee?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Contact Chair at extension 2660 for forms and instructions.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes</td>
<td>□ No</td>
</tr>
<tr>
<td>Does study required approval by Radiation Safety Committee?</td>
<td></td>
<td></td>
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<tr>
<td>(Reference: <a href="http://internal.fccc.edu/departments/safety/radiation/">http://internal.fccc.edu/departments/safety/radiation/</a>)</td>
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<tr>
<td></td>
<td>□ Yes</td>
<td>□ No</td>
</tr>
<tr>
<td>Does this study incorporate genetic testing?</td>
<td></td>
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<tr>
<td>(If yes, refer to IRB Genetic Subcommittee Policy)</td>
<td></td>
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<tr>
<td></td>
<td>□ Yes</td>
<td>□ No</td>
</tr>
<tr>
<td>Does study include a questionnaire?</td>
<td></td>
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<tr>
<td>(If yes, refer to IRB Questionnaire Subcommittee Policy)</td>
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<tr>
<td>Name of Questionnaire(s): InsertNames</td>
<td></td>
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<tr>
<td>Total Number of Questions included on the Questionnaire:</td>
<td>InsertNumber</td>
<td></td>
</tr>
<tr>
<td>Total Number of Times Questionnaire Administered:</td>
<td>InsertNumber</td>
<td></td>
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<tr>
<td>Will recruitment materials be utilized?</td>
<td></td>
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<tr>
<td>(If yes, refer to IRB Recruitment Subcommittee Policy)</td>
<td></td>
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<tr>
<td></td>
<td>□ Yes</td>
<td>□ No</td>
</tr>
<tr>
<td>Will patients receive payment or incentive(s)?</td>
<td></td>
<td></td>
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<tr>
<td>(If yes, refer to IRB Recruitment Subcommittee Policy)</td>
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<tr>
<td></td>
<td>□ Yes</td>
<td>□ No</td>
</tr>
</tbody>
</table>
### Funding and Support Information

**Study-Specific Grant or Contract:** Identification Number: InsertGrantNumber  
Source: [ ] FCCC  [ ] NCI  [ ] DOD  [ ] ACS  [ ] TempleU  [ ] Industry  [ ] Other: InsertSource  
Status: [ ] Grant Submitted  [ ] Grant Approved  [ ] Contract Under Development  [ ] Contract Approved

### Anticipated Support for Clinical Services

(Check All That Apply)  
Non-Investigational Drugs: [ ]  
Diagnostic Studies: [ ]  
Hospitalization: [ ]  
If hospitalization required, include frequency and length of stay? Insert length/frequency

### Pharmacy (Indicate Any Drugs to be Provided)

<table>
<thead>
<tr>
<th>Investigational</th>
<th>Drug Name</th>
<th>Drug Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes  [ ] No</td>
<td>InsertDrugName</td>
<td>InsertDrugSource</td>
</tr>
</tbody>
</table>

### Biospecimens and Anatomic Pathology

Will FCCC pathology materials be submitted to a non-FCCC facility?  
Will non-FCCC pathology materials be submitted for review at FCCC?  
Will biospecimens be collected, processed, and/or analyzed at FCCC?  
Will biospecimens be shipped from FCCC to a non-FCCC laboratory?  
Will biospecimens be shipped from non-FCCC sites to a FCCC laboratory?

### Conflict of Interest

Please review the FCCC IRB Conflict of Interest Policy (http://www.internal.fccc.edu/policies/section1/conflict.html) before responding to these questions. If you answer "yes" to either question, further review of this study will require approval by the Vice President, Office of Business Development and Regulatory Affairs.

- Will you or any co-investigator have, or anticipate having, any significant income from, or other financial interest in, the sponsor or supporting organizations for this study that could be perceived as a conflict of interest (financial interests could include, but are not limited to, professional consulting, lecture honoraria, or ownership of equities)?  
  
- Will you or any sub-investigator participating in this study have, or anticipate having, any non-financial obligations that could constitute a conflict of interest for this study?

