RTOG Procedure Manual

Radiation Therapy Oncology Group
1818 Market Street, Suite 1600
Philadelphia, PA 19103
215-574-3189
215-928-0153 fax

Contents

- TABLE OF CONTENTS
- INTRODUCTION
- GROUP ORGANIZATION
- MEMBERSHIP
- PARTICIPATION REQUIREMENTS
- STUDIES
- PATIENT ENTRY PROCEDURES
- DATA SUBMISSION
- TOXICITY/ADVERSE EVENT REPORTING VS SERIOUS ADVERSE EVENT REPORTING
- QUALITY CONTROL
- STATISTICAL ANALYSIS
- MEETINGS
- WEB SITE LINKS

Supported by National Cancer Institute
Grants CA21661, CA 37422 and CA32115
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
# TABLE OF CONTENTS

## I. INTRODUCTION
- History ................................................................................................................................. 1
- Group Objectives .................................................................................................................... 2
- Headquarters Objectives ....................................................................................................... 3

## II. GROUP ORGANIZATION
- Overview .................................................................................................................................. 4
- Chair, Vice Chairs & Deputy Chair
  - Group Chair ...................................................................................................................... 4
  - Vice Chairs ......................................................................................................................... 4
  - Deputy Chair ...................................................................................................................... 5
- Committees
  - Executive Committee ........................................................................................................ 5
  - Steering Committee .......................................................................................................... 6
  - Research Strategy Committee .......................................................................................... 6
  - Disease Site, Scientific and Oversight Committees ........................................................... 6
- Headquarters
  - Clinical Trials Administration .......................................................................................... 6
  - Protocol Development and Regulatory Compliance ......................................................... 7
  - Radiation Therapy Quality Assurance ............................................................................. 7
- Department of Statistics ........................................................................................................ 8
- Department of Data Management .......................................................................................... 9

## III. MEMBERSHIP
- Types of Membership
  - Full Membership ............................................................................................................. 10
  - Provisional Full Membership .......................................................................................... 10
  - Affiliate Membership ....................................................................................................... 11
  - Satellite Membership ........................................................................................................ 11
  - Community Clinical Oncology Program (CCOP) Membership ....................................... 11
  - CCOP Component ............................................................................................................ 12
- Continuing Membership Criteria and Evaluation
  - Physics Requirements for Group Participation ................................................................. 12
  - Case Credit for RTOG Studies ......................................................................................... 12
  - Case Credit for DCP CCOP and Complementary Studies ............................................... 12
  - Data Submission and Timeliness ..................................................................................... 13
- Case Reimbursement ............................................................................................................. 13

## IV. PARTICIPATION REQUIREMENTS
- Assurance Documentation
  - Federalwide Assurance .................................................................................................... 13
  - Instructions for Application ............................................................................................... 14
  - Renewal ............................................................................................................................. 14
- IRB Approvals
  - Initial Approval ............................................................................................................... 14
  - Amendment Approval ...................................................................................................... 15
  - Renewal / Continuing Review ......................................................................................... 15
- Modality Requirements
  - Medical Oncology .......................................................................................................... 16
  - Surgical Oncology ........................................................................................................... 16
  - Radiation Therapy Requirements for Group Participation ............................................. 17
  - Advanced Technology Quality Assurance ....................................................................... 18
- Limited Participation Studies ............................................................................................... 18
E. Drug Procurement
1. NCI Investigational Drugs
3. Drugs Supplied Through Pharmaceutical Support
4. Drug Accountability
5. Storage of Drug Supplies
6. Transfer of Investigational Drugs
7. Return of Unused Drug

V. STUDIES
A. Types of Studies
1. Overview
2. Phase I Studies
3. Phase II Studies
4. Phase III Studies
5. Symptom Management/Cancer Control
6. CTSU Menu Studies
7. Translational Research

B. Protocol Development
1. Concept Review and Feasibility Survey
2. Group Review
3. NCI Review
4. CIRB Review (Phase III CTEP treatment protocols only)
5. Pre-Activation and Activation
6. RTOG Web Site

C. Committee & Study Chair Responsibilities
1. Committee Responsibilities
2. Study Chair Responsibilities
3. Assignment of Study Chairs

D. Release of Study Data/biospecimen materials
1. Study Data
2. Biospecimen Materials

VI. PATIENT ENTRY PROCEDURES
A. Pre-registration Requirements
B. Computerized Registration and Randomization
1. Institutional Requirements
2. Patient Eligibility and Stratification
3. On-Line Registration
C. Confirmation

VII. DATA SUBMISSION
A. Investigator Obligations
B. Resigned Facilities
C. Research Associate Training
D. General Guidelines
E. Data Calendar
F. Use of Labels & Preparation of Data for Submission
G. Request For Study Information Data Management
H. Request For Study Information - RT Quality Assurance
I. Forms Due Requests
J. Ineligible Patients and Treatment Refusal
K. Lost To Follow-Up
L. Data Issues
1. Data Management
2. Radiation Therapy Quality Assurance
I. INTRODUCTION

A. HISTORY

The Radiation Therapy Oncology Group (RTOG) was initially organized in 1968 under the direction of Dr. Simon Kramer of Thomas Jefferson University as a national clinical cooperative group for the purpose of conducting radiation therapy research and cooperative clinical investigations. Funding from the National Cancer Institute began in 1971. The Group grew considerably since the activation of its first study in 1968, an adjuvant methotrexate study for head and neck cancer that enrolled over 700 patients and formed the baseline for many of the clinical investigations in the area of head and neck cancer.

Since its inception, the RTOG activated over 540 protocols, accrued more than 120,000 patients to cooperative group studies, and published over 1,000 papers reporting the results of its findings. RTOG provides an infrastructure for clinical investigators from the United States, Canada, and international sites to seek more effective treatments for cancer.

RTOG continues to be the leading multicenter research organization systematically testing novel radiotherapy approaches against cancer and pursuing fully integrated translational research to support and further this effort. RTOG is also a leader in formally evaluating the integration of optimized radiotherapy with new classes of anticancer therapies and has completed and conducted a number of practice- and paradigm-changing trials. The Group's research is directed towards evaluating new evidence-based approaches to patients with solid tumors of the brain, upper aerodigestive tract (head and neck), lung, gastrointestinal system, and genitourinary tract (prostate and bladder). Focused efforts are also directed within the RTOG working groups in breast cancer, gynecologic cancer, sarcoma, and symptom management. The Group also has a strong international presence with member sites on four continents. This participation includes leadership from medical oncologists, surgical oncologists, pathologists, and laboratory scientists as well as radiation oncologists. All Group research efforts seek to be transformational in nature, with the goal of improving the quantity and quality of survival of cancer patients.

The RTOG Headquarters and Statistics & Data Management Center are located at the offices of the American College of Radiology in Philadelphia, PA.

In 2012 NCI announced plans to form a new consolidated and integrated NCI National Clinical Trials Network (NCTN) Program. In announcing the guidelines for the new NCTN NCI reduced the number of NCI-supported adult clinical trials groups, now called lead protocol organizations (LPOs) and announced a new funding mechanism to support accrual from high accruing lead academic performance sites (LAPS).

NRG Oncology (NRG) will become the successor LPO for RTOG’s NCI-funded treatment protocols as of March 2014. NRG is a joint venture of the RTOG, the Gynecologic Oncology Group (GOG), and the National Surgical Breast and Bowel Project (NSABP). The three groups came together in 2012 to form NRG Oncology and in 2013 submitted a joint grant application in response to NCI’s request for LPO proposals for the NCTN. As the three legacy groups (RTOG, GOG and NSABP) begin
to consolidate and operate as NRG current policies and procedures will be updated. *This manual details how current (legacy RTOG) research is conducted.* As new procedures for participation in NRG Oncology are developed this manual will be updated and new procedure manuals developed.

### B. GROUP OBJECTIVES

1. To increase survival in common types of cancer afflicting citizens of the United States, Canada and worldwide by effective integration of local-regional therapy in ionizing radiation and/or resection, and systemic therapy with cytotoxic drugs and hormones.

2. To evaluate new methods of radiation therapy and surgery. The technologies that the RTOG aims to evaluate in clinical trials include 3-Dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), stereotactic body radiation therapy (SBRT), image-guided radiation therapy (IGRT), and biological imaging modalities such as positron tomography (PET). IGRT refers broadly to treatment delivery employing modern imaging methods such as CT, MRI, PET and ultrasound to improve local-regional control and survival.

3. To decrease morbidity from cancer and its treatments by conserving structures and preserving functions by using careful integration of surgery, chemotherapy, and radiation therapy.

4. To seek enhancement of radiation therapy efficacy through altered fractionation and/or chemical and biologic modification.

5. To correlate laboratory findings with treatment outcomes: (a) to understand better the fundamental nature of malignant processes; (b) to predict responsiveness of tumors to radiation therapy, hormone therapy, and cytotoxic chemotherapy; (c) to predict and prevent the development of second malignant tumors; and (d) to predict and prevent adverse effects of treatment.

6. To increase the availability of clinical investigations to special populations, especially economically disadvantaged minorities and women, and to evaluate outcomes of RTOG studies with respect to such groups.

7. To assess formal quality-of-life endpoints in RTOG trials in order to seek means to improve the quality as well as the duration of survival.

8. To undertake prospective laboratory-based and translational research and stimulate laboratory-based and translational research using material obtained from prospective clinical trials conducted by RTOG.

9. To refine standards for radiotherapeutic, surgical, and chemotherapeutic delivery and to disseminate them throughout the medical community for improved control of cancer.

10. To understand better the nature of late effects of cancer treatment and to pursue the means to prevent or mitigate them.

11. To collaborate with other clinical cooperative groups in investigations of uncommon malignant diseases to achieve the most rapid treatment advances.
C. HEADQUARTERS OBJECTIVES

1. To coordinate the scientific activities of Group members and committees and to foster the design and implementation of protocols within a unified research program; to communicate with NCI and the study chairs in the review of all protocols.

2. To provide support for Group functions, including:
   a) Distribution of protocols to members;
   b) Entry of patients into studies;
   c) Assistance to study chairs, as required, through communication with individual members and the protocol associates, statisticians, research associates, and dosimetrists;
   d) Compilation and distribution of all Group reports;
   e) Arrangement of all Group and committee meetings; recording and distribution of minutes of these meetings;
   f) Tabulation of submitted forms and requests for overdue ones.

3. To provide data management review and clarification of all submitted patient information.

4. To provide training to investigators and research associates at member institutions.

5. To facilitate access to biospecimens collected on RTOG trials for interested translational research investigators.

6. To establish and maintain the database required by the Department of Statistics for analysis of RTOG studies.

7. To coordinate the Group’s quality assurance program.

8. To coordinate release of data for retrospective secondary analysis by RTOG or 3rd party investigators.

9. To track and facilitate publication of study analyses.

10. To provide administrative support for RTOG committees such as the Translational Research and Pathology, Medical Oncology, and Surgical Oncology committees as well as Membership Evaluation, Publications, etc.

11. To monitor Group grant awards and expenditures including the reimbursement of Group members for accrual related activities.
II. GROUP ORGANIZATION

A. OVERVIEW

RTOG is governed by Bylaws that have been approved and adopted by the Full Member institutions. The Bylaws are posted on the RTOG Web site (see Appendix I for link). Below is an overview of the Group's organization.

The Group is administered by the Executive Committee with the support of the oversight committees. The scientific work of the Group is performed by disease site and scientific core committees and coordinated by the Research Strategy Committee. Committee membership lists are posted on the RTOG Web site.

The Group has standardized membership approval and performance criteria which are applied to all RTOG participating sites. Publication and protocol guidelines, a protocol concept template, procedures to utilize materials from the RTOG Biospecimen Resource and secondary analysis request procedures have also been established. All of these resources can be found on the RTOG Web site (see Appendix I for links).

B. CHAIR, VICE CHAIRS & DEPUTY CHAIR

1. Group Chair

The Group Chair, elected by a majority vote of the Full Member institutions, serves a term of four years and may be re-elected. The Group Chair provides scientific and administrative leadership for the Group. The Group Chair chairs the RTOG Steering and Executive Committees, and co-chairs the Research Strategy Committee. The Group Chair works closely with the vice chairs and other committee chairs as well as Headquarters and the Statistical and Data Management Center to develop and achieve the Group's goals.

Group Chair Elect – this position is created when the Group Chair is unable to complete his/her term, chooses not to run for re-election or is not re-elected by the membership. The Group Chair Elect serves in that position for the final year of the Group Chair's term.

2. Vice Chairs

The Vice Chairs for Membership, Publications, and Disease Sites, are elected by a majority vote of the Full Members at the Group meeting. The remainder of the vice chairs are appointed by the Group Chair with the approval of the Executive Committee. Each vice chair serves a term of four years and may be re-elected/reappointed. The vice chairs serve on the RTOG Steering and Executive Committees.

The Vice Chair for Advanced Technology Integration is responsible for the development and execution of RTOG clinical trials utilizing new technologies for radiation therapy treatment planning, delivery, and assessment of treatment response.

The Vice Chair for Canadian Affairs is responsible for formulation and harmonization of policies affecting the Canadian institutional members.

The Vice Chair for CCOP Research Base Activities monitors and advises the Research Strategy Committee and the Executive Committee on the activities of the CCOP Research Base Program. This vice chair oversees the development of
protocols funded by the CCOP Research Base Program and the work of the Symptom Management and Cancer Prevention Committees.

The Vice Chair for Disease Sites works with the chairs of each of the RTOG disease site committees to help identify research opportunities. The Vice Chair for Disease Sites chairs the RTOG Data Safety Monitoring Board and co-chairs the Research Strategy Committee.

The Vice Chair for Medical Oncology is in charge of overseeing all RTOG medical oncology efforts, including the coordination of activities of the medical oncology co-chairs of the disease site committees, to bring new ideas and developments into the Group.

The Vice Chair for Membership Evaluation chairs the Membership Evaluation Committee which develops criteria for obtaining membership in the RTOG, develops criteria for continuing membership, and regularly evaluates the members according to published criteria.

The Vice Chair for Outcomes is responsible for overseeing all RTOG outcomes efforts including coordination of the Health Services Research and Outcomes Committee and patient recruitment efforts.

The Vice Chair for Publications chairs the Publications Committee which identifies potential publications from RTOG activities, promotes their timely development, develops Group publication guidelines, and reviews all abstracts and manuscripts reporting on Group matters or studies.

The Vice Chair for Surgery is in charge of overseeing all RTOG surgical efforts including the coordination of activities of the surgical co-chairs of the disease site committees to bring new ideas and developments into the Group.

