Policies and Procedures

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Kansas City Clinical Oncology Program (KCCOP)

Institutional Review Board

POLICIES AND PROCEDURES

I. KANSAS CITY CLINICAL ONCOLOGY PROGRAM COMMITMENT

A. Ethical Principles of Human Research

1. All human subjects research conducted at Kansas City Clinical Oncology Program (KCCOP) is guided by the ethical principles of respect, beneficence and justice set forth in *The Belmont Report* and as stated in the KCCOP's Federalwide Assurance document.

2. Ethical principals and assurances to federal authorities apply to all human research at KCCOP, regardless of funding source.

3. Responsibility for ethical conduct rests with all parties involved in the review, oversight or conduct of human research. Parties include the KCCOP Board of Directors, the KCCOP Investigators and research staff, and the KCCOP Institutional Review Board (IRB).

B. Kansas City Clinical Oncology Program (KCCOP) Federalwide Assurance

1. The KCCOP Federalwide Assurance (FWA) confirms that the KCCOP Board of Directors has designated the KCCOP Institutional Review Board (IRB) for the review of cancer research studies conducted by the KCCOP. Regulations require that the KCCOP IRB have written policies and standard operating procedures, and that all research activities of the KCCOP are conducted in compliance with these, as well as federal laws and regulations.

2. The Purpose of the KCCOP IRB is to protect human subjects who participate in KCCOP cancer research studies. The KCCOP IRB's Policies and Procedures reflect not only federal and state laws and regulations, but also the underlying ethical Principles embodied in the Belmont Report, which is cited in the KCCOP's FWA. The Principles outlined in the Belmont Report assure that the rights and welfare of human subjects are protected.

3. The KCCOP FWA also designates the National Cancer Institute Central IRB (NCI CIRB), which may review and oversee selected research studies. In such cases, the KCCOP IRB has the responsibility to conduct a Facilitated Review, and either "accept" or "reject" the CIRB review. The KCCOP IRB retains the responsibility to review local serious adverse events and other study-related unanticipated events, consistent with these KCCOP IRB Policies.

C. Scope of KCCOP IRB Review

1. Research Studies
The research reviewed by the KCCOP IRB includes all research studies directly or indirectly involving human subjects that are conducted by the Kansas City CCOP, a participant in the Community Clinical Oncology Program (CCOP) of the National Cancer Institute. Studies may be developed by NCI Cooperative Group Research Bases, NCI Cancer Centers, or industry sponsors. These may include cancer prevention, treatment, and symptom management studies.

2. Ancillary/Companion Studies
If a protocol requires that its participants also enroll in an ancillary/companion protocol, the IRB must review the ancillary/companion protocol. A separate Ancillary Protocol Application, the ancillary/companion protocol, and associated informed consent document(s) must be submitted to the IRB for review and approval. Once an ancillary/companion protocol has been approved, it will not need to be resubmitted with each treatment protocol that it accompanies.

3. Compassionate Use Protocols and Consent Forms
The IRB may review protocols and consent forms for the compassionate use of Group C investigational drugs available through the Drug Management Branch.

4. Long-term Follow-up Protocols
The IRB may review Long Term Follow-Up Protocols initiated by the NCI Research Bases or the KCCOP to facilitate long term follow-up of study patients. When a study is closed to enrollment, all subjects have completed active treatment and remain on-study for long-term follow-up only, and the study has undergone a subsequent Continuing Review, it may be permanently closed by KCCOP and the study subjects may be transferred to a Long Term Follow-Up Protocol. Subjects will continue to be followed according to the original protocol guidelines. Any unanticipated problems must be reported to the IRB. Each time subjects from a closed study are added to a Long Term Follow-up Protocol a Study Modification form will be submitted to the IRB. Long Term Follow-Up Protocols are subject to annual Continuing Review.

5. Facilitated Review of Studies Approved by the National Cancer Institute's Central IRB

6. Emergency Research
The KCCOP does not engage in emergency research studies and KCCOP studies do not require emergency use of study agents.

7. Research Monitoring
Final reports from Research Base Monitoring visits must be submitted to the IRB Chair, along with the KCCOP Corrective Action Plan, if applicable. The Chair

will summarize these reports for the IRB members, including any unanticipated problems involving risks to subjects and others.

8. Study Patient Characteristics
The KCCOP engages in studies for adult cancer patients. Pregnant females are excluded from all treatment studies. KCCOP does not specifically target prisoners, non-English speakers, or cognitively impaired individuals.

D. Authority of the KCCOP IRB

1. KCCOP Consortium Hospitals
The IRB has the authority to act on behalf of the KCCOP Consortium hospitals, as described in the IRB Authorization Agreement with each institution, and each institution's FWA.

2. The IRB has the authority to
a. Approve, disapprove, or require modification to studies to ensure human subjects' protection

b. Require progress reports from the Principle Investigator and oversee the conduct of the studies

c. Suspend or terminate approval of studies

3. No external body or official may override disapproval of a study by the IRB.

II. GENERAL ADMINISTRATION OF THE IRB

A. Review, Revision, and Approval of Policies and Procedures (P&Ps)

1. Policies will be reviewed and approved by the Chair of the Board of Directors (or designee Board member) for the KCCOP at intervals established by the Board of Directors, but at least annually.

2. Changes to regulations, federal guidelines, or research practice as well as the policies and procedures of the IRB may require a revision.

3. The IRB Chair, the IRB Coordinator, and the designated signatory for the KCCOP Board of Directors will discuss any necessary changes.

4. Documentation of annual review and approval is noted by signature of the Chair of the Board of Directors.

B. SOP Dissemination and Training

1. When new or revised P&Ps are approved, they will be made available to

the investigators and research staff or displayed on the KCCOP web site.

2. Training will be provided to all members of the IRB and IRB staff on any new or revised policy and/or procedure. Evidence of training must be documented in the meeting minutes.

3. Each new IRB member or staff employee must review all applicable SOPs prior to undertaking any responsibilities in the IRB. Evidence of training must be filed in the IRB Office.

C. KCCOP IRB Personnel (IRB Coordinator)

1. The IRB Coordinator and any additional staff that may be employed for the IRB report directly to the KCCOP Board of Directors.

2. IRB personnel will be evaluated annually by the Board of Directors.

3. The IRB Coordinator serves as a KCCOP resource to monitor changes in federal regulations and guidance governing human research protection

4. The IRB Coordinator is a voting member of the IRB.

5. The IRB Coordinator's responsibilities include, but are not limited to:

a. Continuing Review Reminder
The IRB Coordinator will remind the Principal Investigator of the need for IRB continuing review three (3) months prior to the expiration of the current project approval (the study will be reviewed one to two months prior to the month of expiration).

b. Document Receipt and Administrative Check
Documents submitted to the IRB may consist of any or all of the following:
1) Full Protocol document
2) Sponsor's sample informed consent document;
3) Local version of consent document;
4) IRB Review Application;
5) Investigator's Brochure (if applicable);
6) Forms/questionnaires designed for participant completion;
7) Education/recruitment materials intended to be used by participants;
8) Other documents as applicable;
9) Materials for a Facilitated Review of studies approved by the NCI CIRB

c. Generation of meeting Agenda, which includes
1) Date, time, and location of meeting
2) Call to Order/Welcome;
3) Review and approval of Minutes from a previous meeting (meeting

date will be listed);
4) Report of unanticipated, study related serious adverse or other events, Investigator Alerts
5) Review of research study materials for new studies, continuing review of previously approved studies, and study modifications
6) List of expedited actions (full study name) conducted since the last convened meeting
7) List of Facilitated Reviews (full study name) conducted since the last convened meeting
8) Adjournment

For each study review, the following information will be listed on the Agenda:
1) Type of review (new study, continuing review, modification)
2) Full study title and sponsor number of study
3) IRB study number
4) If study modification, the addendum/revision/update number or date)
5) Name of Primary Reviewer
6) Itemization of all study materials included in the review packet

d. Distribution of Meeting Materials
1) The IRB Coordinator will send all Board members the agenda, copies of the signed applications, a protocol summary, informed consent documents, and any other materials (e.g., data forms, questionnaires, etc.) to be reviewed at the meeting approximately 10 days prior to the scheduled meeting.
2) Only the primary reviewer and IRB Chair will receive the full protocol. All other members will receive a study summary;
3) If the protocol involves an investigational drug, the Investigator Brochure will be provided to the primary reviewer

e. Responsibilities During Convened Meetings
1) The IRB Coordinator will ensure that telephones, computers, and projectors or other communication connections are available as necessary.
2) The IRB Coordinator will have the complete files for each study undergoing continuing review or modification available for reference at the meeting.
3) The IRB Coordinator will ensure that provisions such as water, beverages, or meals for the members are available as appropriate
4) The IRB Coordinator will record written minutes of each convened IRB meeting as required in 45 CFR 46 and 21 CFR 50, 56. The IRB Coordinator will revise the minutes in accordance with the member comments and recommendations made at the next convened meeting.