- Will you or any co-investigator have ownership or compensation interests of less than $10,000 when the value, in any amount, may be affected by the outcome of the research?

### Investigator Certification and Compliance

- Is the PI in compliance with NIH/NCI Investigator Registration (requires annual renewal with NCI)?  
- Are all sub-investigators in compliance with the Office of Human Research Protection (OHRP) requirement for Certification in Human Subjects Protection? (verify from IRB website)
<table>
<thead>
<tr>
<th>Statement of Investigator Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>As the Principal Investigator on this research study, you and your sub-investigators are responsible for adherence to the following guidelines. If you have any questions regarding these investigator responsibilities, please address with the Institutional Review Board, Research Review Committee, Protocol Management Office, or Sponsor, as appropriate.</td>
</tr>
</tbody>
</table>

1. Assure that risks to human subjects are minimized by using procedures consistent with sound research design.  

2. Assure that risks are reasonable in relation to possible benefits to participants and importance of knowledge to be gained.  

3. Provide additional safeguards if research participants are likely to be vulnerable. (45 CFR 46.116 subparts B,C,D)  

4. Obtain and document informed consent of subjects or subjects’ legally authorized representatives prior to the subjects’ participation in the research, unless these requirements have been waived by the IRB (45 CFR 46.116; 45 CFR 46.117). If waived, describe information that will be provided to participants.  

5. Obtain prior approval from the IRB for any modifications of the previously approved research, including modifications to the informed consent process and document, except those necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)).  

6. Ensure that progress reports and requests for continuing review and approval are submitted to the IRB in accordance with the policies, procedures, and actions of the IRB as referenced in the FCCC OHRP-approved Federal-wide assurance (45 CFR 46.103(b)(4), 45 CFR 46.109(e), 45 CFR 46.115(a)(1)).  

7. Provide to the IRB prompt reports of any unanticipated problems involving risks to subjects or others (45 CFR 46.103(b)(5));  

8. Provide to the IRB prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB (45 CFR 46.103(b)(5)).  

9. Retain records of informed consent for at least 3 years after completion of a study (45 CFR 46.115(b)).  

10. Stop all research activity involving human subjects if a study has expired.  

11. Promptly notify the IRB if the investigator judges that it is in the best interest of already enrolled subjects to continue to participate in a study that has expired.  

12. Notify the IRB when all research-related interventions or interactions with human subjects have been completed, and all data collection and analysis of identifiable private information described in the IRB-approved research plan have been finished. Thereafter, continuing review is not required.  

13. Review all sponsor generated safety reports and forward to the IRB those that are unanticipated.  

14. Maintain current certification in human subjects protection, as recognized by the IRB.  

15. If a PI or research staff member receives a complaint from a research participant that cannot be easily addressed by the PI or research staff member to the satisfaction of the participant, that complaint should be forwarded by the PI or staff member to the IRB.  

16. For research participants who leave the study before completion, the PI will work with the research participant to ensure that follow-up care and testing are provided as necessary.  

**Signature of Principal Investigator**  
**Acknowledging Responsibilities:**
Verification of Internal Review and Signatures

All interventional protocols require review and approval by the Disease-Site/Working Group Chair (or Phase I Chair), as well as the Department Chair (primary modality related to PI). To promote regulatory compliance, Sub-Investigators should be limited to the individuals who will be directly involved with care of study participants.