The Vice Chair for Translational Research coordinates the introduction of developments in basic science into the research of the scientific core and disease site committees. This Vice Chair also develops educational programs, and works with the management of the biospecimen resource.

3. Deputy Chair

A Deputy Chair may be appointed by the Group Chair with the endorsement of the Executive Committee. The Deputy Chair assists the Group Chair, Headquarters, and Statistical and Data Management Center staff in the development and monitoring of protocols, data collection forms, and publications. At the request of Headquarters, the Deputy Chair resolves questions concerning patient eligibility, morbidity scoring, and quality control procedures. The Deputy Chair represents the Group Chair at various meetings in his/her absence.

C. COMMITTEES

1. Executive Committee

The Executive Committee consists of the Group Chair, the Group Chair Elect (if applicable), the Deputy Chair, the Vice Chairs, the immediate Past Chair, the chairs of the Cancer Disparity Recruitment Program, New Investigators, Quality Control, CCOP Evaluation, CCOP PIs, Medical Physics, Research Associates, Pathology, and Patient Advocate Committees, the Biospecimen Resource Director, the RTOG
Foundation Representative, the Group Statistician, the chair of the Full Member Principal Investigators, two elected members-at-large, and other oncologic specialties as deemed appropriate by the Executive Committee. The Executive Committee, chaired by the Group Chair, oversees the progress of new and ongoing studies, decides on new members, considers new projects and contracts, administers Group policy and resolves questions of policy. The Executive Committee meets at each semiannual meeting and other times as necessary. A Nominating Committee is appointed when needed to nominate candidates for vacancies on the Executive Committee.

2. Steering Committee

The Steering Committee consists of the Group Chair, the Vice Chairs, Deputy Chair, the Immediate Past Group Chair, the Full Member Principal Investigators Chair, and the Group Statistician. It carries out necessary Executive Committee activities between meetings of the Executive Committee and reports to the Executive Committee.

3. Research Strategy Committee

The Research Strategy Committee is composed of the Group Chair, the Deputy Chair, the Vice Chairs, the Group Statistician, senior members of the Department of Statistics, the chairs of the disease site committees, and the chairs of the other scientific core committees. It meets quarterly in addition to each semiannual meeting and considers new protocols for approval and prioritization, reviews the status of previously approved protocols, and considers for probation and closure, if necessary, protocols that are failing to meet patient accrual goals.

4. Disease Site, Scientific and Oversight Committees

The RTOG embodies a complex committee structure reflecting the diversity of the Group's activities. The chairs of all RTOG committees, with the exception of the Membership, Publications, Disease Site, Research Strategy, and Executive Committees are appointed by the Group Chair and reviewed by the Executive Committee. The committees are defined in the Group's Bylaws (See Appendix I for link) and are responsible for setting the scientific and administrative goals of the Group.

D. HEADQUARTERS

The RTOG Headquarters is based in Philadelphia under the direction of the RTOG Group Chair. Day-to-day RTOG operations are administered by the Directors of Clinical Trials Administration, Protocol Development and Regulatory Compliance, and Radiation Therapy Quality Assurance. The RTOG Headquarters is organized in three functional departments: 1) Clinical Trials Administration; 2) Protocol Development and Regulatory Compliance and 3) Radiation Therapy Quality Assurance. The Department of Data Management is part of the Department of Statistics.

1. Clinical Trials Administration

The RTOG Group Administrator is responsible for the fiscal management of the group, the preparation of all Group progress reports, the development of all funding applications, developing budgets and contracts for support of the Group’s work by non-governmental entities, maintaining the Group membership roster and per case
reimbursement and crediting systems. Coordination of the RTOG Web site also resides in this department.

Clinical Trials Administration coordinates the group semiannual meetings and prepares the agendas, coordinates the scientific sessions and records and distributes all meeting minutes.

The evaluation of new Affiliate membership applications is carried out in Clinical Trials Administration in coordination with the Group Physicist.

Pre-publication coordination of scientific reports including abstracts, and manuscripts utilizing RTOG data is facilitated by the Clinical Trials Administration staff (the Publications Associate) in conjunction with the Statistical Department, and the process and resulting documents are monitored by and distributed to the appropriate committees and individuals for review and approval. The Publications Associate maintains the Group publications database and coordinates the committee meetings and conference calls. The Publications Associate also coordinates the review process for requests to use the RTOG database for secondary analyses.

Support for the Translational Research Program (TRP) and management of correlative studies using trial-generated RTOG biospecimens also falls under the auspices of Clinical Trials Administration. The TRP Committee invites interested investigators to conduct these translational research projects in order to promote communication of scientific ideas from the laboratory into prospective clinical trials. The Committee reviews biospecimen requests made through an online application submission that is monitored by Clinical Trials Administration staff (the TRP Administrator), and vets proposals through a formal evaluation process also coordinated by the program administrator.

2. Protocol Development and Regulatory Compliance

Protocol development is coordinated by the Director of Protocol Development and Regulatory Compliance. Developing protocols are routed to the appropriate committees within the RTOG and to the Department of Statistics and Headquarters staff. After committee and Group Chair approval, protocols are submitted to NCI for review, and after NCI approval, distributed to the membership by posting on the RTOG Web site. Data collection forms and other tools necessary for protocol management are developed by Headquarters Data Management Department in concert with the Department of Statistics and the Deputy Chair.

Responsibilities also include registration of patients to studies, working with Canadian and non-North American member sites to facilitate their participation in protocol activities, working with industry and NCI partners to facilitate procurement and distribution of investigational agents for Group protocols, working with member sites to ensure compliance with all mandated regulatory requirements, coordination of adverse event reporting for investigational agents, and management of the Institutional Audit Program.

3. Radiation Therapy Quality Assurance

RTOG has quality assurance monitoring procedures for each treatment modality. A member of this department is also a member of each disease-site team. The department handles protocol review along with the disease site team, credentialing
for advanced technologies, using web-based software tools in the RTOG Core Laboratory to analyze and prepare cases for RT Quality Assurance reviews by the study chairs. The RTOG Core Laboratory is designed to support clinical trials, establish standards, provide individual institution quality assurance, data management and analysis, and report on technical and clinical results. In addition to supporting and establishing standards, the RTOG Core Laboratory provides education and research in clinical trial support. The Core Laboratory is managed by physicists and RTQA technical staff.

E. DEPARTMENT OF STATISTICS

Statistical support for RTOG is primarily provided by a grant from the National Cancer Institute, and the American College of Radiology is the grant recipient. The Department of Statistics is located along with the RTOG Headquarters Office at the American College of Radiology in Philadelphia.

The mission of the Department of Statistics is to collaborate with RTOG investigators in determining the optimum role of radiation therapy, either alone or in combination with other modalities, in the treatment of patients with cancer. Local control, quality of life, survival and ultimate cure of disease are measures (endpoints) used in evaluating radiation therapy.

The Department of Statistics is organized by disease site teams, where each team, led by a senior statistician, is responsible for an RTOG disease site committee. Some teams are also responsible for one or more disease site working groups in addition to a site committee. The statistical department is involved in all research activities of the RTOG. The statisticians collaborate with the Site Committees and study chairs in the design of protocols, developing stratification schemes, setting randomization allocation, monitoring accrual and toxicity, and creating formal interim analysis plans and detailed analysis plans for all study objectives. Other research activities supported by the Department of Statistics are retrospective analyses of data from previously-reported RTOG studies, support of research grants (NCI-funded as well as RTOG grants for translational research), and support of other RTOG sponsored research grants. Summary reports and interim analyses of accrual and adverse events for all studies open to new patient entry or in follow-up prior to publication of the primary endpoint are prepared for each semiannual meeting.

These analyses identify difficulties with protocol execution, usually characterized by not meeting targeted accrual, which may require study revision, and unexpected or unacceptable levels of adverse events which may warrant a revision to the prescribed treatment or the discontinuation of a study. These reports, which do not include any efficacy results, are published in electronic form on the RTOG Website. The RTOG Data Monitoring Committee (DMC) reviews all phase III and randomized phase II trials with a comparison to a standard of care within the trial treatments semiannually. Their reviews include monitoring accrual and adverse events in addition to protocol-specified interim efficacy analyses. Based on these results, the DMC recommends to the Group Chair a possible future course for the study. The RTOG Data Safety and Monitoring Board (DSMB) reviews all phase I, randomized phase II trials where all arms are experimental, and non-randomized phase II trials semiannually. Their reviews include monitoring accrual and adverse events and protocol-specified interim analyses, which usually involve morbidity. Based on these results, the DSMB may make recommendations to the Group Chair regarding the future course for a study. The DMC
and DSMB also review specific trials outside the RTOG semiannual meeting report schedule as needed for any major study issue.

After a study has accrued the required patients and met the requirements for primary endpoint analysis, a detailed statistical analysis is prepared for use in presentations at scientific meetings and in publications regarding treatment results. Some protocols include secondary endpoints beyond efficacy, such as comorbidity, quality of life, or tumor marker measurements in addition to treatment. These endpoints are typically reported separately. Other special analyses are performed for supplemental topics, such as prognostic factors, dose response relationships, correlation of dosimetry data and overviews in combination with other studies. These secondary analyses must be approved formally beforehand by the RTOG Publications Committee.

F. DEPARTMENT OF DATA MANAGEMENT

The primary responsibility of the Department of Data Management is to ensure that complete, accurate, and up-to-date information is available for analysis from data submitted for patients entered into RTOG clinical trials. As new studies are designed and developed, each undergoes review by an RTOG HQ research associate who then plans and carries out the various processes and tasks necessary for study data management, such as the creation of the eligibility check list, developing the study data collection schedule, designing the data collection forms with the study statisticians, writing validations and surveillance programs for the data, and creating special procedures needed to monitor the study.

RTOG HQ research associates are organized into disease site teams. A research associate from the team is assigned as the study coordinator for each new concept after approval by the RTOG Research Strategy Committee. After study activation, eligibility, treatment compliance, disease response, toxicity, and quality of data and data submission are a few of the areas monitored for each case. This monitoring requires frequent interaction with study chairs, statisticians, dosimetrists, and administrative staff. Periodic reviews by the appropriate study chairs are conducted in which data are examined and institutional compliance with respect to treatment delivery is assessed. The modality reviews of medical oncology, surgery and other systemic agents are initiated and prepared by the RTOG research associate.

The RTOG research associate is the primary liaison at Headquarters with regard to the clinical aspects of protocols. Management of questions concerning eligibility, treatment, data reporting, adverse events, protocol interpretation, and forms completion are examples of departmental responsibilities.

III. MEMBERSHIP

Membership in the RTOG is held by the institution. Membership application materials including instructions, criteria, and applications are available on the RTOG Web site. Each institution must designate a Principal Investigator (PI) who is responsible for the institution’s conduct in the RTOG and a lead research associate (LRA) who is the primary contact for all data management concerns for the institution.

Note: RTOG is no longer taking applications for RTOG membership. Institutions are encouraged to apply for NRG Oncology membership at
www.nrgoncology.org. Current RTOG membership categories are detailed in Section A below. (Membership materials are available at: http://www.rtog.org/AboutUs/MembershipMaterials.aspx )

Additions, deletions, or changes to the institution’s membership roster are submitted to the RTOG Membership Associate (RTOG-Membership@acr.org) through the use of the Membership Roster Update Form available on the RTOG Web site. Requests to change the institutional PI must also be accompanied by a letter and a copy of the proposed PI’s cv. Institutions are responsible for maintaining an active RTOG PI at their site. **RTOG must be notified immediately if the designated PI is no longer able to fulfill his/her responsibilities. This is a responsibility of both the institution as the member organization and the PI who is relinquishing his/her responsibilities.** The institution’s ability to enter new patients on clinical trials will be suspended until a new PI is named and approved by RTOG. The institutional PI is also responsible for notifying RTOG and naming a new LRG when the identified LRA is no longer functioning in that capacity for the site’s RTOG membership.

Canadian and non-North American sites are also eligible for membership in the RTOG and follow the same procedures for membership application, membership review, and participation as United States sites with several additional requirements: RTOG must secure US State Department approval for participation of non-US sites before accrual can begin and the one-time application fee and annual membership requirements for non-North American sites is increased due to the complexities of application and audit reviews. Please contact the RTOG Membership Associate (RTOG-Membership@acr.org) for additional information.

**A. TYPES OF MEMBERSHIP**

RTOG has six membership categories: Full, Provisional Full Member, Affiliate, Satellite, CCOP and CCOP Component.

*Note: All membership materials are available on the RTOG Web site at http://www.rtog.org/AboutUs/MembershipMaterials.aspx.*

1. **Full Membership**

   Full membership can be held by an institution by meeting the criteria found in the RTOG Requirements for Institutional Membership. Full Members are responsible for placing 25 case credits on RTOG studies each year and maintaining acceptable data quality and data timeliness scores as detailed in the RTOG Membership Evaluation Policy.

   To become a Full Member an institution must successfully complete a trial period as a Provisional Full Member. An Affiliate Member may request Provisional Member status after accruing 25 case credits on RTOG studies during a 12 month period, submitting an application which is reviewed and approved and undergoing a satisfactory site visit by the Membership Evaluation Committee.

   A Principal Investigator of a Full Member institution is considered a voting member of the Group. Continued membership in the Group is defined in Section III.B and in the RTOG Membership Evaluation Policy.

2. **Provisional Full Membership**

   *Note: As we move into NRG Oncology RTOG is not accepting new applications for Provisional Membership.* Provisional Membership had been
granted to Affiliate Members upon request and after enrolling 25 case credits on studies during a 12 month period.

Application for Provisional membership was made through the Headquarters office to the Group Chair. The Membership Evaluation Committee reviews the membership application and if initial approval is given, the Committee will perform a site visit of the applicant institution. The site visit findings are reported back to the Membership Evaluation Committee, which then votes on the admission of the applicant. If approved by the Executive Committee, the institution is admitted as a Provisional Member. Provisional Members may have their own Affiliate Members. Once achieving Provisional Member status an institution is no longer affiliated with a Full Member.

Provisional membership may be held for a period of one to two years. If performance during that time is deemed satisfactory by the Executive and Membership Evaluation Committees, Full membership will be granted. If the requirements are not met, the institution must either resign from the RTOG or assume membership in a category more suited to the institution's capabilities, (i.e., Affiliate Member).

3. **Affiliate Membership**

Institutions that collaborate with a Full Member Institution may become Affiliate Members as part of that Full Member's efforts. To become an Affiliate the institution must meet the criteria outlined RTOG Criteria for Maintaining Membership.