f. Outcome Letters to Principal Investigator

The IRB Coordinator will draft an outcome letter documenting the study review, to be signed by the IRB Chair or designee. *The following information will be documented in the outcome letter:*
1) Study identification (IRB number, full title and sponsor's number);
2) List of documents approved (protocol with version date, consent form, recruitment materials, questionnaires, etc.);
3) Statement of outcome: Approval, Approval pending minor changes; Table, or Disapproval
4) The stipulations required by the IRB for approval, if any
5) The reason(s) for table or disapproval;
6) IRB approval date (date of the convened meeting)
7) Expiration date of IRB approval (364 days after approval, or less)
8) A reminder that all study modifications must be approved by the IRB before implementation; reporting requirements for unanticipated events and protocol deviation/non-compliance issues.

g. Final Approval Letters following contingencies for approval
1) The IRB Chair or Coordinator will review the PI's response and documentation for acceptability related to the IRB stipulations.
2) Responses determined to be incomplete are returned to the investigator for appropriate follow-up.
3) The IRB Chair or designee(s) will examine the revised documents and may give approval to the study without additional full IRB review.
4) If the response satisfies the IRB's requests and the study is approved, the IRB Coordinator will prepare an approval letter to be signed by the IRB Chair or designee stating that the study activities may begin.
5) The outcome letter will also include all of the elements of a formal approval outcome letter as listed.

h. Expedited Reviews
1) The IRB Coordinator and the Chair will determine whether a submission for continuing review or study modification is eligible for an expedited review.
2) The IRB Coordinator will prepare a letter of approval to be signed by the IRB Chair or designee.
3) If expedited approval is denied, the study will be placed on the agenda for the next convened IRB meeting.

i. IRB Database Management
The IRB Coordinator is responsible for ensuring that all required information is recorded in a timely manner and that the information is complete and accurate. All studies will be maintained indefinitely in the database records.
The database will include:
1) The number and full study title,
2) A notation of IND study drugs subject to FDA oversight

3) The date of initial approval,
4) The date of most recent re-approval,
5) The date of approval expiration,
6) The month of next review to ensure re-approval in <365 days (usually 1-2 months before expiration month)

j. Recordkeeping

1) Meeting Minutes

The IRB Coordinator will maintain minutes of convened meetings as delineated in 45 CFR 46 and 21 CFR 50, 56 as applicable. Minutes will be retained indefinitely.

At a minimum, the minutes will include:

a) Attendance at the meeting; The IRB Coordinator will document the name and scientific or non-scientific status of each IRB member who is participating and will confirm that a quorum is present before official IRB business is conducted. A quorum exists when a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas (45 CFR 46.108(b). A physician member must be present for the discussion and voting on research subject to FDA oversight.

b) Study documents reviewed (submission form, protocol (dated), consent form documents, Investigator Brochure, questionnaires, recruitment materials, etc.)

c) A summary of the discussion of controversial issues and their resolution;

d) IRB findings about risks, benefits, provision for data monitoring, etc;

e) Actions taken by the IRB;

f) The vote on these actions including the numbers For, Against, Abstained, Recused and Total Votes;

g) The basis for requiring changes in or disapproving research;

h) The IRB Coordinator will document any absence or addition to the IRB members during the course of the meeting to assure that a quorum is maintained throughout the meeting.

i) The minutes must show that members who have conflicts of interest were recused and left the room during the discussion and vote on a study, and were not counted in the total number of IRB members voting;

j) The minutes will include a list provided to the convened IRB of all expedited actions that occurred since the last meeting

k) The minutes will include a list provided to the convened IRB of all facilitated reviews that occurred since the last meeting

2) Study Files

The IRB Coordinator will maintain paper and/or electronic files

for all studies that are reviewed by the IRB, including expedited and facilitated reviews. Records will be retained at least three years after completion of the study as mandated in 45 CFR 46.115 and 21 CFR 56.115.

At a minimum, the IRB study files will include:

a) IRB Submission forms and submission materials for initial review, each continuing review, and all study modifications, whether reviewed by the convened IRB, expedited or facilitated

b) The full, current protocol document;

c) All versions of the informed consent document;

d) All relevant unanticipated event reports, Data Monitoring Committee reports*, and Investigator Alert letters from CTEP*

e) Copies of correspondence between the IRB and the Principal Investigator, research sponsor, or regulatory agencies

f) Statements of significant new findings provided to subjects;

g) Any other information pertinent to the protocol or to the drug(s) involved

h) Reviewer checklists

*DMC reports and Investigator Alerts that pertain to multiple studies may be stored in a separate file

3) IRB Membership Rosters and Files

The IRB Coordinator will maintain dated rosters of IRB members indefinitely, noting the member's role (regular or alternate member), and scientific/non-scientific, affiliation status with the KCCOP.

The member files must include the following information:

a) CV or resume including educational degrees

b) Certification of Human Subjects Protection Training

c) Annual signed Conflict of Interest attestation

d) Annual signed Confidentiality Agreement

4) The IRB Coordinator will maintain the following additional administrative records

a) Files of KCCOP consortium hospitals' Federalwide Assurances and IRB Authorization Agreements

b) Documentation of Investigator qualifications (CV), Human Subjects Protection Training, NCI Investigator Registration Number, Individual Investigator Agreement, Conflict of Interest Disclosure

c) IRB Budget and accounting records

5) Additional IRB Coordinator Responsibilities

a) Communicate information regarding IRB deadlines,

procedures, and meeting dates to IRB members, the P.I. and research staff

b) Respond to general inquiries;

c) Provide timely response to participants calling with inquiries regarding their rights as a research subject. All inquiries and/or complaints will be documented and discussed with the IRB Chair and the convened IRB, and noted in the minutes. All subjects expressing a complaint will receive a follow-up letter from the Chair as quickly as possible, describing remedial action if appropriate.

d) Maintain current understanding of human subject protection requirements by reviewing OHRP and FDA guidance materials, attending conferences, workshops, and seminars when possible;

e) Advise the IRB of any new information relating to research, federal regulations and/or guidance.

f) The IRB Coordinator is responsible for updating and maintaining a current OHRP IRB Registration.

D. IRB Office Resources

1. The KCCOP Board of Directors shall provide a separate, locked office space for the IRB, including adequate file storage and a password-protected computer.

2. The KCCOP will insure the IRB has the capability to maintain an electronic IRB spreadsheet or database.

3. The IRB records may not be accessed by the research team or others without the approval of the IRB Chair or designee.

4. IRB records are accessible for inspection and copying by authorized representatives of federal regulatory agencies and accrediting organizations at reasonable times and in a reasonable manner.

5. The KCCOP will make a copier and scanner available to the IRB as needed.

6. KCCOP will provide for a conference room for monthly IRB meetings.

E. Signatory Authority

The IRB Chair may designate another voting member of the IRB, including the IRB Coordinator, to sign in his/her stead.

F. Reporting Requirements

The IRB must ensure that the following are reported promptly to the KCCOP Board of Directors, the research sponsor, and the appropriate federal agency (OHRP and/or FDA):

1. Any unanticipated problems involving risks to human subjects or others;

2. Any instance of serious or continuing noncompliance with federal regulations or the requirements or determinations of the IRB;

3. A "for cause" suspension or termination of IRB approval of research.

III. IRB MEMBERSHIP AND STRUCTURE

A. Selection of Members

1. The membership of the IRB will include a minimum of five and not more than 14 individuals including consumer advocates, physicians (primarily oncologists), ethicists, non-physician healthcare providers, and others as deemed appropriate.

2. The KCCOP Board of Directors will appoint the IRB Chair and will approve additional members to meet the specific requirements of 45 CFR 46.107 and 21 CFR 56.107, so that the membership is sufficiently qualified through expertise, experience, and diversity to ensure its ability to safeguard the rights and welfare of human subjects.

3. The membership will include at least one scientific member, and one non-scientific member, and one or more members who are not affiliated with the KCCOP or the Board of Directors.

4. Alternate members may be designated at the discretion of the Chair. An alternate may vote in the absence of a voting member as long as both have similar qualifications and IRB roles. Voting physician members may only be represented by a physician alternate. Alternates may attend IRB meetings and may participate in discussions and serve as primary reviewers, but may not vote except in the absence of the member they are replacing.

B. Criteria for Selection

1. The KCCOP Board of Directors will solicit names for appointments from a variety of sources to select membership that is sufficiently qualified through expertise, experience, and diversity to insure its ability to safeguard the rights and welfare of human subjects. Membership will not be based on hospital affiliation, although qualified individuals who are employed by a member hospital may serve. Investigators may not take part in the selection of IRB members.