<table>
<thead>
<tr>
<th>Printed Name</th>
<th>Signature</th>
<th>Initials</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>InsertPI</td>
<td></td>
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<tr>
<td>Site/Working Group Chair</td>
<td>InsertSiteChair</td>
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<tr>
<td>Department Chair</td>
<td>InsertDeptChair</td>
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<tr>
<td>Sub-Investigator 1</td>
<td>InsertCoPI1</td>
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<td>Sub-Investigator 2</td>
<td>InsertCoPI2</td>
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<td>Sub-Investigator 3</td>
<td>InsertCoPI3</td>
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<td>Sub-Investigator 4</td>
<td>InsertCoPI4</td>
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<td>Sub-Investigator 5</td>
<td>InsertCoPI5</td>
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<tr>
<td>Sub-Investigator 6</td>
<td>InsertCoPI6</td>
<td></td>
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<tr>
<td>Statistician (Required for all investigator-initiated studies)</td>
<td>InsertStatistician</td>
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<tr>
<td>Modality Support</td>
<td>Pathology</td>
<td></td>
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<tr>
<td>(If another area is involved beyond standard of care, must include representative signature)</td>
<td>Pharmacy</td>
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<td></td>
<td>Nursing</td>
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<td></td>
<td>DiagnosticImaging</td>
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<tr>
<td>Other</td>
<td>InsertOther</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Research Coord</td>
<td>InsertCRC/ProjectMgr</td>
<td></td>
<td></td>
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<tr>
<td>Clinical Research Assoc</td>
<td>InsertCRA/ProjectMgr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

--- RCOOffice Use Only------

<table>
<thead>
<tr>
<th>Date Received:</th>
<th>RRC Number:</th>
<th>IRB Number (if known):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of RRC Meeting:</td>
<td>Study to be managed by: PMO</td>
<td>PI: Other(list):</td>
</tr>
</tbody>
</table>

Notes:
Fox Chase Cancer Center

Request to Open New NCI CIRB Approved Phase III Cooperative Group Study

To promote efficient processing of new NCI CIRB approved Phase III Cooperative Group Protocols, please complete all applicable elements on this form. This application is designed as a protected form and should be opened using MS-Word. All form elements are indicated in blue font. Tab or double-click on BlueTextElements to insert new text, single-click on blue check boxes to add/remove a check mark. When completed, print out a paper copy for signatures and submit to the Clinical Trials Operations Office, Regulatory Department. CTO Regulatory Staff will complete the appropriate request forms on the CIRB website. The PI and the respective CTO Study Team will be notified by CTO Regulatory Staff when CIRB approval has been received and the approved protocol documents will be circulated accordingly.

**Cooperative Group Protocol ID and Title:** InsertProtocolTitle

**FCCC Investigator:** InsertInvestigatorName

**Study Synopsis:** (Provide a concise typed study description, addressing primary hypothesis, feasibility, prioritization, known competition with existing studies, potential risks and benefits. To be completed by local PI.) InsertStudySynopsis

**Trial Category/Type (Check One):**
- [ ] Cancer Therapeutic
- [ ] Cancer Prevention
- [ ] Imaging
- [ ] Behavioral (Intervention)
- [ ] Behavioral (non-Intervention)
- [ ] Supportive Care

**Study Phase:**
- [ ] III

For Therapeutic Trials only: (Check all treatment modalities which apply to this study):
- [ ] Surgery
- [ ] Radiation
- [ ] Chemo
- [ ] Hormone
- [ ] Biologic
- [ ] Other: InsertCategory

**Feasibility for Proposed Study:**
Estimated pool of potentially eligible participants for this study at Fox Chase: 999 (Per Year)
Methods used to determine the estimated pool: [ ] Tumor Registry [ ] Clinical Database [ ] Other: InsertCategory

**Potentially Competing Studies (Excluding Phase I):**
- [ ] There are no competing studies for this patient population at Fox Chase
- [ ] Competing studies exist: InsertCategory

**Note:** If competing studies exist, justification for activation of the proposed study must be provided in the study synopsis section above.
### Anticipated Support for Clinical Services

*(Check All That Apply)*

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<th>FCCC</th>
<th>Other</th>
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<td>Diagnostic Studies:</td>
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### Pharmacy

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<th>Drug Name</th>
<th>Drug Source (CTEP, other sponsor, commercial, etc.)</th>
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<tr>
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<td>InsertDrugSource</td>
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<tr>
<td>☐ Yes ☐ No</td>
<td>InsertDrugName</td>
<td>InsertDrugSource</td>
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</table>