**Applications for Affiliate membership in RTOG are no longer being accepted.**

4. **Satellite Membership**

A Satellite member is a site that delivers radiation therapy consultation, planning treatment, and related services where the radiation oncologists are part of the parent site's faculty or professional services. A Satellite member can be attached to a Full or Affiliate member institution. The Principal Investigator at the parent Full or Affiliate member is responsible for the conduct of the Satellite member. Case accrual, data submission, and data quality scores are included in the accrual and scores of the parent institution. There is no minimum yearly accrual required of a Satellite member; however, if a Satellite member has no accrual for three consecutive years, it will be automatically dropped from the membership role.

Upon approval of a Satellite site and prior to entering cases through that Satellite, the parent site's RTOG Member Agreement will be amended to include responsibility for the participation of the Satellite site. The Satellite institution must be covered under an Office for Human Research Protection (OHRP) Assurance. The radiation therapy facility must be approved by RTOG RT Quality Assurance. Payment for Satellite site accrual is through the parent site.

5. **Community Clinical Oncology Program (CCOP) Membership**

CCOP sites may apply for CCOP membership, utilizing the RTOG as a CCOP Research Base. They are not required to apply through a Full Member institution. They must meet the same criteria as described in the RTOG Membership Evaluation Policy. CCOP membership applications are reviewed by Headquarters
and/or the CCOP Membership Evaluation Committee, and their progress is reviewed semiannually by the CCOP Membership Evaluation Committee. CCOP sites are required to accrue ten case credits on RTOG studies annually with at least five of the credits awarded through the DCP/CCOP program.

6. CCOP Component

Any CCOP member may add additional sites under their RTOG membership which are called CCOP Components. Cases accrued by the component count toward the CCOP’s membership requirements.

Note: All membership materials are available on the RTOG Web site at http://www.rtog.org/AboutUs/MembershipMaterials.aspx.

B. CONTINUING MEMBERSHIP CRITERIA AND EVALUATION

Each RTOG member is evaluated on an annual basis. Full and Provisional Members are reviewed by the RTOG Membership Evaluation Committee and CCOP Members are reviewed by the CCOP Membership Evaluation Committee at the January semiannual meeting. Affiliate members are reviewed and evaluated by headquarters staff after the January semiannual meeting. The evaluation is based upon the prior calendar year for patient accrual, forms submission and the audit results.

1. Physics Requirements for Group Participation

To be a member of RTOG, each member institution must agree to be visited by the Radiological Physics Center (RPC) which serves as a resource to the RTOG for evaluating the accuracy of the delivered dose from any treatment equipment that is used by each institution for the treatment of all protocol patients. All RTOG members are required to participate in the RPC’s ongoing thermoluminescent dosimeter (TLD) program which functions as an interim check mechanism for the accuracy of the institutional machine calibration.

2. Case Credit for RTOG Studies

Below are the minimum case credit requirements for continued RTOG membership:

<table>
<thead>
<tr>
<th>Membership</th>
<th>Treatment or DCP CCOP Credits Required Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>25</td>
</tr>
<tr>
<td>Provisional</td>
<td>25 in a 12 month period (to achieve Provisional Membership status)</td>
</tr>
<tr>
<td>Affiliate</td>
<td>5</td>
</tr>
<tr>
<td>Satellite</td>
<td>1 within 3 years</td>
</tr>
<tr>
<td>CCOP</td>
<td>10 – 5 of which must be DCP CCOP Credits</td>
</tr>
</tbody>
</table>

3. Case Credit for DCP CCOP and Complementary Studies

Institutions participating in RTOG studies sponsored NCI Division of Cancer Prevention (DCP) Community Clinical Oncology Program (CCOP) will receive payment and case credit for their participation. These case credits will be listed as CCOP Credits and count toward the yearly membership accrual requirements for Full, Provisional, Affiliate, Satellite, and CCOP members. Some RTOG treatment
(CTEP) protocols with Quality of Life endpoints receive CCOP credits and payment in addition to the standard protocol credit and payment.

4. Data Submission and Timeliness

All institutions are required to submit complete, accurate, and timely data for all study patients according to the calendar created for each patient registered/randomized to an RTOG study. The requirements for data quality and timeliness are

- % Data Submitted within 90 Days of Due Date – Data Timeliness 80%
- % Data Submitted within 180 Days of Due Date – Data Timeliness 85%
- % Eligible Patients 90%
- % Complete Forms - no additional inquiries – Data Quality 90%

C. CASE REIMBURSEMENT

The RTOG NCI CTEP operations cooperative agreement, CA21661 and the NCI CCOP Research Base cooperative agreement CA37422, provide funding for case reimbursement for member institutions. The NCI specifies the amount of reimbursement for both treatment and DCP CCOP studies. The funding amount and requirements for each study, including reimbursement for the submission of biospecimen materials is detailed in the Case Credit and Reimbursement List available on the RTOG Web site. In addition to grant funding some studies also have corporate support which is paid on a per case basis. This funding is also listed on the Case Credit and Reimbursement List, (http://www.rtog.org/ClinicalTrials/CaseCreditReimbursementList.aspx).

For most studies reimbursement is paid when the case has been determined to be eligible for the study after review of the submitted Initial Evaluation Form (I1) or other key form. Payment for the submission of follow-up forms commences one year after study entry.

Per case reimbursement is paid on a monthly basis.

No reimbursement for cases will be given until there is an appropriately executed membership agreement between the institution and the American College of Radiology on file with RTOG Headquarters.

IV. PARTICIPATION REQUIREMENTS

A. ASSURANCE DOCUMENTATION

1. Federalwide Assurance

The Federalwide Assurance (FWA) is an assurance of compliance with the federal regulations for the protection of human subjects in research. It is approved by the Office for Human Research Protections (OHRP) for all human subjects’ research conducted or supported by the Department of Health and Human Services (DHHS). The FWA is also approved by OHRP for federalwide use, which means other departments and agencies have adopted the Federal Policy for the Protection of Human Subjects (also known as the Common Rule) and may rely upon the FWA for the research they conduct or support.

Institutions engaging in research conducted or supported by federal departments or agencies other than DHHS should consult with the department or agency that is
conducting or supporting the research for guidance regarding whether or not the FWA is appropriate for the research in question.

Each institution that is engaged in DHHS conducted or supported human subjects research must submit an FWA to OHRP. In general, an institution is engaged in human subjects research whenever: (a) the institution’s employees or agents intervene or interact with human subjects for research purposes; (b) the institution’s employees or agents obtain individually identifiable private information about human subjects for research purposes; or (c) the institution receives a direct DHHS award to conduct human subjects research, even where all activities involving human subjects are carried out by a subcontractor or collaborator. For more information to determine whether or not an institution may be engaged in DHHS conducted or support human subjects research, please visit the OHRP Web site at http://www.hhs.gov/ohrp.

2. Instructions for Application

Obtaining an approved assurance from OHRP is a two-step process. First the institution must ensure that the IRBs designated under the assurance are registered with OHRP. This can be checked by accessing the IRB Registration Look-up link (see Appendix I). If the institution’s IRB is not registered with OHRP it will need to register. This can also be done online. (See Appendix I for link).

To apply for a domestic or international assurance, an institution can access the OHRP Web site (see Appendix I for links).

3. Renewal

It is the institution’s responsibility to maintain an active assurance, and it must be renewed every three years. Documentation of renewal must be faxed to the Cancer Trials Support Unit Regulatory Support System (CTSU RSS) to ensure continued ability to register patients.

B. IRB APPROVALS

1. Initial Approval

Before an institution may participate in an RTOG study, the institution's IRB or Ethics Board must review and approve the protocol. All sites must submit certification of that approval to the Cancer Trials Support Unit Regulatory Support System (CTSU RSS). International non English speaking institutions must send their Ethics Committees’ regulatory documents in English.

Compassionate or expedited approvals by an IRB chair will NOT be accepted. NCI requires Full Board approval prior to the entry of any patient on protocol.

In a multi-center arrangement, the primary institution identified with an RTOG membership number is responsible for maintaining a record of IRB approvals for each center associated with it for RTOG membership. OHRP does not require the primary member’s IRB to approve each protocol approved by the subordinate centers; however, in a multi-center arrangement, the patient must be treated at the hospital whose IRB has approved the protocol.

All Phase III, II/III, and select phase IIR CTEP-treatment protocols are reviewed and approved by the NCI Central IRB (CIRB).
All institutions with FWAs currently conducting RTOG trials at their sites were previously eligible to voluntarily join the CIRB Initiative using the facilitated review model, which remains voluntary at this time. It is important to note the CIRB is in the process of transitioning to the CIRB Independent Model, which will become mandatory at the end of 2013, which is also when the facilitated review model will terminate. Under the CIRB Independent Model review for RTOG Phase III CTEP-treatment protocols will continue for the life of the study but the “facilitated review” mechanism will no longer apply. The CIRB is also currently working towards the inclusion of the review of all phases of clinical trials as part of the Independent Model. **Individual institutions who previously opted not to join the CIRB Initiative but now rely instead on the required full board review by the institution’s own IRB are strongly encouraged to initiate the process for joining the CIRB now as this requirement is mandatory for membership in the NCI National Clinical Trials Network (NCTN). More information on the NCTN which will formally roll out in March of 2014. can be found on the NCI website at [ctep.cancer.gov/investigatorResources/docs/NCTN_Program_Guidelines.pdf](http://ctep.cancer.gov/investigatorResources/docs/NCTN_Program_Guidelines.pdf).**


2. **Amendment Approval**

All protocol amendments must obtain IRB approval within 90 days of the broadcast and posting of the amendment to the Web site before being implemented at the site. This includes all protocol amendments reviewed and approved by the NCI CIRB. These protocol amendment approvals will continue to be provided to the local IRBs through the “facilitated review” process until the facilitated process terminates at the end of 2013, Investigators at institutions who previously opted out of the CIRB Initiative are still responsible for ensuring that protocol amendments are reviewed and approved by their local IRB until the mandatory CIRB Independent Model is fully in effect. Please see the bolded statement above in Section 1 strongly encouraging sites not currently part of the CIRB to begin this process to avoid problems opening studies and enrolling subjects in the future. All amendment approvals must be submitted to CTSU RSS.

3. **Renewal / Continuing Review**

Federal regulations stipulate that all clinical research protocols must be IRB reviewed / approved at least once per year during the data collection phase. Individual investigators are responsible for tracking their protocol IRB expiration dates and submitted for annual IRB review. All annual renewals must be submitted to CTSU RSS. Annual IRB reviews are conducted by the NCI CIRB for those trials reviewed by them initially. These annual approvals are provided to the local IRBs through their website. If a protocol is not IRB reviewed and approved prior to the IRB approval expiration date, it will be considered a deviation in OHRP procedures.

Continuing review of studies permanently closed to new accrual and with all patients in the follow-up phase may receive expedited annual IRB approval as per the local IRB procedures.
C. MODALITY REQUIREMENTS

1. Medical Oncology

   a. Participation

   Medical oncologists participating in RTOG studies must be added to the institutions’ roster prior to enrolling patients. To add a medical oncologist to the roster, please use the Membership Roster Update Form, found on the RTOG Web site. Please note that the medical oncologist must also be registered with the NCI Clinical Trials Support Unit (CTSU) roster and have a valid investigator registration packet on file with the NCI Pharmaceutical Management Branch (PMB).

   The Medical Oncologist prior to participation in an RTOG trial must review the protocol to ensure that all patient treatment and data submission is in accordance with RTOG guidelines.

   b. Principal Investigator Responsibilities

   It is the responsibility of the site principal investigator to notify Headquarters of changes in medical oncologists participating in RTOG studies. The principal investigator must ensure that protocols involving chemotherapy in which the institution participates are distributed to the treating medical oncologist prior to patient entry. The name of the treating medical oncologist must be provided at patient registration. Protocol changes or amendments that may affect the modality must also be circulated to all participating medical oncologists at the institution.

   Whenever possible, protocol therapy should be administered by the participating medical oncologist. If this is not feasible, it should be determined in advance of patient entry that the attending medical oncologist agrees to follow the protocol regimen. If protocol compliance (by the patient) appears to be a problem or if the protocol regimen will not be followed by the attending physician despite requests by the site principal investigator the patient should not be entered into a study.

   RTOG abides by the NCI policy regarding protocol deviations, which apply to all components of RTOG CTEP-approved protocols, including eligibility criteria, treatment schedules, dose modifications, toxicity assessment, response criteria, and statistical aspects. For more information on the NCI policy http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm. Problems with treatment compliance for study patients will be referred to the study principal investigator (PI) only for guidance on how to proceed with the case. The study PI cannot approve protocol deviations. Treatment compliance and data submission problems that persist will be referred to the RTOG Medical Oncology Quality Control Chair and/or to the Group Chair.

2. Surgical Oncology

   a. Participation

   Surgeons participating in RTOG protocols must be added to the institutions’ roster prior to enrolling patients. To add a surgeon to the roster please use the Membership Roster Update Form found on the RTOG Web site. Please note that
the surgeon must also be registered with the NCI Clinical Trials Support Unit (CTSU) roster.

Prior to participation in an RTOG trial the surgeon must review the protocol to ensure that all patient treatment and data submission is in accordance with RTOG guidelines.

b. Principal Investigator Responsibilities

It is the responsibility of the site principal investigator to notify Headquarters of changes in the surgical oncologists from their site participating in RTOG protocols. The principal investigator must insure that protocols involving surgery in which the institution participates are distributed to the surgical oncologists prior to patient entry. Protocol changes or amendments that may affect the modality must also be circulated to all participating surgical oncologists at the institution.

Whenever possible, protocol therapy should be performed by a participating surgical oncologist. If this is not feasible, it should be determined in advance of patient entry that the attending surgical oncologist agrees to follow the protocol regimen. If protocol compliance (by the patient) appears to be a problem or if the protocol regimen will not be followed by the attending physician despite requests by the principal investigator the patient should not be entered into the study.

RTOG abides by the NCI policy regarding protocol deviations, which apply to all components of CTEP-approved protocols, including eligibility criteria, treatment schedules, dose modifications, toxicity assessment, response criteria, and statistical aspects. For more information on the NCI policy http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm. Problems with treatment compliance for study patients will be referred to the RTOG study principal investigator (PI) only for guidance on how to proceed with the case. The study PI cannot approve protocol deviations. Treatment compliance and/or data submission problems that persist will be referred to the RTOG Surgical Oncology Quality Control Chair and/or to the Group Chair.