2. Existing IRB members may suggest names of persons in ethics, healthcare, and advocacy, who have demonstrated experience and/or interest in the protection of

the rights and welfare of human volunteers in research, and these will be considered for possible contact and appointment.

3. As IRB members resign and new members are appointed, selections will be made to assure continuing compliance with the requirements of 45 CFR 46.107 and 21 CFR 56.107.

4. A practicing KCCOP Investigator may not serve on the IRB, and may not take part in discussions about studies, except to provide information at the request of the IRB.

5. The IRB Chair will select a Vice-Chair with the concurrence of the IRB members.

6. The IRB Coordinator will serve as a voting member of the IRB.

C. IRB Member Terms

1. Each member will be appointed for a two-year term.

2. A member may be re-appointed for additional terms.

D. Responsibilities

1. The IRB Chair's responsibilities include

a. Maintain current knowledge of the ethical, legal and regulatory issues relating to the type of research studies and consent documents reviewed by the IRB;
b. Review all studies presented to the convened IRB and communicate with other reviewers as needed so that important issues may be resolved or identified prior to the convened meeting;
c. Direct the proceedings and discussion of convened IRB meetings by keeping the dialogue focused and insuring that all members have an opportunity to participate effectively;
d. As appropriate, assist in the development of IRB meeting agendas, policies, and procedures;
e. Adhere to and administer IRB decisions;
f. Conduct expedited review when appropriate, or delegate the authority to a qualified voting IRB member;
g. Review P.I. responses to modifications stipulated by the IRB for approval of research;
h. Review and sign IRB correspondence representing IRB decisions or delegate the authority to do so;
i. As appropriate, facilitate the resolution of controversial issues or procedural matters; and

j. Represent the IRB in discussing IRB decisions with the P.I. and research staff.

2. The Vice Chair's responsibilities include

a. The Vice Chair will assume all responsibilities and obligations of the Chair in the Chair's absence.

b. If the Chair is unable or unwilling to continue to perform his/her duties, the Vice Chair will assume all responsibilities of the Chair until the KCCOP Board of Directors appoints a new Chair.

3. The IRB Members' responsibilities include

a. Attend regularly scheduled Board meetings either in person or via teleconference with the approval of the Chair

b. Review all meeting materials prior to the meetings;

c. Serve as primary reviewer for scheduled studies when assigned, and submit a written review of the assigned protocol using the appropriate IRB reviewer checklist.

d. Actively participate in discussions at IRB meetings;

e. Vote to approve, disapprove, abstain, or table protocol reviews based on the regulatory requirements and personal judgment (unless a conflict of interest exists);

f. Maintain confidentiality of IRB discussions and all meeting material;

g. Study monthly training materials for discussion at monthly meetings to keep abreast of regulations and policies pertaining to human research.

h. If a member cannot attend a particular meeting, the IRB Coordinator must be notified a minimum of fourteen days in advance of the meeting, barring emergencies. If an emergency occurs and the member involved has been assigned to serve as the primary reviewer for a protocol, the written review should be forwarded to the IRB Chair if possible. The IRB Coordinator will reassign the review if necessary.

i. The IRB may use consultants when additional expertise is required.

4. Conflicts of Interest

a. Federal regulations prohibit a member of the IRB from participating in the initial or continuing review of any project in which the member has a

"conflicting interest," except to provide information at the IRB's request. 45 CFR 46.107(e)

b. Any IRB member with a conflicting interest in a project must disclose that to the IRB Chair and leave the room during the final discussion of the project and the related vote. The meeting minutes will document the recusal (*i.e.,* the temporary absence of the member during the final deliberation and vote on the project with respect to which the member has a conflict). If an IRB member is recused from the vote, (s)he may not be counted towards the quorum.

c. In the case of expedited review (outside of a convened meeting, by a designated reviewer), the reviewer must disclose any conflicting interest in a project in advance to the IRB Chair and should not review the project. If the Chair is the reviewer with a conflicting interest, then another qualified member of the IRB should be designated to perform the review.

d. This policy applies to all members of the IRB and to *ad hoc* reviewers, who are not IRB members but sometimes are asked to review a project because of their expertise.

e. A conflict of interest includes participation in the project, a financial interest as defined below, and/or any other examples referenced below. A conflict may arise because of an interest of the IRB member or his/her family (spouse, domestic partner and/or dependent children); the aggregate interest of the IRB member and family is considered.

"Participation in the project," for purposes of this policy, generally means the member is listed on the protocol/project, or will be included (or reasonably may be expected under academic standards to be included) as a co-author on a publication of the project's results. "Participation in the project" does not mean serving as a member of the IRB.

f. A "financial interest" is a conflicting interest under this policy if it is one of the following interests in a business that is supporting or facilitating the project, or the interest is in a business that is known to the IRB member to own (or have license rights to) the technology that the project involves, and the individual is:

1) receiving more than $20,000 annually (not including reimbursement of reasonable travel and other expenses) from a business for any reason, including but not limited to consulting, royalties, attending or speaking at conferences, or being employed;

2) having an equity interest in a business, except for an interest of less than $30,000 in a publicly held, widely traded business. An equity interest includes stock, options, and similar ownership interest. It excludes an interest arising solely from investment in a business by a mutual, pension, or other institutional

investment fund over which the IRB member does not exercise control;
3) having an ownership interest in a patent or a patent application covering the technology that the IRB member knows the project involves.

g. Other examples of conflicting interests include but are not limited to:
1) Serving as a member of a Board of Directors or Scientific Advisory Board or as an executive to a business that is supporting or facilitating the project, or that owns or has license rights to the technology the project involves;
2) Having certain non-financial interests that may create a real or perceived conflict. Any real or perceived conflict, or a concern that there may be a real or perceived conflict, that is not addressed above should be raised with the IRB Chair. If the IRB Chair determines there is a potential conflicting interest, then the member shall recuse him/herself. The IRB Chair reserves the right to request recusal as appropriate in any particular circumstance.

h. An IRB member must disclose a potential conflicting interest to the IRB Chair in advance of the meeting when possible. At the beginning of each IRB meeting, members also will be reminded of the conflicts policy and may disclose any potential conflict at that time.

i. Individuals with greater responsibilities for reviewing human subjects research (primary reviewers) may have potentially more influence over the review and approval of a project and thus should be particularly sensitive to any perceived or real conflicting interest.

j. An IRB member may not consult for a business to assist it in shepherding a project through the IRB process.

k. "Consultant" reviewers must receive a copy of this policy with materials for the project they are reviewing.

l. An entry in each meeting's minutes will reflect adherence to this policy.

5. Termination of Appointment

If a member is unwilling or unable to fulfill IRB member responsibilities, he/she will be excused from membership in the IRB by the Chair. IRB members may be terminated by a joint decision by the IRB Chair and Vice Chair with the concurrence of the KCCOP Board of Directors. IRB members who wish to resign before the end of their term shall notify the IRB Chair. The KCCOP Board of Directors may remove the Chair at their

discretion. Justification for removal will be documented in the Board of Directors' meeting minutes.

6. IRB Member Education and Training

a. Each new member will be required to complete initial training offered by the NIH or CITI and will be oriented by the IRB Coordinator.

b. New IRB members will receive the Belmont Report, information about cancer clinical trials and the KCCOP, IRB Policies and Standard Operating Procedures, and other resources.

c. The IRB Chair will also complete the web-based OHRP Federalwide Assurance training.

d. All members will participate in continuing education at the IRB meetings. Training information will be included in the monthly meeting packet.

e. Continuing education will include updates during regular IRB meetings on relevant procedural and policy changes as appropriate.

f. Members will be provided access to texts and other resource documents in the IRB Office.

7. Compensation of IRB Members

a. The Chair will receive an honorarium for his/her administrative responsibilities to be determined by the KCCOP Board of Directors.

b. IRB Members will not be paid for their participation on the committee.

c. IRB Members will receive a quarterly reimbursement for mileage based on the current federal rate or an annual gift as thanks for their service.

d. The IRB Coordinator will be paid a contract fee determined by the Board of Directors.

8. Liability of IRB members

IRB members are considered volunteers of the KCCOP, and are covered under the organization's general liability policy.

IV. STUDY REVIEW PROCEDURES

A. Schedule of Meetings

1. The IRB will hold convened meetings on the third Thursday each month. IRB Members will receive a schedule for the upcoming year's meetings. The IRB Coordinator will contact all committee members via e-mail approximately three weeks prior to a scheduled meeting.