### Biospecimens and Anatomic Pathology

- Will FCCC pathology materials be submitted to a non-FCCC facility? ☐ Yes ☐ No ☐ N/A
- Will non-FCCC pathology materials be submitted for review at FCCC? ☐ Yes ☐ No ☐ N/A
- Will biospecimens be collected, processed, and/or analyzed at FCCC? ☐ Yes ☐ No ☐ N/A
- Will biospecimens be shipped from FCCC to a non-FCCC laboratory? ☐ Yes ☐ No ☐ N/A
- Will biospecimens be shipped from non-FCCC sites to a FCCC laboratory? ☐ Yes ☐ No ☐ N/A

### Investigator Certification and Compliance

- Is the PI in compliance with NCI Investigator Registration (requires annual renewal with NCI)? ☐ Yes ☐ No
- Are all sub-investigators in compliance with the Office of Human Research Protection (OHRP) requirement for Certification in Human Subjects Protection? (verify from IRB website) ☐ Yes ☐ No
Verification of Internal Review and Signatures
All interventional protocols require review and approval by the Disease-Site/Working Group Chair (or Phase I Chair), as well as the Department Chair (primary modality related to PI). To promote regulatory compliance, Sub-Investigators should be limited to the individuals who will be directly involved with care of study participants.

<table>
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<th>Printed Name</th>
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<tr>
<td>Principal Investigator</td>
<td>InsertPI</td>
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<td>Site/Working Group Chair</td>
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<td>Department Chair</td>
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<td>Sub-Investigator 1</td>
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<td>Sub-Investigator 6</td>
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</table>

Modality Support
(If another area is involved beyond standard of care, must include representative signature)
Pathology
Pharmacy
Nursing
Diagnostic Imaging

--- CTO Office Use Only ---

Date Received: □□□□□□□□ RRC Number: □□□□□□□□ CIRB Number: □□□□□□□□

Notes:
Changes to DSMP March 8, 2012

1. Cover page
   Massimo Cristofanilli MD PhD
   Associate Cancer Center Director for Clinical Research
   Chairman, Medical Oncology, Division of Medical Science

   Changed to
   Barbara Burtness, MD
   Associate Director for Clinical Research
   Professor of Medical Oncology
   Co-Leader, Developmental Therapeutics
   Chair, Phase I-II Committee

2. Cover Page
   Lainie P. Martin, MD
   Assistant Professor of Medical Oncology

   Changed to
   Margaret von Mehren, MD
   Professor of Medical Oncology

3. Cover page
   Russell J. Schilder, MD
   Professor of Medical Oncology

   Changed to
   Hossein Borghaei, MD
   Associate Professor of Medical Oncology

4. Cover Page
   Barbara Burtness, MD – omitted

5. Cover Page
   Paul Engstrom - omitted

6. Michael Millenson, MD
   Associate Member, Division of Medical Science

   Changed to
Associate Professor of Medical Oncology

7. Cover Page
  
  W. Thomas London, MD  
  Chairman, Institutional Review Board  
  Senior Member, Division of Population Science

Changed to

  Adam Cohen, MD  
  Co-Chair, Institutional Review Board  
  Assistant Professor of Medical Oncology

  Clifford S. Perlis, MD  
  Co-Chair, Institutional Review Board  
  Assistant Professor of Medicine

8  p. 3 FCCC Protocol Management Office (PMO)

Changed to

  Clinical Trials Operations (CTO)

9  Response Verification Committee (RVC) – omitted

10  but will also receive initial and ongoing review at FCCC by RRC and IRB.

Changed to

  These studies are reviewed at RRC for programmatic fit and accrual feasibility and subsequently reviewed by central IRB (c-IRB).

11  Introduction – corrected spelling of “although”

12  objective analysis of tumor response by the Response Verification Committee (RVC); - omitted

13  While these activities have played a vital and important role for our clinical trials program, the new NIH guidelines require a more comprehensive and detailed data and safety monitoring plan.