3. Radiation Therapy Requirements for Group Participation

To be a member of RTOG, each member institution must agree to be visited by the Radiological Physics Center (RPC) which serves as a resource to the RTOG for evaluating the accuracy of the delivered dose from treatment equipment that is used by institutions for the treatment of protocol patients. RTOG receives a copy of the institution’s machine calibration data, which is entered into the RTOG computer system and utilized in the verification of the radiation dose delivered for treatment of protocol patients. All RTOG members are required to participate in the RPC’s ongoing optically stimulated luminescent dosimeter (OSLD) program, which functions as an interim check mechanism for the accuracy of the institutional machine calibration.

Before participating in certain types of radiation oncology studies, each institution is required to be credentialed by the RTOG Medical Physics Committee, RTOG Headquarters RT QA, and the Radiological Physics Center (RPC) and is required to submit specified information to Headquarters RT QA, and/or RPC about RT equipment and dosimetry.
4. Advanced Technology Quality Assurance

The technology used for radiation oncology is changing rapidly. RTOG strives to devise QA processes that are generic so that they can accommodate a broad array of different imaging and dose delivery technologies. In order to meet this need, the Advanced Technology Integration Committee (ATIC) (under NRG Oncology it will be call the Radiation Oncology Committee) has worked closely with the Image-Guided Therapy Center (ITC), RTOG Medical Physics Committee, RPC, and RT QA group at RTOG headquarters to develop procedures and guidelines aimed at controlling the safe and effective use of new technologies. The technologies that the RTOG aims to evaluate in clinical trials include 3-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), stereotactic body radiation therapy (SBRT), particle therapy (protons), image-guided radiation therapy (IGRT), image-guided brachytherapy (IGBT), and biological imaging modalities such as positron tomography (PET). IGRT refers broadly to treatment delivery employing modern imaging methods such as CT, MRI, PET, and ultrasound. Each institution planning to participate in RTOG 3DCRT, IMRT and proton protocols must be credentialled.

D. LIMITED PARTICIPATION STUDIES

Only a defined set of institutions may enter patients on a limited participation study. A protocol is designated as a limited participation study, following a discussion among the appropriate disease site chairs, the HQ disease site team and the Steering Committee. This designation will appear on the front sheet of the protocol with a list of the institutions allowed to participate in the study.

Studies receive limited participation status because the protocol requires unusually strict monitoring of the participants, uses special equipment or treatment techniques, or the protocol competes with a higher priority study. Requests to become a participant in a limited participation study must be sent to Headquarters in writing and then approved by the study chair and the group chair or his/her designee.

E. DRUG PROCUREMENT

There are several ways drug is supplied for RTOG studies involving a drug component.

- NCI
- Pharmaceutical Companies
- Third Party Distributor
- Commercially available products

More than one method can apply in the same study.

Section 7.0 of each protocol provides detailed information about supply and distribution of the study agent. Commercially available products are usually obtained via a prescription from the physician; however, these products may also be supplied through other sources.

Prior to patient entry, the protocol should be checked to determine whether the agents are supplied commercially, or by pharmaceutical companies, by NCI-PMB or through special procedures. The protocol will specify the method of procurement in Section 7.0.

Unless the study drug is commercially available, the investigator should follow all steps outlined in the protocol for ensuring drug is appropriately triggered or ordered and make
sure that the specific agent is available on site prior to the time it will be needed. Studies using NCI investigational drugs may also require special data reporting and monitoring procedures. These special reporting procedures will be outlined in the protocol and must be followed by the investigator if he/she wishes to continue participation in the protocol.

1. NCI Investigational Drugs

Physicians requesting investigational drugs from the Pharmaceutical Management Branch (PMB) of the NCI for use in a CTEP-approved protocol must have an identification number (NCI Investigator Number) issued by PMB. To obtain and maintain a number, the investigator must be registered annually with PMB, CTEP, DCTD through the submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

NCI/PMB provided drug must be ordered via the NCI On-line Agent Order Processing (OAOP) mechanism. The NCI OAOP Training Guide is available prior to logging in on the OAOP portal https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx

Ordered drugs will be shipped directly to the investigator. Investigational drugs provided by NCI to a registered investigator are the direct responsibility of that investigator. Secondary distribution to other registered physicians does not relieve the original physician of his/her responsibility. Orders will only be shipped to the investigator’s designated shipping address. Investigators may only have a single shipping address.

The principal investigator (or authorized designee listed by the investigator on the site’s most recent Supplemental [IDF] on file with the PMB) at each participating institution may request study agent via OAOP. PMB’s Drug Authorization Review and Tracking System (DARTS) requires selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the investigator during the annual investigator registration process. This process must be completed before a drug order can be entered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the investigator sign the revised IDF, and returning it to the PMB via fax at (301) 402-4870. Questions about the process should be directed to the PMB at (301) 496-5725 Monday through Friday from 8:30 – 4:30 Eastern Standard Time or via email to PMBRegPend@ctep.nci.nih.gov. PMB guidelines require that investigational agents be shipped directly to the institution where the agent is to be prepared and administered with the exception of satellite distribution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. PMB does not permit the transfer of agents between institutions unless prior approval from PMB is obtained. Agent must be requested via the OAOP. For questions call (301) 496-5725 or email PMBAfterHours@mail.nih.gov. All forms can be accessed on the NCI Web site, http://ctep.cancer.gov/forms/index.html
If the NCI is supplying the drug for a study, they will also be responsible for providing the related investigator brochure, when applicable. The investigator brochure (IB), if available, for the drug will be supplied by the PMB/NCI. All requests for IBs should be e-mailed to ibcoordinator@mail.nih.gov or the IB Coordinator may be contacted at (301) 496-5725.

Sites should also become familiar with the PMB Policy and Guidelines for Investigational Agents before participating in any trials with NCI supplied agents. The guidelines contain important information regarding shipment, storage of and redistribution of PMB supplied drug. (See Appendix I for PMB Policy Guidelines for Investigational Agents link.)

When a drug supply is received, the supply must be inventoried and checked against the request. The drug lot numbers and the quantity received are recorded on the NCI drug accountability form NIH 2564. Drug inventories and receipts must be maintained according to NCI guidelines as outlined in the manual available below.

2. **Investigational Drug Resource Manual**

   A booklet is on the RTOG Web site for practitioners who use NCI investigational drugs. (See Appendix I for PMB Policy Guidelines for Investigational Agents link.)

3. **Drugs Supplied Through Pharmaceutical Support**

   The protocol will specify and give instructions regarding the method of procurement and timeframe for delivery for study agents being provided directly through a pharmaceutical company or third party distributor. **It is important to read and understand this protocol information and the important points below to determine realistic treatment start dates before registering the patient.**

   If the SASF has already been processed, drug is received much faster, generally for overnight or two day delivery.

   Most distributors will not ship prior to a weekend or holiday.

   Shipments are restricted between December 23 and January 1.

   The potential for customs delays for Canadian and international shipments should be taken into consideration.

   For trials in which a pharmaceutical sponsor supplies the study agent, the SASF which is referenced in the protocol and can be found under the protocol specific regulatory resources section of the RTOG Web site, must be submitted to CTSU, as soon as the individual responsible for the drug has been identified. This is a pre-registration requirement. Patient registration will be blocked if the required SASF has not been submitted and logged in as received by the CTSU.

   Submission of the SASF does not trigger drug shipment; registration of the patient is the trigger.

4. **Drug Accountability**

   Drugs provided to an investigator by NCI or another source on behalf of RTOG are the direct responsibility of that investigator. Secondary distribution to other sources or other physicians does not absolve that responsibility or relieve the physician to
whom the original shipment was sent. As sponsors of investigational drug trials, the NCI is required to follow and enforce regulations of the Food and Drug Administration (FDA) which require investigators to establish a record of receipt, use and disposition of all investigational agents. To assure compliance with these FDA requirements, NCI has developed a standardized Drug Accountability Record. This form must be used for each agent supplied by NCI.

A separate record must be kept for each study and for each specific drug formulation. Each drug dose dispensed must be accounted for on the Drug Accountability Form (DARF) (NIH-2564). Drugs supplied from the primary source to a secondary or satellite location must also be accounted for on Drug Accountability Forms maintained at the satellite location. A complete drug inventory including shelf count should be done routinely with satellite records collected and checked periodically.

The NCI Drug Accountability Forms may be maintained in the institutional database, if the following requirements are met:

1. The electronic printout of the investigational drug accountability record must include all the information required on the NCI Investigational Drug Accountability Record and the paper printout should be identical to the NCI accountability record.

2. There must be a valid audit trail for all data entries. This should include electronic entries of whom, what and when. Corrections of any previously entered data require a new entry and not modification to the existing data.

3. An appropriate backup system must be in place to prevent loss of data.

4. A security system must be in place recognizing only authorized users.

All drug accountability records must be available to NCI or RTOG upon request and will be reviewed as part of the RTOG institutional audit program.

Chemotherapy drugs may not be mailed to patients’ homes.

Drug Provided through Pharmaceutical Support

To assure compliance with FDA requirements for drugs provided through pharmaceutical support, RTOG has developed study specific Investigational Agent Accountability Records (IAAR). These forms can be found on the forms page for each study involving a pharmaceutical supplied agent and may be used for each agent supplied through pharmaceutical support on RTOG studies. A separate record must be kept for each study and for each specific drug formulation. Each drug dose dispensed must be accounted for on the form. Drugs supplied from the primary source to a secondary or satellite location must also be accounted for on Drug Accountability Forms maintained at the satellite location. A complete drug inventory including shelf count should be done routinely with satellite records collected and checked periodically. Studies with patient specific drug require an accountability record be available for each patient, who receives the study drug or placebo as applicable. The NCI/PMB Drug Accountability Record (DARF) may also be used in place of the RTOG study specific IAAR but not vice versa.
5. Storage of Drug Supplies

All drug supplies should be maintained according to the manufacturers’ specifications, in a secured area and accessible only to authorized personnel. It is recommended that, whenever possible, drug supplies be maintained in the pharmacy.

6. Transfer of Investigational Drugs

a. PMB/NCI Provided Drug

Please refer to the PMB Policies and Guidelines for Investigational Agents for information regarding storage of and redistribution of PMB supplied drug from a central pharmacy to an RTOG recognized chemotherapy delivery site (satellite dispensing area). (See Appendix I for PMB Policy Guidelines for Investigational Agents link.) An investigator may request to transfer drug from a completed NCI protocol to an active NCI-approved protocol within the same institution. The drug transfer information will become a part of the NCI investigational drug accountability record.

Drug transferred from completed protocols must be recorded on the Transfer Investigational Drug Form (NIH-2564), the completed Protocol Drug Accountability Record, and the active Protocol Drug Accountability Record. A copy of the Transfer Form must be faxed or mailed to NCI.

b. Drug Provided through Pharmaceutical Support

Drug provided through RTOG by a pharmaceutical company or third party distributor may be transferred from the site that received the shipment to another affiliated RTOG recognized site for drug administration. Any drug stored overnight at another location will require reconcilable accountability records available for both the site where the drug was initially shipped and the administration site. Drug provided through RTOG by a pharmaceutical company or third party distributor may also be available for transfer from one patient to another, once the appropriate forms available through the drug distributor have been completed and approved.

7. Return of Unused Drug

Unless otherwise stated in the protocol, investigators are required to return any remaining drug within 90 days of the study closure broadcast or last study patient dose. Damaged or expired drug should be destroyed at the site according to institutional policy. If the site does not have a written drug destruction policy, drug should be returned to the distributor for destruction. Unused, unopened, non-expired drug must be returned to the supplier unless stated otherwise in the protocol. Please review Section 7.0 of the protocol for specific end of study drug return or destruction information. A return receipt should be requested for all returns and the applicable Drug Accountability Form must be updated to reflect returned drugs. In a case where drug expires and requires replacing during the study, the drug can be destroyed on site. Please contact the specific supplier to replace expired or damaged drug.
V. STUDIES

A. TYPES OF STUDIES

1. Overview

The various types of studies undertaken by RTOG to evaluate new treatments are best defined in terms of the objectives. There are three primary types of trials: phase I, phase II, and phase III.

2. Phase I Studies

Phase I trials have a single objective: to determine the maximum tolerable dose (MTD) for a treatment regimen using the incidence of predefined dose limiting toxicities (DLTs). The study chairs classify those toxicities as DLTs that are considered severe and of concern. The protocol defines these toxicities using the latest NCI Common Toxicity Criteria in terms of the types, grades, and duration (if applicable). Because the tolerability of the treatment regimen is not yet established phase I trials try to minimize the numbers of patients. An acceptable upper limit on the number of patients with DLTs treated at each dose level is specified in the protocol, and the dose just below the dose with an unacceptable number of DLTs is the MTD.

3. Phase II Studies

The primary goal of a phase II trial is to determine if a particular treatment regimen shows evidence of efficacy and has an acceptable toxicity profile, and so warrants further investigation in a phase III trial. Ideally, a phase II study evaluates a selected regimen following successful determination of the MTD in a phase I trial. Although radiation oncologists may use initial tumor response as an endpoint, local regional control of the tumor at some specified time point, disease-free survival, or overall survival (depending on the disease site) are often more relevant measures of efficacy. These latter three endpoints require longer patient follow-up than the endpoint of initial tumor response.

Randomized phase II trials in RTOG were historically used to evaluate two or more experimental treatment regimens in the same trial, with each regimen being evaluated individually unless the protocol design explicitly calls for a direct comparison. More recently, RTOG has been designing randomized phase II trials that include a control arm. In these trials the experimental arm is compared to the control arm to determine if there is a sufficient enough signal to warrant pursuing a phase III trial.

4. Phase III Studies

Phase III trials are a randomized prospective comparison of one or more experimental regimens with the standard of care regimen. Phase III trials are conducted with patients who generally have had no previous treatment for the cancer site under study. Phase III trials are definitive, and therefore usually require much larger sample sizes than either phase I or phase II studies. Phase III trials support additional study objectives such as quality of life (QOL) differences between treatment arms, and genomic and proteomic studies.
5. **Symptom Management/Cancer Control**

Symptom management/cancer control studies evaluate an intervention to lessen the symptoms of cancer or side effects of its treatment. Quality of life, cancer prevention, and late effects can also be investigated. Cancer control studies are typically phase III trials or randomized phase II trials with a historical control to lead to a phase III study. These trials are supported by the NCI Division of Cancer Prevention (DCP) CCOP program.

6. **CTSU Menu Studies**

All Phase II/III and III studies, and some Phase II studies, are available for participation by the members of any cooperative group via patient entry through the NCI Clinical Trials Support Unit (CTSU). RTOG member institutions may enter patients onto trials on the CTSU “Menu” that are conducted by other cooperative groups (i.e. SWOG, ECOG) and receive RTOG membership credit. If the member institution belongs to the lead group they must credit the lead group with the accrual. If they do not belong to the lead group for that trial they may credit any of the groups to which they belong. This system replaces the former Endorsement and Endorsement-Plus policy.