2. In the event that a meeting must be postponed (lack of quorum, severe weather or other emergency), it will be rescheduled at the earliest possible date to ensure that no study re-approval exceeds its expiration date. The IRB Coordinator will inform the IRB members of such circumstances if they arise.

3. The IRB may allow some members to participate in convened meetings by telephone or video conferencing as long as they have received a copy of all of the documents under review at the meeting, a quorum as defined above is present, and discussion occurs in real time. Such members count as part of the quorum and may vote.

B. Scope of Meetings

The IRB will conduct initial reviews of studies, continuing reviews at least annually, reviews of proposed modifications to approved study materials, reviews of serious unanticipated adverse events occurring locally, and significant unanticipated events occurring locally, and the sponsor's Data Monitoring Committee reports and/or other communications regarding new risks to subjects.

C. Initial Review of New Studies

1. All new studies must be reviewed and approved by the IRB at a convened meeting.

2. PI Submission Requirements

a. The study materials required for initial IRB review include

1) A list of investigators including their professional qualifications to do the research, certification of completion of the NCI online "Human Subjects Protection Training for Research Teams" (files may be maintained in the IRB office).
2) The IRB's Submission Form for a new treatment (or non-treatment) study
3) The current study protocol, which includes the title of the study, sponsor of the study, purpose of the study (including the expected benefits obtained by doing the study), results of previous related research, eligibility criteria, justification for use of any special/vulnerable subject populations, study design, description of procedures to be performed, provisions for managing adverse reactions, the circumstances surrounding consent procedure, including setting, subject autonomy concerns, language difficulties, vulnerable populations, the procedures for documentation of informed consent

4) The sponsor's sample consent form
5) The KCCOP's local version of the consent form
6) Any documents (such as questionnaires, diaries, recruitment materials) that the patient will see
7) If applicable, a Form 1572
8) If applicable, the Investigator Brochure for study drugs

b. The study materials must be submitted by the deadline set by the IRB, which is generally two weeks before the meeting date of the month preceding the meeting.

3. Pre-Meeting Preparation for Primary Reviewers and Other Board Members

a. IRB members will be selected as primary reviewers based on background and expertise.
1) The Primary Reviewer for new treatment studies will be an oncologist.
2) The Primary Reviewer for a new non-treatment study will be a member of the committee with appropriate expertise.
3) The Informed Consent Reviewer will be chosen from the non-scientific members on the committee.
4) Members will be chosen as primary reviewers on a rotating basis to ensure responsibilities are shared equitably.

b. The committee members will receive meeting materials 10 days prior to the scheduled IRB meeting by US mail or by electronic transfer.

c. All committee members will receive a copy of the completed submission application including a summary of the protocol, the KCCOP revised consent form, and any other documents the study participant will see (e.g. recruitment material, descriptions of side effects, questionnaires, diaries, etc.)

d. Committee members will have access to all study materials both before and during the meeting. If materials are distributed electronically, they will be projected from a laptop during the meeting for reference.
1) The Primary Reviewer will receive all of the documents described above as well as a copy of the full protocol, the Investigator Brochure and/or Package Insert for study drugs (if available), and the KCCOP's Cost Assessment for the study procedures (if applicable).
2) The Primary Reviewer will ensure that s/he has all the necessary information to determine whether the study meets the requirements for approval as required by 21 CFR 56.111 and 45 CFR 46.111.
a) that risks to subjects are minimized,
b) that risks are reasonable in relation to anticipated benefits,
c) subject selection is equitable,

d) informed consent is adequate and documented,
e) the study monitoring plan and plan for protecting privacy and confidentiality of data are adequate
f) safeguards for vulnerable subjects have been established
(See *Initial Review Checklist).*

3) The Informed Consent Reviewer will receive all of the documents described in c) above as well as the sponsor's sample informed consent. The Informed Consent Reviewer will receive an *Informed Consent Review Checklist.*

a) The Informed Consent Reviewer will ensure that the consent form includes all the basic elements of information as set forth in federal regulations in 45 CFR 46.116(a-b) and detailed on the Informed Consent Review Checklist.
b) If payment is offered to study subjects, the reviewer should ensure that both the amount of payment and the schedule of payments are stated in the consent form.
c) The reviewer should consider KCCOP's "Cost Assessment" of study procedures to ensure that subjects are fully informed about additional expenses they may incur as study participants.
d) The reviewer must ensure that the consent form does not contain any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the organization or its agents from liability for negligence.
e) The Reviewer should verify that the local KCCOP "boilerplate" additions have been made to the informed consent, although no specific information from the sponsor's sample consent concerning Study Procedures, Risks, or Alternatives may be deleted from the informed consent document. The reviewer or other committee members may make minor word substitutions or additions in the informed consent document if necessary to facilitate better comprehension as long as the proposed changes do not alter the meaning of the sponsor's consent contents. Additional risks may be added to the informed consent document at the discretion of the convened IRB. As a general rule, the IRB subscribes to the language used in the NCI's *Informed Consent Template for Cancer Treatment Trials.*
f) In the event that the KCCOP requests the use of a "short form" consent for non-English speakers, this document must be reviewed as well as the English version of the consent form.

e. Reviewers are urged to discuss significant concerns about studies with the KCCOP Principal Investigator prior to the meeting to obtain clarification and/or additional information.

f. Primary Reviewers will present their findings and recommendations to the committee. IRB members will raise questions, discuss controverted issues, identify necessary changes to the study materials, and reach a conclusion regarding approval.

g. Each primary reviewer will complete and sign the relevant checklist prior to the meeting. The checklists will be submitted to the Compliance Coordinator to be filed as a source document in the IRB Study File.

4. Meeting Format

a. The IRB Chair will preside over each IRB meeting.

1) If the Chair is absent, the IRB Vice Chair will serve as the acting Chair.

2) In the event that neither the Chair nor the Vice Chair will be available to preside over a specific meeting, the Chair will designate another member of the committee to serve as the acting Chair at the meeting.

3) If the IRB Chair has disclosed a conflict of interest with a scheduled review, the Vice Chair or another member designated by the Chair will serve as the chairperson for that discussion and review.

b. The Primary Reviewer, using the *Initial Review Checklist*, will briefly summarize the study and her/his succinct review for the committee, focusing on issues or concerns, and provide a recommendation to approve, approve with minor modifications, table, or disapprove the study. The Primary Reviewer will recommend the re-review period, based on the degree of risk, the nature of the study, the vulnerability of the study subjects (if applicable), and provisions for safety reviews and summary reports to be provided by the sponsor.

c. All members attending in-person or via teleconference may then participate in a discussion of the study, offering additional concerns and recommendations as appropriate.

d. The Informed Consent Reviewer will present a succinct review based on the sponsor's sample consent form, the IRB consent form, and the *Informed Consent Checklist.*

e. All members attending in-person or via teleconference may then participate in a discussion of the consent form, offering additional concerns and recommendations as appropriate. The IRB may not make changes to the meaning and intent of the Study Procedures, Risks, Alternatives to Study Participation, or other sections of the sample consent form. However, it is the IRB's responsibility to ensure that the consent form is comprehensible to study subjects. Additional risks may be added with the concurrence of the physician members of the IRB, language clarifications may be made, and typos corrected. Minor clarifications, corrections, and additions will be noted on a copy of the

KCCOP form and retained in the IRB file. These changes will be made administratively by the IRB Coordinator, and the dates of approval and expiration will be recorded in the upper right corner of each page of the document, which will be returned to the research team with the approval letter.
If the KCCOP requests the use of a "short form" consent, the Principal Investigator must assure the IRB that appropriate staff are available to serve as interpreters.

f. Verification of material changes: The Cooperative Group studies to be reviewed by the IRB are overseen by the Research Bases, and confirmation of IRB review and approval of all changes is required and tracked. Amendments, revisions, and updates made by the Sponsor are listed on the cover of each protocol. The KCCOP study coordinator (CRA) monitors performance and data collection at the local study sites. In addition, the NCI conducts regular monitoring of these studies and monitoring visit reports must be submitted to the IRB Chair for review. These safeguards ensure that material changes to the studies will be reported to the IRB.

g. All reviewer checklists will be signed and submitted to the IRB Coordinator after the meeting for inclusion in the IRB study file.

5. Exceptions to Consent Requirements

a. In general, the KCCOP research studies involve the treatment or prevention of cancer, or the treatment of cancer symptoms or side effects.

b. For certain studies such as quality of life questionnaires, the IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or may waive the requirements to obtain informed consent provided the IRB finds that:

1) the research involves no more than minimal risk to the subjects;
2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
3) the research could not practicably be carried out without the waiver or alteration; and
4) whenever appropriate, the subjects will be provided with additional information after participation.

c. Short form consents may be used by investigators under the following circumstances:

1) there must be an oral presentation (in a language understandable to the subject or the subject's legally authorized representative) of all information contained in the complete informed consent document.
2) a short-form written document (in a language understandable to the subject or the subject's legally authorized representative) to be presented to the subject includes a statement that the elements of informed consent have been presented orally;

3) a summary of the oral presentation is provided (the English version of the informed consent may serve as the summary);
4) there must be a witness to the oral presentation
5) the written summary must be approved by the IRB;
6) the written summary must be signed by the person obtaining consent and the consent witness;
7) a copy of the written summary and a copy of the short form should be given to the subject's legally authorized representative.