14. Removed: Depending on the nature of the conflict, a principal investigator may be removed from the study, and would not be expected to have a direct impact on accrual or treatment decisions which could compromise patient safety.
Added: An individual will be deemed to have a potential conflict of interest if the individual (or the individual’s spouse or dependent child) knowingly receives anything that when aggregated for the individual, the individual’s spouse and dependent children equals or exceeds $5,000 for 12 months. This includes, but is not limited to, salary or other payments for service (e.g. consulting fees or honoraria); equity interests (e.g. stocks, stock options, or other equity interests); debt interests, capital holding or other remuneration or financial consideration, or thing of value for services as an employee, consultant, officer or board member in an entity which will reasonably appear to be directly and significantly affected by the Center’s research or other activities. Also included are intellectual property rights of any value (e.g. patents, copyrights and royalties from such rights) related to a matter affecting the Center.


Changed to:

Clinical Trials Operations (CTO)

16. Page 7 Added: Within the CTO, Extramural Research Program of the Clinical Trials Office

Removed: Protocol and also

17. Page 7 Removed PMO

Changed to CTO

18. Page 7 Changed: scientific leadership of Margaret von Mehren, MD, Professor of Medical Oncology,

Removed: Lainie Martin, M.D., Associate Member, Division of Medical Science

19. Removed: Dorothy Reihs, Hospital Administration

Changed to: John Gricoski, Research Administration

20. Added: The Regulatory Affairs team is responsible for reporting to the NCI Program Director responsible for funding a trial, as well as to other pertinent agencies, if that trial is suspended temporarily or permanently.

21. Added: as well as actively providing support to the medical staff in identifying patients who are candidates for trial. This function is carried out via attendance at tumor boards, interaction in the clinics, and e-mail reminders and queries
22. Added: Extramural Research Program

Removed:

Multi-site team and primarily but not exclusively

23. Removed: Office of Extramural Research

Changed to Extramural Research Program (ERP)

24. Added:

The Extramural Research Program (ERP) was formerly known as the Office of Extramural Research (OER). OER was fully integrated with the Clinical Trials Operations (CTO, formerly the Protocol Management Office) March 2010. The Extramural Research Program was established to provide a centralized resource for research studies conducted at sites affiliated with Fox Chase Cancer Center. This program facilitates the development, conduct, quality assurance monitoring, and evaluation of investigator-initiated studies. The staff works with investigators on all levels of the study to include attention to ethical and regulatory issues, protocol compliance, quality assurance, and development of study-specific standard operating procedures, databases and case report forms. Regulatory staff manages the flow of documents to participating sites and external agencies to facilitate ongoing and timely review of the protocol and associated documents and events. ERP adheres to local and federal guidelines and regulations. The Extramural Research Program operates within the Clinical Trials Operations (CTO) Office under the direction of the Facility Director and the Assistant Vice-president of Clinical Trials Operations and Extramural Research Program. The staff designated for the ERP consists of a regulatory coordinator, monitor, quality assurance coordinator and a project manager for Protocol Development. CTO staff supports data quality and data management for the ERP. All research conducted through this mechanism is prioritized and monitored by the FCCC RRC, IRB and the Extramural Data and Safety Monitoring Committee. The CTO facilitates the flow of these studies through the RRC and IRB and Extramural Data and Safety Monitoring Committee.

Removed:

The office of Extramural Research was established to provide a centralized resource for research studies conducted at sites affiliated with Fox Chase Cancer Center. This office facilitates the development, conduct, quality assurance monitoring, and evaluation of investigator-initiated studies and staff work with investigators on all levels of the study to include attention to ethical and regulatory issues, protocol compliance, quality assurance and development of study specific standard operating procedures, databases and case report forms. Staff manages the flow of documents to participating sites and external agencies to facilitate ongoing and timely review of the protocol and associated documents and events. OER adheres to local and federal
guidelines and regulations. The Office of Extramural Research operates within the PMO under the direction of the Facility Director and the Coordinator of Clinical Investigations. The Extramural Research team consists of clinical research coordinators with designated roles as project manager, auditor, and traveling data manager. The team includes a regulatory coordinator. All research conducted through this mechanism depends on the support of the FCCC RRC and IRB. The PMO supports the flow of these studies through the RRC and IRB as appropriate.