7. **Translational Research**

Some RTOG protocols require the submission of biospecimen materials to confirm eligibility or to allow for stratification based on prognostic markers. In addition most RTOG protocols request the submission or “banking” of biospecimen materials to be used in future research projects. Investigators who wish to use materials from the RTOG Biospecimen Resource bank must submit an application detailing the materials needed and the proposed research project. The application and instructions for submission and details of the review procedure can be found on the RTOG Web site. (See Appendix I for the link.) All translational research projects that use specimens from RTOG grant-supported trials require NCI approval before specimens can be released, regardless of other of the source of the funding for the translational work.

B. **PROTOCOL DEVELOPMENT**

All protocols are reviewed and approved by both the Group through the committee system and the NCI prior to activation. A procedure has been designed by Headquarters to assist the RTOG investigators in the development, review, and activation of an approved protocol. This procedure consists of six phases: 1) Development of the LOI/Concept for HQ and NCI Disease Site Steering Committee review and approval; 2) Headquarters review 3) review and approval of the protocol among the group oversight committees; 4) NCI/CIRB review; 5) protocol activation; and 6) protocol amendments.

1. **Concept Review and Feasibility Survey**

Prior to writing a full draft of a protocol, an investigator must present the idea to the members of the responsible RTOG disease site committee. The proposed study will be examined in relation to the overall goals of the committee and the Group’s current research strategy.
To assess if the Group has sufficient patient resources and interest to complete the proposed study in a timely fashion, a concept sheet (see Appendix I for Protocol Concept Form link) is prepared by the study chair following discussion with the senior disease site statistician and site committee chair and submitted to the Headquarters protocol associate. The protocol associate circulates the concept to the statistician, the data manager, the dosimetrist, medical physics, the contract liaison, and the disease site patient advocate for feedback, and when relevant, the health services research and outcomes (HSRO) committee chair. The protocol associate (PA) then forwards the concept and comments to the disease site chair for his/her approval. If approved, the disease site chair or the Study Chair will present the concept to the Research Strategy Committee for consideration. If the Group decides to proceed, the study chair is charged with developing the NCI letter of intent (LOI) or concept for submission to NCI.

2. Group Review

Upon NCI approval of the LOI or concept the study chair writes a draft of the protocol, according to the directions embedded in the Protocol Template with input from the PA, senior disease site statistician and the site chair, and submits it to Headquarters. Study co-chairs are assigned according to guidelines found below in Section C.3. The PA initiates circulation of the protocol based on the type of timeline required for the respective protocol submission, edits the study chair's draft protocol, and begins the HQ disease team review. The disease teams are comprised of:

a. Protocol Associate

The protocol associate (PA) ensures that the protocol is in the proper format and contains all necessary information and documentation (i.e., consent form, pathology, modality review guidelines, registration procedures, drug distribution procedures, staging and toxicity criteria, etc.). The PA also verifies that the administrative procedures are consistent with established policy. The consent form is reviewed to make sure that all of the required elements, as mandated by federal policy, are contained in the document.

b. Statistics

The statistician initially reviews the design and feasibility of each study by providing an estimate of the number of patients needed to complete the study and an estimate of the expected duration of the study. In addition, the statistician writes a section describing the monitoring procedures, the type of analyses to be employed in the study, and the applicable gender and minority issues. The statistician also reviews the study's requirements, eligibility criteria and endpoints for feasibility.

c. Data Management

The disease site statistician and research associate (RA) review the data items to be collected relative to the protocol's eligibility criteria and the endpoints and then construct the data submission schedule. The pre-treatment and the follow-up sections are reviewed to verify that these sections will satisfy the study-specific data collection requirements. During the review process, the development of the data collection forms is begun as a joint effort by the disease
site working group including the statistician, RA and RT QA staff member. The research associate and RT QA staff member also reviews the pre-treatment evaluation and study parameter sections to ensure that the protocol specifies the monitoring studies and tools appropriate for the study. The eligibility criteria are reviewed to verify that they adequately define the required study population. If the study involves chemotherapy or other systemic therapy, the RA evaluates the prescription and dose modifications to ensure clarity.

Discrepancies, ambiguities, and unclear instructions are referred to the relevant modality study chair for resolution. Failure to resolve problem issues may delay protocol activation.

3. NCI Review

All submissions to NCI are done by the PA. Phase I, I/II (< 100 patients), and phase II trials < 100 patients must be submitted to NCI as a Letter of Intent (LOI). A concept sheet for randomized phase II studies requiring at least 100 patients and phase III protocols must be submitted to NCI (Disease Site Task Force and Disease Site Steering Committee) for review prior to submission of the full protocol. NCI reviewers generally have comments or request revisions that require an answer and re-review of the protocol. The NCI consensus review is circulated by the protocol associate to the disease site team, the site chair, and study chair, and the response to the NCI review is coordinated and the protocol resubmitted to the NCI.

4. CIRB Review (Phase III, II/III, and select IIR CTEP treatment protocols only)

Once a Phase III, II/III, and select IIR CTEP protocol receives NCI approval, the HQ disease site team is responsible for obtaining NCI CIRB approval.

5. Pre-Activation and Activation

Once NCI (and NCI CIRB, as appropriate) approves the protocol, the HQ disease site team ensures that all administrative procedures and tools are in place for protocol pre-activation and activation. When the study is pre-activated, it becomes available to the membership on the RTOG Web site for IRB review. When the study is activated, it is opened to patient accrual. Any special procedures must be documented (i.e., drug ordering for double-blinded studies, special institutional requirements, data flow for Intergroup studies, etc.). Studies are activated once the first IRB approval for the study has been received by CTSU and the RTOG disease site team has verified that all systems (i.e., patient registration in the OPEN network and data collection in Medidata RAVE) have been reviewed, approved, and finalized. All changes to active studies are coordinated by the PA. Amendments must be submitted to the PA by the study chair in writing. These amendments are circulated for review to the site chair, disease site team, and all study chairs for discussion and approval prior to submission to NCI. Amendments are submitted to NCI for approval and once approved, are distributed to the member institutions and posted on the RTOG Web site. The PA notifies the membership of protocol amendments and status changes (e.g., temporary closures for routine toxicity evaluation) by broadcast.

An institution may not make any institution-specific changes to an NCI-approved RTOG protocol. This is an RTOG requirement, which complies with NCI policy. The only exceptions are consent form additions mandated by an institution's IRB;
however, no protocol risks as stated in the NCI-approved RTOG version may be excluded.

6. RTOG Web Site

All protocols coordinated by RTOG are on the Web site www.rtog.org for on-line viewing and/or printing. Some protocols and protocol forms are password protected. Amendments, if any, are summarized within each protocol link under “Summary of Changes”. Additional features of the site include member relevant information such as updates (activations, closure, meetings, etc.), study summary reports, safety reports, adverse event reporting guidelines, toxicity tables, and forms. Some of this information is password protected and available only to RTOG member sites.

Further information available to both members and non-members consists of study brochures, publication references, and government/regulatory links.

C. COMMITTEE & STUDY CHAIR RESPONSIBILITIES

1. Committee Responsibilities

   a. Criteria for Committee Member Selection

      • Potential committee members should be affiliated with RTOG institutions in good standing.

      • Committee members should have an established record of active participation within RTOG prior to appointment.

      • Chairpersons may on occasion appoint an individual without a prior association to RTOG. Such appointments should be limited to persons with unique abilities and should be conditional upon future active participation within the Group.

      • Committee membership will be reviewed regularly by the committee chair to confirm that it appropriately reflects both scientific and accrual contributions.

      • While there is no defined term to committee membership, periodic rotation of membership is encouraged.

      • The New Investigators Committee should be tapped as a potential source of new site/modality committee members.

      • Changes in committee membership must be made in writing and sent to RTOG Headquarters.

   b. Committee Members’ Responsibilities

      • Participate in patient accrual and successful execution of RTOG clinical trials.

      • Provide thoughtful and timely responses to RTOG “concept” sheets and protocol drafts.

      • Advocate RTOG clinical research among colleagues within one’s own institution and specialty.
- Provide input into the development of new research initiatives within the committee.
- Continue to monitor research efforts within and outside RTOG with relevance to the committee’s research goals.

c. Disease Site Committee Chair Responsibilities

- Develop a strategy for treatment of all types and stages of tumors involving the disease site and for which the group has sufficient resources.
- Implement this strategy by assigning study chairs to develop appropriate randomized studies.
- Oversee the development and review the status of developing and ongoing protocols with the study chairs.
- Attend the Research Strategy Committee meeting at each semiannual RTOG meeting.

2. Study Chair Responsibilities

- Prepare a draft of the study and discuss with the statistician to determine study objectives, the sample size, and the likely availability of patients. Work with Headquarters RAs to develop the appropriate data collection forms and other tools or procedures necessary to activate the study. Work with Headquarters’ PAs to obtain ACR IRB approval and NCI CIRB approval, as appropriate, and NCI CTEP/DCP approval.
- Monitor the progress of the study, including ongoing review of the eligibility, treatment, and follow-up data. The study chair may need to make periodic visits to Headquarters to review data and resolve problems identified by the data management or RT QA staff. The RT QA reviews are on-going and performed remotely through a secure portal to the Core Lab. In addition, cases may undergo modality review by the applicable study chair or co-chair (dosimetry review or medical oncology review, and surgical review). The first of such reviews should be undertaken as soon as the protocol-specified number of patients have been enrolled and have completed treatment. The purpose of the review is to evaluate various aspects of the conduct of the study: application of entry criteria, compliance with treatment delivery, adequacy of data, evaluation of toxicity, etc. Modality reviews are performed remotely via CD on an ongoing basis, often in batches, as patients are accrued and treatment data is received. The review process allows the chair to clarify procedures in the protocol and to evaluate compliance with the protocol specifications.
- Restrict patient entries to those fitting the eligibility criteria in Section 3.0 of each protocol. Requests for exceptions to these requirements are not permitted by NCI. Changes to eligibility must be done through an NCI-approved protocol amendment. Neither the Group Chair nor the principal study chair can override the stated eligibility criteria.
- Collaborate with statistical, protocol development, data management, and RTQA staff, including close collaboration with the study statisticians during the development of the study and during the preparation of interim and final study
reports. Ongoing collaboration with the data management and RTQA staff is needed during the accrual and follow-up phase of the study to identify any problems with treatment delivery, toxicity, data collection, or monitoring.

- Prepare an abstract and/or a manuscript reporting the final results of the study.

3. Assignment of Study Chairs

- Each protocol will have one principal investigator or study chair who is responsible for the development, conduct, and initial analysis of the protocol.

- A co-chair will be appointed for each treatment modality found in the protocol that is not represented by the chair. All modality chairs will be required to review and sign a modality-specific Roles and Responsibilities Form in the protocol development phase.

- If a central review is planned for the study, the appropriate co-chair(s) will be named. (e.g. radiation oncologist, medical physicist, medical oncologist, surgical oncologist, pathologist and/or proton investigator. If the study allows the use of protons then a proton co-chair must be named.

- If translational research is planned, a TRP co-chair will be identified.

- If quality of life and neurocognitive function is part of the protocol, co-chairs for those sections will be named.

- Other study chairs may be appointed to assist with modality reviews as well as additional correlative studies not mentioned above.

D. RELEASE OF STUDY DATA/BIOSPECIMEN MATERIALS

1. Study Data

RTOG will give non-Headquarters personnel access to patient charts and data only under the following circumstances:

- The study chair is reviewing individual patient charts for the study.

- An individual other than the study chair has a project approved by the RTOG Publications Committee. Requests must be made using the RTOG Secondary Analysis Request form found on the RTOG Web site (http://www.rtog.org/Publications/Welcome.aspx) to the RTOG Publications Committee via headquarters stating the data which is needed and the purpose for which it will be used. In certain circumstances, it may be necessary to receive ACR IRB approval as well.

- Data that is to be used for reporting purposes, (e.g., abstracts, manuscripts) must be prepared and/or reviewed by the disease site senior statistician prior to being released to a study chair or other approved individual.

2. Biospecimen Materials

Many RTOG protocols request the submission or “banking” of biospecimen materials to be used in future research projects. Investigators who wish to use materials from the RTOG Biospecimen Resource bank must submit an application detailing the materials needed and the proposed research project. The application and
instructions for submission and details of the review procedure can be found on the RTOG Web site. (See Appendix I for link.) All translational research projects that use specimens from RTOG grant-supported trials require NCI approval before specimens can be released, regardless of other of the source of the funding for the translational work.

VI. PATIENT ENTRY PROCEDURES

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to the start of any protocol therapy via Web registration. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by e-mail. The completed, signed, and dated Eligibility Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

A. PRE-REGISTRATION REQUIREMENTS

In addition to site submission of regulatory documentation, there may be protocol-specific requirements (PSRs) for institutions to fulfill prior to being granted accrual access. These may include special certification in neurocognitive training, submission of study agent shipment forms or special radiological advanced technology certification. These requirements and how to fulfill them are described in detail in the protocol. It is the responsibility of the institution to review the protocol to see if these apply.

B. COMPUTERIZED REGISTRATION AND RANDOMIZATION

1. Institutional Requirements

Federal regulations and RTOG policy mandate that certain requirements are met before an institution can begin to accrue patients to cooperative group studies. All institutions must have an OHRP-approved assurance document and a current IRB approval and sample consent form for the protocol in the computerized database on file at CTSU. In addition, RTOG may have special requirements for participation in a particular study such as the completion of modality-specific physics forms or credentialing for protocol treatment delivery. Institutional attributes are stored in the computerized database and institutions not meeting the study-specific requirements are not able to enter patients on protocol.

When considering participation in studies that include randomization, the principal investigator must be prepared to accept assignment of all defined treatments. Refusal of an assigned option for a patient by the treating investigator will result in the following: no additional cases can be enrolled in the study by the institution.

2. Patient Eligibility and Stratification

All patients entered on study must meet the eligibility requirements as defined in Section 3.0 of all RTOG protocols. **The study chair cannot approve cases for entry that do not meet the eligibility requirements.** All questions related to eligibility must be addressed prior to case enrollment by a telephone call to the RTOG research associate assigned to the study. In addition to eligibility information, other baseline and prognostic information may be collected at the time of registration/randomization. The stratification variables for randomized trials can be found in the Schema and in Section 13.0 of the protocol. Institutions must complete the Eligibility Checklist for each patient prior to registering the patient.
3. On-Line Registration

Online registration is mandatory for all studies. Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG Web site. To obtain a user name and password institutions must complete the Password Authorization Form available on the RTOG Web site (see Appendix I for Password Authorization Form link). The Investigator must have completed Human Subjects Training and been issued a certificate before a password will be issued.