6. Member Recusal from Voting

In accordance with the IRB Conflict of Interest Policy for IRB Members any member reporting a conflict of interest to the IRB Chair regarding a study for review must recuse from the discussion and voting on the study by physically leaving the room.

7. Conditions for Approval

a. In accordance with 45 CFR 46. 111 and 21 CFR 56.111, the IRB must confirm that the following conditions have been met to approve a new study:

1) Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

a) The Principal Investigator must assure the IRB that study-related unanticipated adverse events involving study participants for whom the IRB is responsible will be reported promptly to the IRB.

b) The Principal Investigator must assure the IRB that study-related unanticipated problems that may involve risk to the participants or others will be reported promptly to the IRB.
c) In addition, the sponsor's monitoring plan for the research, if deemed appropriate by the IRB, must address the following:

(1) The type of data or events that are to be captured under the monitoring plan.

(2) Who will be responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a DSMB or DMC, and/or some other entity).

(3) The time frames for reporting adverse events and unanticipated problems to the monitoring entity.

(4) The frequency of assessments of data or events captured by the monitoring plan.

(5) Definition of specific triggers or stopping rules that will dictate when some action is required.

(6) As appropriate, procedures for communicating to the IRB, the study sponsor, and other appropriate entities the outcome of the reviews by the monitoring entity.

7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

8) If some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. The IRB acknowledges that the KCCOP studies do not target children, prisoners, pregnant women, or mentally disabled persons.

9) If cognitively impaired individuals are likely to be enrolled, the research plan should describe the role of the physician investigator and study coordinator in assessing the appropriateness of the individual for participation in a clinical trial (i.e. compliance with study procedures, etc.). The plan should specify how the treating investigator will evaluate the level of risk and the potential for benefit to the individual over standard of care (if available). In addition, the investigator must assess the ability of a legally authorized representative (if appropriate) to understand and make an informed consent about the research on behalf of a cognitively impaired individual.

8. Voting

a. After discussion of the study has been completed, all committee members have had an opportunity to raise issues of concern, and a reasonable attempt at resolution has been made, the Chair will call for a motion for action.

b. Committee members will submit a motion and second of the motion.

1) Before a vote can be taken, the Chair must confirm a quorum is present, including at least one member whose primary concerns are in nonscientific areas.

2) For studies involving FDA-regulated articles, at least one physician member must be present.

3) A quorum is defined as the majority of the members of the IRB. All IRB members at the meeting have full voting rights.

4) For each action, a majority of the members present at the meeting must approve the action. There may be no proxy votes.

c. The IRB may approve the research study, approve contingent on minor changes, table or disapprove the research (see section on *REVIEW OUTCOMES* in this document).

9. Notification and Follow-Up

a. As mandated in 45 CFR 46.109(d), for each initial review of a new study that is conducted by the IRB, an outcome letter, signed by the Chair or designee, will be sent to the KCCOP Principal Investigator advising of the outcome of the IRB review within one week.

1) In the case of a study for which approval is pending, the minor changes required by the committee will be documented in the outcome letter. Revised materials must be submitted by the Principal Investigator to the IRB Coordinator, who will review them for compliance with the committee's requests. A letter stating approval to begin enrollment, signed by the IRB Coordinator, will be sent to the P.I. within one week. Expedited approval of such changes will be reported to the IRB at the next convened meeting. If the study is approved with stipulations that may be germane to the IRB's full approval, the information will be discussed at the next convened meeting.

2) Minor changes to the consent form required by the IRB will be made administratively by the IRB Office. The approved consent form with the approval date and expiration date in the upper right header, and the version notation in the lower left footer, will be sent with the approval letter.

3) In the case of a study that is tabled requiring substantive changes or additional information, the Principal Investigator will

be informed of the reason(s) for the action in the outcome letter. Additional information may be requested. When revised materials are submitted, the study will be reassigned to the original primary and other reviewers if possible, and presented for full board review at a subsequent meeting.

4) For a study that has been "approved pending minor modification" or "tabled," a response from the P.I. is expected not later than 60 days after the date of the outcome letter. The IRB Coordinator will specify this deadline in the outcome letter. In the event that no response is received by the deadline, the study submission will be inactivated.

5) If a protocol has been "disapproved," the P.I. will have a maximum of 60 days to respond before the IRB study submission is inactivated.

6) In the event that a protocol is disapproved, an outcome letter, signed by the Chair or designee, will be sent to the KCCOP Principal Investigator detailing the reasons for the action within one week. Per 45 CFR 46.109(d), the Principal Investigator will be given the opportunity to respond to the IRB in person or in writing.

7) The PI is expected to report the IRB action to the study sponsor.

b. The approval letter will include the following reminder to the PI: *"You are reminded that modifications to this study must be approved by the IRB prior to implementation. Reportable serious adverse events and unanticipated problems associated with the research must be reported to the IRB consistent with federal regulations and IRB policies."*

D. Continuing Review of Research

1. PI Submission requirements

a. The IRB will send a reminder notice to the KCCOP PI of studies due for continuing review at the first of the month two months in advance of the expiration date.

b. Continuing Review submissions from the Principal Investigator must include the following information in the IRB *Submission Form for Continuing Review of Research*:

1) The number, gender, and race of participants accrued;

2) A description of any vulnerable populations targeted for inclusion;

3) A summary of unanticipated serious, study-related adverse events and/or unanticipated problems involving risks to participants or others;

4) An explanation of withdrawal of participants from the research, or complaints about the research;

5) A summary of major protocol deviations;
6) A summary of recent literature, findings or other relevant information, such as multi-center trial reports from the sponsor/ NCI Research Base;

c. The current version of the protocol containing all modifications to date

d. A copy of the current approved consent form document and a proposed new consent, if applicable.

e. In the case of a multi-center trial, a report from the sponsor that includes study-wide treatment toxicities and adverse events, interim findings and relevant literature if any, the most recent Data Safety Monitoring Board or Data Monitoring Committee report, with recommendations about the study, if available;

f. An updated Investigator Brochure or Package Insert (if applicable);

g. The study materials for continuing review must be submitted by the deadline set by the IRB, which is generally two weeks prior to the meeting date.

2. Continuing reviews of each active study will be performed by the convened IRB within 365 days of initial approval, unless the initial review has stipulated that review is required more frequently in accordance with the requirements of 45 CFR 46.108(b), 45 CFR 46.110, 45 CFR 46.111, and 45 CFR 46.115 (a)(2), and 45 CFR 46.116(b)(5)

a. More frequent review, at intervals appropriate to the degree of risk, may be required at the discretion of the IRB.

b. Continuing review will be conducted as long as a study remains open (e.g. study participants are being followed as stipulated by the protocol).

c. Continuing review for a specific study will no longer be required when
1) The study is closed (no study participants are being followed) or
2) The study is closed and long-term follow-up of study participants is transferred to a Long Term Follow-up Protocol.

d. Continuing Review may be expedited if the study meets the requirements of 45 CFR 46. (see 'Use of Expedited Review') determined by the IRB Chair or designee.

3. Verification from Sources Other Than the P.I.
The KCCOP does not engage in investigator-initiated research. All studies are multi-site studies sponsored by NCI-funded entities and industry sponsors, and

researchers are monitored regularly. Modifications to the study are initiated by the sponsor, which ensures that IRB approval is obtained. The KCCOP conducts internal monitoring of protocol compliance and reports significant deviations to the IRB. Additional verification that no material changes have occurred since the last IRB approval are not required in this research setting.

4. Pre-Meeting Preparation

a. IRB members will be selected as primary reviewers based on their background and expertise.