Changed to: Clinical Trials Operations

26. Removed: Senior Vice President, Division of Medical Science Russell Schilder, M.D.

Changed to: Associate Director, Clinical Research. Hossein Borghaei, DO a clinical and laboratory investigator who is an Associate Professor in the Department of Medical Oncology, has served as RRC Chair since September, 2011. Elizabeth Plimack, MD, Assistant Professor of Medical Oncology, serves as Associate Chair of the RRC. A prior chair of RRC, Gary Hudes, MD, Professor of Medical Oncology, continues to serve as a member of RRC.

27. Removed: The RRC reviews studies regardless of sponsor.

Added: RRC is charged not only with ensuring that the studies activated at FCCC represent the best possible science, utilizing the most rigorous trial designs, but also with ensuring that the entire menu of trials which are activated at Fox Chase makes optimal use of the center’s resources, permitting accrual to novel and early phase studies. Prioritization of studies begins in the disease specific working groups, closely aligned with the clinical service lines. Medical Oncology departmental review discusses the majority of multidisease and phase I studies. The RRC submission form collects data on competing studies, and the estimated accrual potential for the relevant target patient population. Studies are given highest priority when investigator-initiated, if the research question arose from primary research conducted at FCCC or by a FCCC investigator, if a very novel drug or treatment assignment strategy is under investigation, or when a FCCC investigator played an integral role in trial design and development. However, there is also a strong commitment to cooperative group trials across the disease teams at Fox Chase.

All studies are reviewed by the RRC. Cooperative group studies and other studies which have undergone peer-review at NIH are not reviewed for scientific content or study design, but only for programmatic priority and for the feasibility of accrual targets.

28. Added:
RRC members file conflict of interest reports annually. In addition, they are required to report new potential conflicts of interest within 30 days to the chair of the RRC. No reviewer with a potential conflict of interest may vote on the approval of a study with which said reviewer has a potential conflict. In the event that the RRC Chair, has a potential conflict of interest with a given study, he shall recuse himself and the Associate Chair of the RRC, or another RRC member, shall chair the committee during discussion and voting on the trial in question, and prepare the written comments returned to the Principal Investigator. Failure to disclose or recuse when necessary shall be referred to the President of FCCC.

29. Changed: and to read and/or

30. Added: *Not a reviewed element for cooperative group and other NIH funded studies.

Consonant with its responsibility for global oversight of the clinical trials portfolio and utilization of the center’s resources, the RRC is charged with identifying low-accruing trials. Trials with accrual which is <50% of projected will be recommended for closure. Investigators will have the opportunity to provide a written plan to enhance accrual. This will be reviewed by the RRC Chair with or without full committee review. If the plan is accepted, the study will be reviewed again after 6 months. If substantial improvement is not demonstrated, the RRC Chair has authority to close the study. This decision will be communicated to the full committee as well as to the A DCR, and the Regulatory Affairs team in the CTO. Regulatory Affairs will take responsibility for reporting study closure to the IRB as well as to any relevant external agencies or other clinical trials sites.

31. Added:
Cooperative group studies that have been reviewed by the Central IRB (CIRB) will not undergo review by the FCCC IRB; the CIRB will serve as the IRB for these trials.

32. Added:
The present IRB Co-Chairs are Adam Cohen, MD, Assistant Professor of Medical Oncology, and Clifford S. Perlis, MD, Assistant Professor of Medicine.