An institution can register the patient by logging onto the RTOG Web site (www.rtog.org), going to “Data Center Login” and selecting the link for new patient registration. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed by the patient.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, the system assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. An e-mail is generated and sent to the registering site including the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the SDMC (Statistical Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system notifies the user including a brief explanation of the reason(s) registration was denied. This screen can be printed.

In the event that the RTOG Web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m.

In addition to the RTOG web registration system RTOG also utilizes the NCI/CTSU Oncology Patient Enrollment Network (OPEN) registration system for select studies. The development of OPEN is a joint effort between the CTSU and the Cooperative Groups with the support of CTEP/NCI. The main goal is to provide a standardized web-based environment, available 24/7, for the enrollment of patients in clinical trials across the NCI-sponsored clinical trials program.

Please note to access OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members’ web site.
Be aligned with an institution on an organization roster in RSS (CTSU roster, Cooperative Group roster, or other network roster)

Section 5 of the protocol gives specifics on which registration system is used for the study.

C. CONFIRMATION

Following a successful registration, the registration system generates a printout of the information, the treatment assignment and case number. This confirmation form is emailed to the investigator along with a copy of the answered eligibility questions, a calendar listing forms due and their due date. The Headquarters randomization registrar must be notified immediately if, upon receipt of the confirmation forms, any errors are noted.

The RTOG case record includes a field for a patient identifier. This identifier must be the patient's initials (first-middle-last). This ID is used to verify subject identification when data are submitted for the case. If the patient ID is incorrect or requires modification, a signed request for change must be submitted to the registrar.

VII. DATA SUBMISSION

A. INVESTIGATOR OBLIGATIONS

For each registration on a study, the principal investigator of the enrolling institution is obligated to submit the required data according to protocol specifications unless written notification to the contrary is received by the investigator.

Data submission on each patient continues as long as the patient is alive and the case status is designated as "open" or until a study is terminated to further data collection. When the patient has died and all outstanding data have been submitted to Headquarters, the case will be "closed". An exception to follow-up until death is found in most cancer control and correlative studies where survival may not be a study endpoint. For example, follow-up may be terminated when the endpoint of the study is reached and the data collection section of the protocol indicates a finite follow-up duration. Termination of a study means that data submission ceases and all cases in the study are closed regardless of the patient's survival status. Open or closed case status should not be confused with open or closed study status. For the latter, open means that the study is open to new patient entries. Studies that are closed to new patient entries continue to have data submitted.

B. RESIGNED FACILITIES

Cases entered on study by an institution that subsequently resigns membership in the RTOG will remain "open" unless criteria for closure (see Section A) are met, as the institution is still responsible for following patients entered onto trials through RTOG and submitting all required data. IRB oversight is necessary to continue patient follow up. If a Site has any questions about transferring patients or transferring IRB responsibility, the site is to contact the RTOG Regulatory Compliance Department. For contact information refer to Contact Us on the RTOG website.

Periodic requests for data from resigned facilities will be made. If an institution reapplications for RTOG membership, the current investigator seeking membership will assume the obligation for any remaining delinquent case data. The RTOG institution number for membership identification will remain the same.
C. RESEARCH ASSOCIATE TRAINING

Training modules are accessible on the RTOG website for RTOG clinical trials data managers, site coordinators and research nurses involved in RTOG protocol participation and data collection. Review questions are imbedded in the PowerPoints. When all required modules are complete a RTOG certification for this training will be awarded.

D. GENERAL GUIDELINES

THE MAJORITY OF DATA IS SUBMITTED ELECTRONICALLY VIA THE RTOG WEBSITE OR RAVE. DATA QUERIES THAT ARE NOT ABLE TO BE RESOLVED ELECTRONICALLY WILL BE EMAILED TO THE DESIGNATED EMAIL ADDRESS AS INSTRUCTED ON THE QUERY.

- Unless otherwise indicated in the protocol, all information for study patients that is not able to be submitted electronically including data forms that are not available for electronic submission, films, and reports, are mailed to the following address:

  American College of Radiology
  RTOG Headquarters
  Suite 1600
  1818 Market Street
  Philadelphia, PA 19103

- All RTQA mail should be sent to the attention of RTOG RTQA. All non RTQA data forms/reports should be sent to the attention of RTOG Data Management. Do not submit case information to a specific person unless specifically requested to do so. Failure to follow this advice will delay processing of the material. Each item submitted to Headquarters must have a label attached. Case specific labels must be printed from the RTOG website. These labels will be printed with the RTOG study and RTOG case number, patient initials, institution name, and institution number. See Section F for specific instructions on the application and use of labels.

- Non-electronically submitted data for cases registered by sites through CTSU should be submitted to the lead cooperative group unless otherwise specified in the protocol. Queries will be sent directly to the CTSU sites by the lead cooperative group.

- Follow-up evaluations must be submitted for the time periods specified by the protocol or notification must be sent that the evaluation was not done via the communication memo available on the RTOG Web site. Missed assessments will result in accumulation of delinquent forms that, when tabulated, may adversely affect institutional evaluation (i.e., missed protocol-required evaluations may not be dismissed or suppressed regardless of the reason not done).

- **Revisions to data submitted electronically must be done via the RTOG web portal** or using RAVE, whichever is appropriate for the study. If a data form is not available for web submission and can only be submitted via hard copy, revisions must follow acceptable guidelines: Use a single line to cross through the information being changed, initial and date the revision on the original paper data collection form
or the confirmatory web entry complete summary form. Mark the page "revision" or check the revision box, if available. Be sure the revision is clearly identifiable (you may circle the question or write on top of the page. Q XX and XX have been revised. Do not use whiteout or highlighter as this will obscure the information when it is scanned into the electronic filing system at headquarters. Only forms previously accepted by Headquarters and subsequently corrected should be marked as a revision. Do not mark a form as a revision when submitting or resubmitting an original item that has been rejected and/or returned to the institution for correction. If you make an error while initially filling out the form and correct your error using the guidelines above, do not mark this form as a revision.

- Data forms and all communication that includes patient information (e.g., queries, memos) must be signed and dated by the investigator or the person responsible for submission of the information.

E. DATA CALENDAR

A case specific data collection calendar is issued for each patient placed on all non-RAVE RTOG protocols. The calendar contains relevant case identification information and lists the required data items and the date each is due as the patient goes through the study. The submission of additional data may be requested.

All non-RAVE patient calendars can be viewed and printed via the RTOG Web site (click on Site Tools and then the OPS Tools) with the appropriate user name and password.

Data collection calendars for RAVE studies are configured programmatically during study design and are based on protocol defined variables. Forms and folders, with relevant target and overdue dates, will be added to a patient’s calendar based on predefined values. For example, all patients will receive a set of standard forms and folders. Additional forms and folders will be dynamically added depending upon the treatment arm assigned and/or the patient’s agreement to participate Quality of Life data. In the RAVE EDC environment, calendars are displayed and updated dynamically during the course of a study.

Data submission requirements for patients in multi-step registration studies may change once the patient undergoes registration to the next step. A new calendar incorporating outstanding data requirements from the first assigned option and items relevant to the new registration option is produced for studies requiring multiple registrations. Failure to follow multiple step registration guidelines will result in an incorrect data collection calendar and accumulation of delinquent items.

Institutions may view the calendar immediately via the RTOG Website or through the RAVE EDC environment; however, the investigator should check the Data Collection Section of the protocol for submission requirements. Most forms for newly activated studies are available via the RTOG Website or through the RAVE EDC environment.

All items on the calendar must be addressed by either submission of required/requested information or notification via a communication memo explaining the reason for non-submission. Upon Headquarters receiving notification of a patient’s death on the appropriate data collection form, all forms due after the patient’s date of death are suppressed, except for outstanding queries. All outstanding data forms due prior to the patient’s death must still be submitted to Headquarters.
Most data forms are available for electronic submission via the RTOG Website or through the RAVE EDC environment. Data forms that are not available electronically and all communications that include patient information must be signed and dated by the investigator or the person responsible for submission of the information. Flow sheets, replies to memos, Request for Study Information replies, queries and General Communication memoranda must be signed.

If forms are submitted electronically, these forms must be revised electronically via the appropriate electronic data capture system (RTOG Website or RAVE). Do not change signature lines and/or dates of original submission. Electronic signatures are not available at this time.

Material gathered as source documentation should not be routinely mailed to Headquarters unless required by the study (e.g., pathology, operative reports, and radiotherapy record) or unless a specific request for documentation is made. When submitting requested source documentation, all pages must be labeled with the appropriate study/case/patient/institutional identifiers. Source documents may not be submitted in lieu of data forms. Headquarters will not complete the required data forms when only source documents are submitted.

All paper forms are available on the RTOG Web site. The form title is identified in the heading (top left corner) and in the lower right corner of the data form for non-RAVE studies. If forms are modified or changed in any way, the date and version letter is updated in the lower right hand corner of the form. The RTOG Web site contains the current version of all non-RAVE forms. The institutional research associate should check to see that any supply of forms maintained at the institution matches the current version. Notification of forms modification and/or revision is distributed to investigators via broadcast message and is also available under members update. For RAVE studies, an electronic PDF file is maintained on the RTOG Website that contains a report showing examples of the blank case report form data that will be collected. Actual forms are electronic and are available in the RAVE EDC environment.

Forms for one study cannot be used for another study. The forms are study-specific.

Laboratory results must be reported in US equivalents unless otherwise specified. Required reports: (e.g., pathology, surgery) must be in English. Unless specified otherwise on RTOG data forms, dates are reported as mm/dd/yyyy (month/day/year) for non-RAVE studies and as dd MTH yyyy for RAVE studies.

In an instance when a form is not available for web data entry, data forms should be completed in black ink for photocopying purposes. DO NOT use colored ink on data forms. A copy of each form should be retained by the investigator and the original mailed to Headquarters.

RTOG data forms cannot be substituted for forms in a study coordinated by another cooperative group. Data on cases registered through RTOG are submitted to RTOG, unless the protocol states otherwise. Both the RTOG and the coordinating group’s study and case numbers must be recorded on all data. RTOG conventions and procedures will not apply to studies coordinated by another group; check the protocol for specific instructions about eligibility or data submission. If the protocol does not address the concern or question, please contact the coordinating group for direction.
F. USE OF LABELS & PREPARATION OF DATA FOR SUBMISSION

- All case specific non electronic material, e.g., reports, memos, treatment records, dosimetry calculation, films, and some data forms, etc., submitted on cases registered to RTOG studies must contain case-specific labels. Labels are immediately available on the RTOG Web site (Data Center Login) for each newly registered case. All pages (e.g., data forms reports) must contain a label, have all the required identifiers recorded (study numbers, case numbers, institution number, patient initials), and the Intergroup study and case number must be included, if applicable.

- Reports uploaded into RAVE must have a case-specific label affixed to the report and patient’s name should be deidentified-showing only initials on the actual report.

- Labels replace manual recording of case identifiers. Labels may not obscure data. The RTOG labels contain a "form/film type" box in which to record the form ID code when this code is not included on the data item (e.g., pathology reports, surgical reports). Always record the form ID code for non-form items. Credit for submission may be delayed or missed entirely when the form ID is not identified.

- Do not include an institutional cover page or use the general communication memo as a cover page when sending forms, except when one is part of the data form. Cover pages are discarded.

- Do not send two-sided forms or reports

- Do not attach "post-its" to source documentation or data forms. Make comments in the comment section of forms or directly on the document in an area that does not obscure information. Comments must be signed/initialed.

- Each form and report must be legible without missing text or data at the edge of pages. There should be at least a ¼ inch margin on all borders of pages.

- Use black ink. Forms completed in pencil will be returned.

- Unsigned forms will be returned.

Do not apply highlighter over or through data or coding. The use of a highlighter obliterates information on scanned documents. If the form is unreadable, it will be returned for a better copy.

G. REQUEST FOR STUDY INFORMATION DATA MANAGEMENT

Incomplete forms will be returned to the institution. Forms containing conflicting information will result in a request for study information from the institution. These requests for information should be treated with urgency. If a reply to the request is not received within 30 days a second request will be issued. After 60 days a third request for study information will be issued and after 90 days a fourth request for study information will be issued. The original request for study information must be returned and or revision must be completed online for the calendar to be credited. When inquiring about a request for study information use the due date in the upper right corner as a reference to the specific request for information. To avoid unnecessary requests for information data forms should be carefully checked to ensure that all questions have been properly completed before submission to headquarters.
H. REQUEST FOR STUDY INFORMATION - RT QUALITY ASSURANCE

Within one week of initiation of treatment the digital radiation therapy data must be submitted per section 12.2 of the protocol. Credit for submission of this data is given when complete data has been received. For trials with pretreatment rapid reviews the cases that require a rapid review can not commence treatment until the case has been approved by the study chair. Three business days are required to complete this review once complete data has been received. Queries are sent by the RTQA staff for any incomplete or delinquent data that is needed.

I. FORMS DUE REQUESTS

All RTOG member institutions have access to their institution’s listing of forms due 24hrs/day – 7 days/week. For non-RAVE studies this information is available via the Calendar Ops Tool on the RTOG Web site. For RAVE studies, this information is provided through the EDC interface on each subject’s main page.

J. INELIGIBLE PATIENTS AND TREATMENT REFUSAL

When a patient is deemed ineligible for study, written notification is sent to the responsible investigator. Ineligible patients on phase III and randomized phase II studies are required to be followed and to have data submitted according to schedule unless notification to the contrary is sent to the investigator.

Investigator Refusal

An investigator should not enroll patients in a study unless she/he has reviewed the protocol and agrees to accept all of the study treatment options if randomization applies. Failure to accept an assigned option will result in suspension of the investigator from enrollment of subsequent cases in the study.

Patient Refusal

All treatment options in a study must be explained to potential study participants and the role of randomization explained, if applicable. If a patient changes his/her mind and is unwilling to start or continue with the assigned option, Headquarters should be notified in writing. Follow-up should continue to be submitted according to schedule unless directed otherwise by Headquarters. Once enrolled in a study, the patient will need to be accounted for in the analysis; therefore, it is important to obtain an agreement from the patient to be followed so that accumulation of delinquent data by the institution will not occur.

Withdrawal of Consent

Patients have the right to withdraw consent to continue treatment or discontinue follow-up at any time. The investigator must determine the level or withdrawal or discontinuation and provide adequate explanation to RTOG. Both the patient and the investigator must agree on expectations regarding study data.