1) The Primary Reviewer for treatment studies will be an oncologist, preferably the individual who serves as Primary Reviewer during the initial review.
2) The Primary Reviewer for a non-treatment study will be a member of the committee with appropriate expertise.

b. The committee members will receive meeting materials 10 days prior to the scheduled IRB meeting.

c. All committee members will receive:

1) A copy of the completed Continuing Review submission form with a status report including the number and description of subjects enrolled, the number of subjects who have withdrawn, complaints about the research, a summary of unanticipated adverse events and/or problems, a summary of any new information that is available (especially information about new risks)
2) A current summary of the study (which may be the sponsor's meeting summary)
3) The current KCCOP consent form (and a revised consent when applicable)
4) Data Monitoring Committee reports (If these are submitted for several studies and stored separately, the IRB Coordinator may report the individual study findings verbally.)

d. The Primary Reviewer will receive all of the documents described in c), as well as a copy of the full protocol containing all modifications approved during the review period and the updated Investigator Brochure and/or Package Insert, if available. The Primary Reviewer may have access to the entire study file including minutes of previous meetings upon request to the IRB Coordinator. The Primary Reviewer will receive a *Continuing Review Checklist* to report findings.

e. The Primary Reviewer will complete and sign the *Continuing Review Checklist* prior to the meeting. The checklist will be submitted to the IRB Coordinator after the meeting to be filed as a source document in the IRB study file.

f. The reviewer is urged to discuss significant concerns with the KCCOP Principal Investigator prior to the meeting to obtain clarification and/or additional information.

5. Meeting Format

a. The meeting format for a convened IRB continuing review is the same as described for initial reviews (see 'Initial Review,' section II).

b. Each study will be reviewed, discussed and voted on separately by the convened IRB.

c. The current complete protocol and all supporting documentation will be reviewed to ensure that the information is still accurate and complete.

d. The IRB will consider changes or additions that have been made to the study materials including changes in the research design, data monitoring reports, protocol violations and/or deviations, and any reports of investigator non-compliance.

e. The IRB will note whether Data Monitoring Committee (or other central entity) reports have been submitted by the Sponsor according to the plan provided at the time of initial study review.

f. The IRB must determine whether new information or the identification of new risks which may affect study participants' willingness to continue participation should be communicated to them, and the method by which this should be accomplished (i.e. at the next scheduled visit, by letter, etc.)

g. Copies of any new information conveyed to participants must be submitted to the IRB for approval.

h. The Primary Reviewer will re-assess the risk level of the study and recommend the next re-review period.

6. IRB Member Recusals from Voting
In accordance with the IRB Conflict of Interest Policy for IRB Members a member reporting a conflict of interest to the IRB Chair regarding a study for review must recuse from the discussion and voting on the study and physically leave the room.

7. Conditions for Re-Approval
The IRB must confirm that the following conditions have been met to re-approve a new study:

a. Risks to subjects are minimized

b. Local, study-related, unanticipated, serious adverse events and unanticipated problems involving risks to subjects or others have been reported appropriately to the IRB during the review period.

c. The IRB may rely on reports from oversight entities such as Data Monitoring Committees for review of study-wide adverse events, interim findings, and any recent new information that may be relevant to the research.

d. Risks to subjects continue to be reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

e. Selection of subjects is equitable and/or acceptable.

f. The correct version of the consent form is in use and contains any new information as appropriate.

g. The privacy of subjects and the confidentiality of data have been maintained.

8. Voting

a. After discussion of the study has been completed, all committee members have had an opportunity to raise issues of concern, and a reasonable attempt at resolution has been made, the Chair will call for a motion for action.

b**.** An IRB member will submit a motion for approval of the study and second of the motion.

1) Before a vote can be taken, the Chair must confirm a quorum is present, including at least one member whose primary concerns are in nonscientific areas.
2) For studies involving FDA-regulated articles, at least one physician member must be present.
3) A quorum is defined as the majority of the members of the IRB.
4) For each action, a majority of the members present at the meeting must approve the action (45 CFR 46.108(b).

c. The IRB may approve the research study, approve pending minor modifications, table or disapprove the research (see section on *REVIEW OUTCOMES* in this document).

9. Notification and Follow-Up

a. Notification procedures subsequent to continuing review of a study are the same as those specified for initial reviews (see *INITIAL REVIEW*). The approval letter will contain the following reminder: *"Approval of this research is contingent upon your agreement to: (1) Adhere to all KCCOP Policies and Procedures Relating to Human Subjects, as written in accordance with the Code of Federal Regulations (45 CFR 46). (2) Maintain copies of all pertinent information related to the research study including, but not limited to, video and audio tapes, instruments, copies of written informed consent agreements, and any other supportive documents in accordance with the KCCOP Research Records Retention Policy. (3) Report potentially serious events to KCCOP IRB by completing the KCCOP "Adverse Event Report". (4) Submit deviations from previously approved research activities which were immediately necessary to eliminate apparent and immediate dangers to the subjects. (5) Submit Amendments to the KCCOP IRB for any proposed changes from the previously approved project. Changes may not be initiated without prior KCCOP IRB review and approval. (6) Submit a Continuing Review (CR) to the KCCOP IRB before the expiration date. Federal regulations and KCCOP policies require continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. If you have any questions regarding the human subject protection process, please do not hesitate to contact our office."*

b. In the event that the IRB decides to terminate a study "for cause" the KCCOP Board of Directors, the study sponsor, and appropriate federal agencies will be notified.

10. Expiration of Approval

a. Suspension of Research Activities
If the IRB has not reviewed and approved a research study by the study's current expiration date all research activities must stop. No new subjects may be enrolled in the study.

b. Notification of Principal Investigator
The IRB Coordinator will warn the Principal Investigator of the impending expiration of study approval at the earliest opportunity and will send a final notification of expiration and suspension of study activities on the expiration date.

c. Permission for specific activities to continue
The Principal Investigator may send written assurance within three days that s/he is actively pursuing renewal and request that patients currently enrolled in the study and undergoing active treatment be allowed to

continue the study regimen for their own well-being and safety. The IRB Chair may grant permission for the treatment and care to continue.

d. In this event a letter, signed by the IRB Chair must be sent to the P.I. requiring that the study materials for Continuing Review must be submitted for the next regularly scheduled IRB meeting.

e. If the study is not submitted for Continuing Review as required, the study must be terminated and notification must be sent to the Principal Investigator immediately. The PI must re-submit the study as a new study if s/he wishes to continue the study.

11. Study termination by the IRB

a. The Principal Investigator must ensure that subjects currently enrolled in the study are notified in writing that the study has been terminated. Patients must also be informed if follow-up of subjects for safety reasons is permitted or required by the IRB.

b. The Principal Investigator must describe in writing to the IRB the procedures for withdrawal of enrolled subjects including how the rights and welfare of subjects will be protected.

c. Any adverse events or outcomes must be reported to the IRB and the sponsor.

E. Review of Study Modifications and New Information

1. Modifications include amendments, revisions, updates, notice of enrollment closure, and new study information. New information may include Data Monitoring Committee reports, sponsor's notification of new risk, patient letters, notice of final study closure, etc.

2. All modifications made to a previously approved study must be reviewed and approved by the IRB prior to implementation (45 CFR 46.103 (b)(4) including

a. Modifications made in response to requests by the IRB PI

b. Modifications made by the Sponsor

c. Deviations or changes made by an Investigator

1) Modifications to an approved protocol that an investigator anticipates prospectively must be submitted to the IRB Chair in writing. Unless such a modification is required for the safety of the study subject, with the concurrence of the Research Base Study

Chair, such a modification may be considered a protocol violation, and will be reported to the convened IRB.
2) Any exceptions to the protocol design or procedures that have been made inadvertently by an investigator should be reported to the IRB as promptly as possible.

d. Research Base Modifications must be submitted for IRB review and approval within 90 days of issue by the sponsor.

3. A protocol modification may qualify for expedited review if it meets the requirements of 45 CFR 46.110 (b)(2) and, when applicable, 21 CFR 56.110(b)(2)

a. This determination will be made by the IRB Chair or his/her designee.

b. If the modification does not meet the requirements for expedited review it will be scheduled for a convened IRB review at the next regularly scheduled meeting, provided that it is received on or prior to the submission deadline. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects [21 CFR 56.108(a)(4)]. In such a case, the KCCOP Principal Investigator must notify the IRB promptly of the change. The IRB must review the change at the next regularly scheduled meeting to determine that it is consistent with ensuring the subjects' continued welfare.

c. Modifications to the risk section of the consent form may, or may not change the risk/benefit balance of the study. This determination must be made by the Chair or an experienced designee, who must also determine whether study subjects must sign a revised consent form. If re-consent is required by the IRB, the approval of the modification must include a statement to that effect. In general, expedited changes to the consent form will not involve significant new risks, and re-consent may not be required by either the Sponsor or the IRB.

4. Modifications to the consent form for studies that are permanently closed to enrollment will be reviewed by the IRB, but an approved consent form will not be provided back to the Principal Investigator unless requested for a subject transferred from another location.

5. Study modifications for studies that have been permanently closed, but patients are in long-term follow-up under a IRB-approved Long Term Follow-up Protocol need not be submitted to the IRB except for information regarding a new long-term risk associated with the study.