Removed: is W. Thomas London, M.D., Senior Member Division Population Science

33. Added:
The members must recuse themselves from discussion or voting in the case of a trial where a conflict of interest exists. In addition, they are required to report new potential conflicts of interest within 30 days to the chair of the IRB. In the case that the potential conflict is held by one of the IRB Co-Chairs, new potential conflicts must be reported to the Chief Academic Officer within 30 days. In the event that the IRB Co-Chair has a potential conflict of interest with a given study,
the study should be referred to a session chaired by the alternate Co-Chair. Failure to disclose or recuse when necessary shall be referred to the President of FCCC.

34. Deleted: PMO
   Changed to: CTO

35. Removed L. Martin
   Changed to: M. von Mehren

36. Removed Response Verification Committee Section

37. Removed: and
   Changed to: or

38. Removed: R. Schilder
   Changed to: H. Borghaei

39. Removed: L. Martin
   Changed to: M. von Mehren

40. Added: Denise Connelly, Ph.D.

41. Removed: Drs. Schilder, Martin, Olszanski
   Changed to: another committee member will chair the discussion and voting, and the Chair will recuse herself

42. Deleted serve as back-up Chairs for the committee meetings.

43. Added: communicated to the Associate Director, Clinical Research, who will decide on study closure. In the event of a conflict of interest arising for the ADCR with respect to the study to be closed, the matter will be referred to the PMEC for rapid resolution.

   Deleted: involvement of the PMEC also minimized the potential for conflict of interest in the event that a study chair is the Program Director or one of the other as hoc members of the Phase I Committee.

44. Added: ADCR or

45. Deleted: and

   Added: or FCCC investigator-initiated trials which are activated as multicenter studies. The committee

46. Deleted: Senior
Added: Associate Director, Clinical Research, as well as the

47. Deleted: Division

48. Deleted: Research

Added: Programs. The ADCR will be responsible for implementing decisions respecting study closure. In the event of a conflict of interest for the ADCR, the matter will be referred to the PMEC. Regulatory Affairs and the ERP staff will ensure that IRB, all external sites, and appropriate granting agencies and/or FDA are alerted as necessary.

49. Deleted: who will work with the Office of Extramural Research and the study Principal Investigators to address each recommendation. It is the role of the Senior Vice President to ensure all recommendations have been adequately addressed in a timely manner.

50. Page 12 removed T. Cardoso

Added: C. Jerome

51. Removed: PMO

Added CTO

52. Corrected: Oversight

53. Added: Numerous


Changed to Clinical Trials Operations (CTO)


Changed to Clinical Trials Operations

56. Deleted: usually

Added or weekly

57. Added: review of prioritization and feasibility

58. Deleted: Protocol Office

Changed to: Clinical Trials Operations


Changed to: Clinical Trials Operations

60. Added: ERP and Regulatory Affairs assist with this function.
61. Deleted: Protocol Office  
Changed to Clinical Trials Operations


63. Deleted: and

64. Added: and the Associate Director, Clinical Research

65. Deleted: The trial principal investigator, DSMB Chair, and the Associate Cancer  
Center Director will be responsible for reaching a mutually acceptable decision  
about the study. Confidentiality must be maintained during these discussions

Added: The ADCR will make the final determination. In the event of a conflict of  
interest on the part of the ADCR, the matter will be referred to the Chair, RRC,  
Chair, IRB or the PMEC.

66. Deleted: invited to serve on the DSMB as either voting or non-voting members will  
disclose any potential conflicts of interest, whether real or perceived, to the trial  
principal investigator and the appropriate FCCC official(s), in accordance with  
the institutions policies.

Added: may not serve on an independent DSMB if a conflict of interest exists.  
Conflict of interest must be declared at the initiation of the DSMB and annually  
thereafter. If a conflict of interest arises during the course of the year, prior to a  
DSMB interim review, this must be declared and the principal investigator will be  
required to replace the DSMB member who has a new conflict of interest. Failure  
to disclose this information, or to withdraw from the DSMB, will be referred to  
the President of Fox Chase, who will resolve the matter.

Changed to CTO

68. Page 21. Added: for Phase I Trials

69. Page 21. Added: Regulatory Affairs will take responsibility for this notification.

70. Page 22. Added: These activities supported by ERP.