- If a patient wishes only to discontinue protocol therapy, this refusal and all relevant treatment information must be reported to the cooperative group data center, however, follow-up should continue unless specified otherwise in the protocol.
• If the patient decides to discontinue follow-up with the RTOG investigator, a process to obtain information from other sources should be discussed, i.e. release of information by other sources, etc. If this is not acceptable to the patient, the investigator should encourage the patient and request permission to submit survival status data. Although the patient has the right to refuse submission of all data, she/he should be informed that failure to provide survival status and information about treatment toxicity may adversely affect the study results. Patients rarely refuse to be contacted for follow up or survival information. A “release of information” document may need to be signed by the patient, however, consult institutional policy regarding this process. The policy and duration of the release may vary among institutions.

• If the patient refuses all contact, this decision must be documented by using the consent withdraw (CW) form. and submitted to RTOG headquarters. At RTOG, the case will be closed once all data due prior to the date of withdrawal has been received.

• If the patient only refuses to continue with the QOL data submission this decision must be documented by utilizing the QOL consent withdraw form and submitted to RTOG headquarters.

In studies that require separate consent for submission of specimens (tissue, blood, serum, etc.), patients may elect to refuse participation in this aspect of the study provided that submission of the material is not a condition of eligibility or a study endpoint. When consent for specimen collection is refused, it is the institution’s responsibility to maintain record of the refusal and to notify RTOG that the material will not be submitted.

K. LOST TO FOLLOW-UP

Patients will be categorized “lost to follow-up” only after all efforts to obtain information have been exhausted and the patient cannot be traced for at least 36 months. Documentation of effort will be requested by Data Management. When a case is verified as lost to follow-up by Data Management, periodic survival updates will be requested. When the patient's status is changed to “lost”, for non-RAVE studies all subsequent follow-up requests are deleted and replaced with a V5 (survival update). This is not a form but serves as a reminder to the institution that the case is open. For RAVE studies, the Patient Contacted form is completed at each follow-up interval to indicate whether the patient was able to be contacted. At this time the investigator should renew efforts to locate the patient or information regarding survival. Updating survival means that either the last date known alive is determined to be more recent than previously reported or that the patient's death is documented. When survival is updated, the appropriate data form in the study (Follow-up form) is completed as much as possible and submitted. If survival cannot be updated, the original V5 or Patient Contacted form, as appropriate remain on the case calendar as a signal to recheck for information periodically.

The principal investigator of an institution with frequent occurrences of lost patients may be requested to submit in writing an assessment of the reason(s) for the problem and an action plan to avoid additional lost to follow-up occurrences.
L. DATA ISSUES

1. Data Management

General data-related problems can be discussed by calling the Data Management Department at (215) 574-3214. Protocol specific questions can be discussed by contacting one of the research associates assigned to the specific disease site. The aforementioned listing is located on the RTOG Web site under Contact Us.

2. Radiation Therapy Quality Assurance

Problems related to radiotherapy quality assurance material or radiation oncology treatment planning should be directed to Radiation Therapy Quality Assurance Department at (215) 574-3219. The fax number is (215) 923-1737.

M. TRANSFER OF PATIENT TO ANOTHER FACILITY

To transfer the care of a protocol patient enrolled on an RTOG trial by an RTOG site to another RTOG institution, the investigator who originally enrolled the patient must complete the RTOG Patient Transfer Form (see Appendix I for link) and submit it to the RTOG Administrator for approval. The transfer form must include signatures of the principal investigators at both the transferring and recipient sites. Documentation of IRB study approval for the recipient investigator must be on file at RTOG HQ before the transfer can be finalized.

If the case was registered through CTSU for RTOG credit the institution must notify the CTSU according to their guidelines.

If the study includes patient specific NCI/Pharmaceutical Management Branch (PMB) drug distribution, the appropriate approval documentation will be required to complete the drug transfer. Please review the drug transfer requirements in the PMB Policy & Guidelines for Investigational Agents (see Appendix I for link to the PMB Policy Guidelines for Investigational Agents). RTOG will notify all non-NCI drug distributors when a patient transfer has been successfully completed.

Transfer of a case to another institution results in transfer of case credit and case reimbursement, unless reimbursement has already been distributed. Case reimbursement will be made to only one institution. Issues related to medical insurance are the responsibility of the investigators involved in the case transfer. All delinquent data through the date of transfer should have been resolved before the transfer. For example, the recipient investigator should request an updated calendar from the original investigator prior to the transfer so that submission of delinquent data is resolved. Subsequent to case transfer, responsibility for all data requests and data submission is transferred to the recipient investigator including institutional requirements.

Transfer of cases from an RTOG member institution to a member of a different cooperative group or transfer of a case from another cooperative group to an RTOG member institution cannot be made.

N. FOREIGN LANGUAGE / TRANSLATION REQUIREMENTS

All submitted data must be in English. Reports (e.g. pathology and MRI reports) that originate in a language other than English must be translated into English and the translated report is submitted to fulfill the data submission requirement. The institution is responsible for all translation costs. Certification of the translation is optimal but due
to the prohibitive costs involved, RTOG will accept, at a minimum, a verified translation. A **verified report translation** consists of the English language translation of the report along with a cover letter on organizational or letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

**CRFs** may be translated into a local language for completion by site investigators and staff. The institution is responsible for all translation costs. Certification of the translation is optimal but due to the prohibitive costs involved, RTOG will accept, at a minimum, a verified translation. A **verified CRF translation** consists of the actual data form in English and in the native language, along with a cover letter on organizational or letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well. *Note that Quality of Life and other validated and/or trademarked tools may not be translated.*

**VIII. TOXICITY/ADVERSE EVENT REPORTING Vs. SERIOUS ADVERSE EVENT REPORTING**

**A. ADVERSE EVENT REPORTING GUIDELINES**

Federal Regulations require that investigators report adverse events in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI); whereby, new findings and important safety-related information can be more widely disseminated to investigators and clinicians.

1. **Definitions and Terminology**

   An adverse event (AE or Adverse Experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite”).

   Currently, the NCI Common Terminology Criteria for Adverse Events (CTCAE) is the tool (i.e., an AE dictionary) used to report all AEs. CTCAE provides descriptive terminology, along with a grading (severity) scale for each AE term.

   **Expectedness:** An unexpected AE is any AE, the specificity or severity of which is not consistent with the current IB, or the Instructions for Use or other device documentation; or, if an IB or equivalent is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the IND/IDE (21 CFR 312.32 and/or 21 CFR 812). Additionally the ICH E2A defines an unexpected adverse drug reaction as an AE, the nature and severity of which is not consistent with the applicable product information (e.g., IB for investigational agent).
Unexpected events are those not listed on available sources including the package insert, Investigator’s Brochure, or the protocol.

Hospitalization (or prolongation of hospitalization): NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the AE and should ONLY be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. (e.g., a hospital visit where a patient is admitted for observation or minor treatment such as, hydration and released in less than 24 hours). Furthermore, hospitalization for pharmacokinetic sampling is not an AE, and therefore is not to be reported either as a routine AE or in an expedited report.

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily “caused by a therapeutic intervention”. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

<table>
<thead>
<tr>
<th>RELATIONSHIP</th>
<th>ATTRIBUTION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated to investigational agent/intervention¹</td>
<td>Unrelated</td>
<td>The AE is clearly NOT related to the intervention</td>
</tr>
<tr>
<td>Likely</td>
<td>Unlikely</td>
<td>The AE is doubtfully related to the intervention</td>
</tr>
<tr>
<td>Possible</td>
<td>Possible</td>
<td>The AE may be related to the intervention</td>
</tr>
<tr>
<td>Probable</td>
<td>Probable</td>
<td>The AE is likely related to the intervention</td>
</tr>
<tr>
<td>Definite</td>
<td>Definite</td>
<td>The AE is clearly related to the intervention</td>
</tr>
</tbody>
</table>

¹NOTE: AEs listed as “possibly, probably, or definitely” related to the investigational agent/intervention in AdEERS are considered to have a suspected “reasonable causal relationship” to the investigational agent/intervention (ICH E2A). For routine, CDUS adverse event reporting purposes, “Attribution” defines the relationship between the adverse event and the investigational agent(s)/intervention as defined in Clinical Data Update System (CDUS) Instructions and Guidelines

Investigator Responsibility
Clinical investigators and ultimately the protocol principal investigator have the primary responsibility for AE identification, documentation, grading, and assignment of attribution. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. If source documentation is requested, it is the responsibility of the investigator to supply the medical documentation needed to support the expedited AE report(s) in a timely manner.

2. Grading of Adverse Events

Unless specified otherwise, the NCI CTCAE (see CTEP, NCI Guidelines: Adverse Event Reporting Requirements, February 29, 2012) is used to grade severity of adverse events. Protocols approved prior to March, 2003 will use one of several
different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol for the appropriate grading system.

3. Expedited Adverse Event Reporting

For NCI/RTOG protocols, all expedited AE reporting (based on CTEP’s criteria and protocol-specific guidelines, if applicable, is done via CTEP’s Adverse Event Expedited Reporting System (AdEERS). Expedited reporting via AdEERS provides an early detection system for potential safety problems. AEs that must be reported (initiated) within 24 hours of learning of the event are dependent upon phase of trial, the agent/intervention (investigational or commercial), and the grade of the event.

For all medical and policy related issues, please contact the AdEERS Content Help Desk by telephone (301-897-7497) or email (adeersmd@tech-res.com).

For all technical and training related issues please contact the NCI CTEP Technical Help Desk by telephone (888-283-7457) or email (ncictephelp@ctep.nci.nih.gov).

4. RTOG Adverse Event Data Collection Forms

All routine AEs are also collected on RTOG’s Data Collection Forms. All expedited AEs reported through AdEERS must also be reported consistently on RTOG’s Data Collection Forms. In addition, routine AEs not requiring expedited reporting, based on CTEP’s reporting guidelines and requirements, RTOG routine AE reporting guidelines, and any protocol-specific guidelines are required to be reported on RTOG’s Data Collection Forms throughout the life of the protocol.

Contact the RTOG protocol primary RTOG HQ Research Associate via telephone or e-mail with any questions concerning AE reporting and RTOG AE Data Collection Forms.

B. SERIOUS ADVERSE EVENT REPORTING GUIDELINES

1. Definitions and Terminology

A Serious Adverse Event (SAE) is defined by the Code of Federal Regulations (CFR) as: Any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Any pregnancy, including a male patient’s impregnation of his partner, occurring on study must be reported via AdEERS as a medically significant event.
The phrase “at any dose” should be replaced with “during protocol treatment and 30 days after” for RTOG purposes to capture SAEs that occur during any part of protocol therapy including radiation therapy or surgery.

During protocol treatment and for 30 days after, investigators must report any SAE whether or not they are considered related to the investigational agent(s)/intervention.

Please note certain grade SAEs require expedited reporting outside the 30 day window when the event is determined to be possibly, probably or definitely related to any part of protocol treatment.

It is important not to conflate CTCAE grade, a measure of severity or intensity, with seriousness. Seriousness reflects outcome and is defined by FDA regulations and guides safety reporting regulations. Severity is a gradient scale, in part informed by subjective symptoms.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the SAE definition above. They should also usually be considered serious.

Some medically significant events could be intensive ER or home treatments that do not result in an admission for
1. allergic bronchospasm
2. blood dyscrasias
3. convulsions
4. the development of drug dependency or drug abuse.

2. Reporting Serious Adverse Events (SAE)

All serious adverse events that meet expedited reporting criteria must be reported to NCI and the lead group (RTOG) via AdEERS. Refer to the AdEERS expedited reporting table in the protocol to assist with assessment of adverse events to determine if an AE is serious and to ascertain the timeframe for expedited reporting. Expedited SAE reporting via AdEERS is separate, and in addition to Data Management AE reporting (on the CRF). SAEs must reported to your IRB

Any AE that is a suspected adverse reaction, i.e. reasonably related to treatment, and is both serious and unexpected must be reported to the FDA within a mandated timeframe (for timelines, see 21 CFR 312.31 and ICH E6). To ensure compliance with FDA regulations, the IND/IDE sponsor requires SAEs be reported in an expedited manner for evaluation. The IND/IDE sponsor reports unexpected and reasonably related serious adverse events to the FDA. Serious AEs are defined by FDA and therefore seriousness (not severity) serves as a guide for defining regulatory reporting obligations for patient/subject safety. ‘Serious’ is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. FDA Federal Regulations require IND sponsors to report serious AEs via expedited reporting. RTOG SAE Safety Reporting Requirements
Submitting a report via AdEERS serves as notification to RTOG and satisfies RTOG requirements for expedited adverse event reporting. Every RTOG protocol includes an expedited reporting table for adverse events to guide SAE reporting and details reporting timeframes. In general, a report must be submitted to NCI as a 24 hour notification with a full report in five calendar days or as a ten day report; phase of study, agent/intervention, and grade determine which type of report.

For all RTOG protocols, i.e. RTOG is the lead group (whether or not RTOG holds the IND/IDE), when the clinical site submits the AdEERS report it goes to RTOG first for central review. Therefore, it is imperative to accommodate for the additional time necessary for RTOG central review when submitting an AdEERS report. The time clock starts with the initiation of a report in AdEERS and ends when the report is submitted to NCI by the lead group. SAE reporting is safety related, separate from and in addition to data management toxicity reporting requirements on the case report form.

3. 24 Hour AdEERS Notifications Requirements

SAEs that meet the criteria for a 24 hour AdEERS notification require a complete report to be submitted to NCI within 5 calendar days.

All other SAEs that meet expedited reporting criteria must be reported to NCI via AdEERS using the 10 day reporting timeline.

It is important to note the initiation of a 24 Hour AdEERS Notification when it is not necessary will still require a complete report within 5 CALENDAR days.

All SAE reporting guidelines must be adhered to regardless of whether the protocol has been amended to include them or not.

The clock begins when the report (24h/5day or 10 day) is initiated in the AdEERS system. AdEERS sends automatic reminders to facilitate submission of the report to NCI within the mandated timeframe. Because the report is submitted to the lead group for central review, this additional time requirement must be considered. The clock stops when the report is submitted to NCI by the lead group NOT when the clinical site submits the report to RTOG.

Supporting source documentation is not mandatory. However, if the AdEERS reporter indicates in the Additional Information section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an AdEERS report, include the protocol number, patient ID number, and AdEERS ticket number on each page and fax supporting documentation to the RTOG dedicated SAE fax: 215-717-0990.