6. Modifications that include new or modified risk information to be added to the consent form may require suspension of enrollment by the KCCOP until IRB approval of the revised consent form is obtained.

7. Modifications to studies in which enrollment is closed, and no subjects are on active treatment may not require IRB approval at the discretion of the Chair or designee.

8. Modifications such as amendments, revisions, and updates that are issued shortly after study Submission Forms for a New Study or Continuing Review may be appended to these submissions and distributed with the meeting materials to the IRB members. The IRB approval or re-approval must specify that the modification is included.

9. PI Submission Requirements

a. The IRB *Submission Form for Study Modification*

b. A copy of the sponsor's description of the modification

c. New or updated study materials, as applicable

d. A revised consent form, if required by the modification

e. A current protocol containing the modification, if applicable

f. A study Summary

10. Pre-Meeting Preparation

a. An IRB member with appropriate background and expertise will serve as primary reviewer.

b. The committee members will receive study materials 10 days prior to the scheduled IRB meeting.

c. All committee members will receive a copy of the completed Modification submission application including a current summary of the protocol, and the current KCCOP consent form.

d. The Primary Reviewer will receive all of the documents described above, as well as a copy of the full protocol and the and the Sponsor's sample informed consent (if applicable). The Primary Reviewer will receive a *Modification Checklist*.

e. The reviewer will complete and sign the *Modification Checklist* prior to the meeting. The checklist will be submitted to the Compliance Coordinator after the meeting to be filed as a source document in the IRB study file.

11. Meeting Format

a. The meeting format for a full Board review of a modification is the same as described above for initial reviews (see Initial Review).

b. The consent form will be reviewed to ensure that information relevant to the modification has been included.

12. Voting

a. After discussion of the study has been completed, all committee members have had an opportunity to raise issues of concern, and a reasonable attempt at resolution has been made, the Chair will call for a motion for action.

b. Committee members will submit a motion and second of the motion.

1) Before a vote can be taken, the Chair must confirm a quorum is present, including at least one member whose primary concerns are in nonscientific areas.
2) For studies involving FDA-regulated articles, at least one physician member must be present.
3) A quorum is defined as the majority of the members of the IRB.
4) For each action, a majority of the members present at the meeting must approve the action (45 CFR 46.108(b).

c. The outcomes that the Board may vote for an amendment review are the same as those for an initial review, except as noted:

1) Approve: The amendment may be implemented as designed.
2) Approve with minor changes:
    a) Minor additional information and/or modifications are required.
    b) The P.I. must make written revisions of specified documents and return them to the IRB in order to gain full approval.
    c) The IRB must indicate in the outcome letter to the P.I. whether or not the study can continue pending approval of the additional changes.
3) Table
    (a) The amendment cannot be approved without substantive changes and/or there is insufficient information available to evaluate the modification.

(b) The IRB must indicate in the outcome letter to the P.I. whether or not the study can continue without modification.

4) Disapprove

a) The modification should not be implemented as designed.

b) The IRB must indicate in its letter to the P.I. whether or not the study can continue without modification.

13. Notification and Follow-Up

Notification procedures for modification reviews are the same as those specified for initial reviews (see Initial Review).

14. Modifications Submitted in Response to an NCI CTEP Action or Sponsor's Warning Letter

a. Modifications submitted in response to NCI CTEP Action or Warning Letters follow the same procedures for modification review as outlined above; however, the timeline for IRB review differs.

1) Action and Warning letters may be issued by the CTEP and may require change(s) in the protocol and/or informed consent document due to participant safety issues or revisions in the description of risks.

2) In order to permit the investigator to meet the 90 day deadline for implementation, revisions that require full IRB review must be reviewed within 90 days of receipt of the Lead Cooperative Group's modification request from the CTEP. If this deadline cannot be met by the regularly scheduled IRB meeting date, an ad-hoc meeting may be scheduled.

3) Action Letters may be discussed by the convened IRB at the time they are issued. Subsequent changes may be required in several studies, and these changes may be given expedited approval.

4) Ad-hoc meetings, which must meet the same requirements as a fully convened meeting, are scheduled when specific items of concern arise that cannot reasonably wait until the next regularly scheduled Board meeting.

F. Research Review Outcomes and Communications

1. After reviewing a new study, conducting continuing review of a study, or reviewing a modification to an approved study, the IRB will vote for one of the following actions (45 CFR 46.109, 21CFR 56.109):

2. Approve: The protocol may be implemented as designed, or may continue, or may continue with modifications.

3. Approve pending minor changes: Minor additional information and/or changes are required. The P.I. must make written revisions of specified documents in order to gain full approval. Once the revisions are completed, the IRB Chair or designee(s) will examine the revised documents and may give expedited approval or refer it to the full Board for further review. When minor clarifications are required to the consent form, these will be made administratively by the IRB and contained in the final approved version.

4. Table: The protocol cannot be approved without substantive modification and/or there is insufficient information available to adequately review the protocol. When the protocol has been revised and/or the additional information has been obtained, the study will be reconsidered by full IRB review at the next available regularly scheduled board meeting.

5. Disapprove: The protocol cannot be implemented or continued as designed. If a protocol that has been disapproved by the IRB is resubmitted, it must be submitted as a new protocol.

G. Expedited Review

1. All new studies, regardless of risk level, require full IRB approval at a convened meeting.

2. In accordance with 45 CFR 46.110 and 21 CFR 56.110, the IRB may utilize expedited review procedures under the following circumstances:

a. Review of minor changes in research previously approved by the convened IRB during the period (of one year or less) for which approval is authorized.

1) minor modifications may include

a) changes in study protocol, consent form, or other documents, such as spelling corrections, reformatting, or clarifications;

b) changes to administrative information such as names, addresses, telephone numbers, dates, data submission guidelines;

c) minor scientific changes in eligibility, study procedures, or therapy guidelines;

d) new or modified risk information may be considered minor if it does not alter the overall risk-benefit profile for participants who already incur significant risks associated with the potential lethality of their disease;

e) risk information related to a specific drug that has previously been reviewed by the convened IRB for one study may be expedited by the Chair or designee for additional studies;

f) oncology office fliers describing a study, but offering no financial incentive may be expedited.

2) Study-related information that does not require IRB approval may be given expedited handling and may be recorded as "noted" or "received". This includes Data Monitoring Committee reports for multiple studies, when the recommendations are that the study continue as planned; reports of study closure; letters to patients or physicians regarding information that has been previously discussed at a convened IRB meeting; letters to patients and physicians regarding study closure, unless new risks are identified; administrative changes to the consent form, such as new telephone numbers, etc.

3. Modifications that include significant scientific changes in the eligibility requirements or to the treatment design are not considered 'minor' and must be approved by the convened IRB.

a. Any new information that may alter the overall risk/benefit evaluation made by the IRB at initial review is not considered 'minor' and must be approved by the convened IRB.

b. Modifications that might affect a participant's willingness to continue participation in the study, such as significant new risks, additional and/or new procedures, etc. are not considered 'minor' and must be approved by the convened IRB.

4. Continuing review of research previously approved by the convened IRB may be expedited in the following circumstances:

a. Where the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions, and the research remains active only for long-term follow-up of participants; or

b. Where no participants have been enrolled and no additional risks have been identified; or

c. Where the remaining research activities are limited to data analysis.

5. Studies submitted to the IRB for initial review are not eligible for expedited review.

6. Expedited review may be conducted by the IRB Chair, or by an experienced reviewer who is a voting member of the IRB, designated by the Chair.

a. The individual conducting expedited review must have appropriate expertise and experience.

b. The individual conducting expedited review may exercise all IRB authority except that the action may not include disapproval.

c. Disapproval requires full IRB review (45 CFR 46.110(b)).

7. The convened IRB will receive a list of all expedited actions at the next regularly scheduled meeting, including the regulatory basis for the action.

8. Notification procedures for expedited reviews are the same as those specified for initial reviews (see 'Initial Review').

H. Facilitated Review of Studies Approved by the NCI Central IRB (CIRB)

1. The KCCOP Board of Directors may designate the Central Institutional Review Board (CIRB), sponsored by the National Cancer Institute (NCI), for the review of selected multi-center Cooperative Group cancer treatment trials.

2. In these circumstances, the IRB Chair and an additional IRB member will conduct a Facilitated Review of the study materials provided electronically to KCCOP by the NCI CIRB.

3. Local boilerplate additions to the informed consent dealing with state and local law, institutional requirements, or IRB policies may be added to the local consent form. The IRB may also make minor word substitutions or clarifications in the informed consent document, particularly to facilitate better comprehension by the local population, as long as the proposed changes do not alter the meaning of the NCI CIRB approved consent form.

4. The IRB Chair may determine that the NCI CIRB review is acceptable and the consent form is acceptable with inclusion of boilerplate language, OR

5. The IRB Chair may determine that the NCI CIRB review is **not** acceptable. The IRB may not modify any of the required language in the NCI CIRB consent document. If consent modifications are deemed crucial, the NCI CIRB review will not be accepted. The IRB Chair will document the rationale for the decision and request that KCCOP staff prepare the standard IRB submission forms. The PI will be notified in writing that the usual IRB review will be conducted, and the reasons for this decision.

6. The KCCOP PI will be notified in writing when a Facilitated Review of study materials has been conducted by the IRB Chair.

7. Serious adverse events and unanticipated problems associated with a study approved by the NCI CIRB that occur locally must be reported to the IRB as described in these Policies and should not be reported to the CIRB. The KCCOP should continue to report SAEs to the Cooperative Group per the study protocol. If the IRB determines that an unexpected incident, event or outcome meets the regulatory definition of an unanticipated problem, it must be reported to OHRP/FDA.

I. Review of Unanticipated Problems and Unanticipated Serious Adverse Events

1. OHRP Guidance states that **t**he majority of adverse events, both serious and non-serious, occurring in the context of research are expected in light of the known toxicities and side effects of the research procedures or are due to the natural history of subjects' underlying diseases and conditions. Most individual adverse events do not represent unanticipated problems, and therefore, do not need to be reported to the IRB under the HHS regulations for the protection of human subjects.

2. OHRP advises that it is neither useful nor necessary under the HHS regulations for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. The IRBs at all these institutions are not appropriately situated or constituted to assess the significance of individual adverse events. The IRB will not accept these reports.

3. Adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a central monitoring entity (e.g., a Data Safety Monitoring Board or Committee, a coordinating or statistical center, or the research sponsor) in accordance with a monitoring plan required in the approved protocol. The reports generated by the central monitoring entity should be submitted to the IRB as they are received and will be included at the time of continuing review in the assessment of risks, unless the entity recommends that the study should be suspended or halted.

4. Only when this central monitoring entity determines that a particular adverse event or series of adverse events represents an unanticipated problem should a report of the adverse event(s) be submitted to the IRB. OHRP recommends that these reports to all sites include:

a. A clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and

b. A description of proposed actions to be taken by the investigators and/or IRB in response to the unanticipated problem (e.g., suspension of new subject enrollment, modification of the research protocol, and/or modification of the informed consent process).

5. The PI should provide the following information to the IRB when reporting an external adverse event determined to be an unanticipated problem:

a. Appropriate identifying information, such as
1) the title of the research protocol;
2) the PI's name;
3) the IRB project number;
4) the name of the supporting agency and the relevant award number; and
5) any relevant investigational new drug (IND) or investigational device exemption (IDE) number.

b. A complete, detailed description of the external adverse event and the basis for determining that it represents an unanticipated problem.

c. A description of any actions that have been taken or proposed by the study sponsor, the study coordinating site, any other monitoring entity (such as a DSMB/DMC), and/or the local PI in response to the unanticipated problem (e.g., suspension of new subject enrollment, modification of the research protocol, and/or modification of the informed consent information and/or process).

d. Reports of external adverse events submitted to the IRB should present the adverse event in the context of the entire multicenter study, if possible. In addition, the PI should consult with the study sponsor or coordinating center regarding any changes to the protocol and/or informed consent documents independently proposed by the PI.

e. For any report of an external adverse event determined not to be an unanticipated problem, the PI should maintain a copy of the external adverse event report and documentation of the basis for his/her determination. This record is to be made available to the IRB or OHRP on request.

6. Local unanticipated serious adverse events and unanticipated problems

a. Local adverse events that meet the following criteria must be reported to the IRB:
1) Serious: Involves death, a life-threatening event, a new or prolonged inpatient hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly or birth defect. In

addition, important medical events that may not result in death, but are life threatening or require hospitalization, may be considered an SAE when, based on appropriate medical judgment, they may jeopardize research participants.

2) Unexpected or occurring at a significantly higher frequency or severity. Any AE, the specificity or severity of which is not consistent with the risks described in the current protocol and consent form, the Investigator's Brochure or product labeling. Any event that may alter the risk/benefit analysis and may require substantive changes in the protocol and/or consent form.

3) Event is possibly, probably or definitely related to the study design, procedures, or treatment intervention. If clearly not related, a report is not required.

b. Unanticipated problems that must be reported to the IRB are those that resulted in circumstances that increased the risk of harm, including physical, psychological, or social harm) to study subjects or others (breach of confidentiality of study data, drug management or drug treatment errors, etc.)

c. All unanticipated problems and serious adverse events that meet the requirements for submission to the IRB must be submitted to the IRB Chair within fifteen days of notification to the treating physician or the KCCOP.

1) The P.I. must submit at least the first page of the *IRB Report Form for Local Serious Adverse Events and Unanticipated Problems* as promptly as possible, but within fifteen days or seven days of an unanticipated death during or within on month of study participation.

2) The second page of the report, signed by both the treating investigator and the Principal Investigator must be submitted within fifteen days, even if additional information is anticipated or requested.

d. The Chair will review the report, as well as any additional study documents including a copy of the current consent form, the protocol, the current Investigator's Brochure, etc. as appropriate.

e. If an adverse event occurs on a IRB approved protocol, the Chair will review the event for that protocol only.

f. The Chair will review the consent form utilizing the following guidelines:

1) Review the SAE(s)

2) Review the pertinent documents relating to drug toxicities for the agent of concern to assess whether the SAE is appropriately described in the consent or if changes to the existing consent are warranted.
3) The Chair may request the P.I. to contact the Cooperative Group Study Chair for additional information.
4) If the Chair feels that an urgent safety issue for study participants exists, communication between IRB committee members may take place via conference call or e-mail within 24 hours.

g. The Chair's assessment will be documented. If no changes to the protocol or consent form are required, the Chair may simply file the report or refer it to the convened IRB.

7. The IRB may render one of the following decisions:

a. The risk/benefit ratio in the trial has not changed and no change is necessary in the informed consent.

b. Specific additional information is required in the consent form

c. Modifications to the Protocol are required

d. Enrollment must be suspended until the concerns are resolved (45 CFR 46.113)

e. The IRB may terminate the approval of the study (45 CFR 46.113 and 21 CFR 56.113)

8. Notification

a. In the event that the IRB decides, due to the review outcome of an adverse event, changes must be made to the consent and/or protocol in question the IRB Coordinator will draft a letter to the P.I. in the same manner as an outcome letter.

b. The IRB will confirm that the sponsor, the appropriate federal agency, and the KCCOP Board of Directors is notified as required.

V. GRANT APPLICATION REVIEW

The IRB will review the KCCOP Grant application prior to the release of grant funds, as required by the National Cancer Institute Office of Grants and Contracts.

VI. KCCOP PHYSICIAN INVESTIGATORS

A. The KCCOP Principal Investigator must provide the IRB with a current list of participating physician investigators each time a study is submitted for review, unless a physician file is maintained in the IRB office. The Principal Investigator is responsible for ensuring that KCCOP Investigators are qualified to perform the research.

B. KCCOP Physician investigators who enroll and treat study participants on IRB-approved studies will be registered with the NCI and have a current NCI Investigator Number.

C. KCCOP Physician investigators who enroll and treat study participants on IRB-approved studies will have submitted a signed Individual Investigator Agreement to the IRB Office.

D. KCCOP Physician investigators who enroll and treat study participants on IRB-approved studies will have completed Human Subjects Protection Training.

E. KCCOP physician investigators who enroll and treat study participants on IRB-approved studies will have submitted a signed Conflict of Interest Disclosure form.

VII. RESPONSE TO COMPLAINTS AND/OR ALLEGATIONS OF NONCOMPLIANCE WITH IRB POLICIES

A. The IRB Coordinator will maintain a log of any complaint made by a study subject, or allegation of noncompliance, documenting the date received.

B. The IRB Coordinator will evaluate the complaint with the IRB Chair and Vice Chair. Additional information may be requested, including interviews with investigators or staff as necessary to address the situation.

C. A remedial action plan will be required if appropriate. In cases of persistent investigator non-compliance with federal regulations and/or IRB Policies and SOPs, an investigator may be excluded from participation in research under the review of the IRB.

D. The complainant will be informed by letter, signed by the IRB Chair, of the findings and remedial action taken, if any.

E. The IRB will be informed of the complaint or allegation at the next convened meeting.

F. The KCCOP Board of Directors will be informed of the complaint or allegation at the next convened meeting.

G. As required by federal regulations, the sponsor and appropriate federal agencies will be notified of investigator misconduct.

H. When an investigator determines that a study subject should be removed from a study without the subject's concurrence, the subject should be informed of the reasons for this action in writing.