4. Pharmaceutical Query Follow-Up

For RTOG protocols with pharmaceutical support, the pharmaceutical company receives AdEERS reports generated on the study. If the pharmaceutical company requires further documentation or clarification, RTOG Regulatory Compliance acts as interlocutor between the pharmaceutical company and the clinical site. RTOG will contact the site reporter listed on the AdEERS report via RTOG Queries email with the request for more information or clarification.
For RTOG protocols in which NCI is the IND holder, NCI may contact the clinical site directly to request specific information or documentation; please also copy RTOG via the dedicated SAE Fax line on any information provided to the NCI.

IX. QUALITY CONTROL

A. PATIENT ELIGIBILITY

RTOG employs a sophisticated system of computerized checks to ensure that all patients entered on protocols meet the requirements for eligibility. Section IV, Participation Requirements, and Section VI, Patient Entry Procedures, outline these procedures. If, subsequent to initial entry, the patient is found to be ineligible, Headquarters will notify the institution depending on the phase of the study, data on the patient may continue to be collected. A tally of ineligible patients is kept for each institution and a less than 90% score for eligible patient’s results in a disciplinary action.

B. TREATMENT DELIVERY

1. Radiation Therapy Quality Assurance

RTOG has quality assurance monitoring procedures for each treatment modality. An integrated approach has been developed and adopted with the following specific aims:

- Credentialing and monitoring (by RTOG Medical Physics Committee, RPC, RTOG Headquarters RT QA).
- Assurance of the clarity, consistency, and accuracy of the treatment specification for each specific protocol (protocol review).
- Prevention or minimization of potential variations from the protocol treatment guidelines (Rapid/Pre TX review).
- Categorization of any variations from the protocol treatment prescription that do occur, so that they can be considered in a statistical analysis (final/Post TX review).
- For Advanced Technology Protocols remote reviews are performed using the web-based tools at the RTOG Core Lab to facilitate QA reviews, which allows visualization of images, structure sets, and dose distributions.
- Compilation and reporting of the review results for statistical analyses.
- Education of research associates through organized orientation programs.

a. Review of Developing Protocols

The radiation oncology component of each developing protocol is reviewed by the medical physicist consultant to the RTOG RT QA Department, chair of the Medical Physics Committee, RPC for credentialing, and the RTOG RT Quality Assurance staff to ensure the clarity, consistency, and accuracy of the treatment specification for each specific protocol. Particular attention is given to the method of radiation dose specification, target volume definition, treatment planning requirements, and total volume definition, treatment planning
requirements, total dose and time of delivery to the primary, nodes and critical structures. This consistent attention to radiation therapy detail is intended to eliminate the potential for variation from the intent of the protocol.

Guidelines for dose specification for all RTOG protocols follow the recommendations contained in ICRU 50, 1993, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). The intent of the dose specification is to assure uniformity in dose recording and reporting for all protocols.

b. Initial Radiation Oncology (RT) Rapid/Pre TX Review

For studies that require a rapid/pre tx review, the digital RT data must be submitted immediately. Once complete data has been received 3 business days are required for review and feedback on the case. The patient can not be treated until the plan has been approved by the study chair. In many cases re-planning and re-review are required. Please allow enough time for this process.

c. Final/Post TX Review

The purpose of the final/post tx RT review is to confirm the treatment was delivered based on the protocol criteria compliance for the statistician. If the patient did not receive the total protocol dose the Dose Volume Analysis (DVA) is adjusted and re-scored based in the protocol criteria. The RTQA staff works closely with each study chair to maintain protocol-specific evaluation criteria. These compliance criteria are designed to ensure consistency in scoring each case and are derived from the protocol stipulations.

d. Educational Research Associates Orientation Programs in Radiation Oncology

Training modules are accessible on the RTOG website for RTOG clinical trials data managers, site coordinators and research nurses involved in RTOG protocol participation and data collection. Review questions are imbedded in the PowerPoint modules. When all required modules are complete an RTOG certification for this training will be awarded.

e. Image-Guided Radiotherapy Quality Assurance

Image-guided radiation therapy (IGRT) refers broadly to treatment delivery employing modern imaging methods such as CT, MRI, PET, and ultrasound. Each institution planning to participate in RTOG protocols that requires IGRT credentialing must submit specific information and data that is defined in the IGRT submission page under each trial located on the ATC Web site. An updated Facility Questionnaire (FQ) is to be submitted to RTOG HQ for review. The submitted IGRT is reviewed in the RTOG RTQA Core Lab using web-based software tools.

f. Credentialing

Sites must undergo a credentialing process to participate in protocols with new treatment modalities such as SBRT, 3D-CRT, IMRT, Proton, brachytherapy and IGRT. This is protocol specific and details are located in section 5 (5.0 REGISTRATION PROCEDURES) of every protocol.
2. Medical Oncology Quality Control

a. Requirements for Participation

- Prior to each case registration, the medical oncologist must be consulted or see the patient and be in agreement that the patient is eligible for the protocol treatment.

- At the time of case registration, the facility must provide the name of the responsible medical oncologist.

- The registering investigator is required to inform the medical oncologist of the treatment assignment. A copy of the protocol, the RTOG flow sheets or treatment summary forms, toxicity criteria, and toxicity reporting guidelines should be given to the treating medical oncologist.

b. Following Registration/Randomization

- Investigators must be vigilant in verification of dosage calculations and in interpreting treatment administration instructions in chemotherapy studies. Dose intensification programs, new agents and creative regimens warrant a continuing focus on patient safety. Individual treatment prescriptions for delivery of protocol chemotherapy and other systemic agents should be recorded in the institutional record. This information should include all details and parameters necessary for treatment delivery including those parameters necessary in calculation of individual dosage, e.g., height, weight, surface area, area under the curve, creatinine clearance, etc. Any variation from the protocol must be fully explained, e.g., if a reduction in dosage is made based on ideal weight; both the actual and idealized weight used in the drug calculation must be documented.

- If chemotherapy is not given, this should be coded on the appropriate case report form, including the reason, and submitted without delay.

- When RTOG is the coordinating center for a study, the site clinical research associate will provide the treating medical oncologist with the treatment summary form used in the study and instructions regarding the required submission schedule. When another cooperative group is the coordinating center, the institutional clinical research associate will provide the treating medical oncologist with appropriate forms and instructions.

  Completed data forms will be returned by the treating medical oncologist to the research associate following each course of treatment or with each follow-up form, but not less frequently.

- All chemotherapy laboratory data (including interim and nadir values), treatment related toxicities, actual drug dose and dose/m² and area under the curve (AUC), if applicable, must be recorded on the case report form. All modifications in dosage or in the interval between treatments including termination, refusal or delays in therapy must be clearly documented. The reasons for all modifications must be coded appropriately or reported in the remarks. If treatment is discontinued prior to completion, the reason must be documented.
Toxicity reporting requirements must be observed, including reporting of significant negatives, i.e., absence of side effects. See the protocol for specific requirements and Section VIII for general guidelines.

c. Review of Treatment

The medical oncology treatment forms will be reviewed for compliance with the protocol specifications. Body surface area and drug dose calculations will be rechecked. Discrepancies or errors will be brought to the attention of the investigator by written inquiry and clarification or correction will be sought. Documentation of modification is required.

Unresolved deficiencies or problems are reported to the study chair or the medical oncology quality control consultant.

d. Noncompliance with Submission of Medical Oncology Treatment

Failure to submit the medical oncology data forms results in a case status of "unevaluable". Significant delinquencies may be reported to the medical oncology quality control chair, to the study chair and the group chair with the recommendation that case entry into chemotherapy studies be suspended until delinquencies are resolved.

e. Final Review

A final evaluation of the case with regard to study compliance is done by the medical oncology study chair or the medical oncology quality control chair. The reviewer completes and signs the Final Medical Oncology Evaluation Form. The evaluation form documenting the review is entered in the computerized medical data files where it is available for use in statistical analysis.

f. Treatment Compliance

The RTOG Quality Control Guidelines for Chemotherapy Administration will be used to evaluate treatment compliance. If additional or different guidelines are necessary, they must be identified prospectively and included in the protocol prior to activation.

g. Quality Control Guidelines for Evaluation of Chemotherapy Administration

Overall case evaluation ratings are specified in institutional quality control reports.

3. Surgical Oncology Quality Control

When surgery is part of the therapy, the surgical study chair clearly specifies the surgical technique in the protocol. Surgical and operative pathology reports are subsequently reviewed for technical and therapeutic compliance. In most studies this review is documented on an evaluation form, which is used in statistical analysis.

A surgical evaluation format has been developed and approved for use. This requires study specific customization by the study chair with regard to specification of variations and study endpoints. A sample of the standard at form and examples used in previous studies are obtained from the Headquarters research associate for the study. Using the standard format, the evaluation form is developed by the
modality study chair as soon as an adequate number of cases have been enrolled and data have been submitted.

The institutional investigator must communicate to his surgical colleagues the protocol specifications for surgical treatment prior to case entry. For specific protocols, the investigator may be required to register a surgical representative with Headquarters prior to case entry or may be required to identify the treating surgeon at registration. This will be noted in the protocol.

C. DATA MONITORING - DATA MANAGEMENT

In order to provide the study chair and the statistician with data of high quality for analysis, the monitoring of information occurs at many stages. Data review actually begins at patient registration through the use of a computer automated system, which includes an eligibility check as well as other administrative information. As data are received, the data are reviewed through various methods (e.g., auto-validation, surveillance, and manual review) by the assigned Headquarters research associate for accuracy, consistency and completeness. Discrepancies and missing data are clarified through the use of queries, some of which are followed by computer-generated reminders if a response is not received. Significant adverse events are validated and reported according to established procedures (Section VIII). For each new study, the research associate staff creates and maintains the database record and the medical data file. Treatment regimens, definitions for each computerized data element, as well as eligibility and range checks are specified. These processes provide the mechanism for registration of cases and the entry of medical information.

Computer entry of the data collection forms includes entry checks as well as numerous logic and cross-validation checks on previously reported information.

Additional monitoring of study data is accomplished through periodic formal study chair reviews. These are conducted at Headquarters where cases are evaluated for treatment compliance, toxicity, and evaluability. Questions related to eligibility, response, and toxicity are also communicated to the study chair as an ongoing process through the use of a mailed Chair Query or by computer message. Unresolved problems are finalized during the formal chair review.

D. PATHOLOGY/BIOSPECIMEN MATERIALS

1. Introduction

On some studies, central pathology review is conducted to confirm the diagnosis, which is a quality control aspect, and to evaluate the histologic parameters for prognostic value with respect to response or survival, which is a scientific question.

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for Central Review of pathology, as mentioned above. Central Review of tissue can be required to determine eligibility and/or as part of the study analysis.
2. Specimen Transmittal Form

When a study requires the submission of pathology material, a “Specimen Transmittal Form” is included in the forms packet for that study. This form must be submitted to the RTOG Biospecimen Resource at UCSF with the pathology material. The form aids in the identification of the submitted material. A pathology section describing materials requested for the particular protocol is provided in Section 10.0 (and appendices as appropriate) of the protocol. Appropriate pathology reports, clearly photocopied to include patient initials, case number, slide numbers and diagnosis must accompany any specimens submitted (e.g., tissue, serum, plasma, buffy coat, urine). Specimen numbers must be identical as those on the reports. All materials must be labeled with the RTOG study and case numbers.

3. Materials Preparation

Tissue specimens must be clearly marked with the surgical pathology accession number. All specimens must be collected, stored, and shipped as specified in the protocol. The RTOG Biospecimen Resource provides kits with supplies and instructions regarding collection, storage, and shipment free of charge to sites participating in the study upon the request of the site.

4. Shipment of Specimens

Unless specified otherwise in Section 10.0 of each RTOG protocol, pathology materials will be submitted to:

Mailing Address: For Non-frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter St., Room S341
San Francisco, CA 94143-1800
Telephone: 415-476-7864 (476-RTOG)
Fax: 415-476-5271
EMAIL: RTOG@ucsf.edu

Courier (FedEx DHL, etc.)Address: For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter St., Room S341
San Francisco, CA 94115
Telephone: 415-476-7864

5. Return of Pathology Material

Specimens submitted for review are not routinely returned to the institutions, but will be preserved in the RTOG Biospecimen Resource at UCSF for access during future studies. If the patient withdraws consent, he/she may request in writing, that her/his specimens be returned to the institution.
6. **Unavailable Pathology Material**

   Inability to provide pathology materials should be indicated on the pathology submission form as "MATERIAL UNAVAILABLE", with the pathology report attached and mailed to RTOG Headquarters. A patient label should be included on the form and report.

7. **Translational Research Embedded in the Protocol**

   If translational research is identified in the protocol, project specifics must be carefully documented including the materials to be collected and the time points.

8. **Reimbursement**

   Reimbursement for submission of biospecimen materials is provided as detailed in the [Reimbursement and Case Credit List](http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=335) found on the RTOG Web site.

E. **INSTITUTIONAL AUDITS**

1. **Purpose**

   All member facilities are eligible for an audit at least once every thirty-six months. However, all institutions may be audited at any time. New full member institutions are audited within 18 months of membership approval. New affiliate members and satellites are audited within 18-36 months of the date the first case is accrued. The scope of this program is to audit investigators for the purpose of: 1) corroborating that information submitted to RTOG, especially when impacting on study endpoints, can be supported by material in the source documentation (records, films, reports, etc.) at the institution; 2) verifying that quality control procedures mandated by NCI and by RTOG, especially those related to investigational drugs, are being followed; 3) confirming that policies designed for the protection of human subjects (IRB study approval, informed consent, etc.) are in effect.

   Institutions remain eligible for audit even if their membership in RTOG is withdrawn or terminated.

2. **Institutional Preparation**

   The institutions are notified up to two to three months in advance of the visit. An audit packet (consisting of an IRB protocol list, a patient case list and a list of investigative agents) will be reviewed, and is sent to the investigator and lead research associate approximately two to four weeks before the visit. While most cases are selected from accruals since the last audit, all cases are at risk for selection, including cases enrolled to other cooperative group studies on the CTSU menu. All regulatory, investigative agent accountability forms and patient case source documentation must be available even if maintained at a location other than the institution; *i.e.*, referred cases or patients receiving some treatment elsewhere. RTOG has developed a Quality Control Audit Manual and Guidelines which is referred to in the audit letter and found on the RTOG Web site which details audit preparation and process. It is updated regularly to stay current with the Cancer Trials Management Board (CTMB) requirements.
3. The Audit

The audit team will consist of one or more RTOG quality control auditor(s), and/or a physician, and occasionally, an NCI representative. The team visits the institution and reviews all institutional records, which pertain to the selected protocols, investigative agents and patient cases. Copies of RTOG data forms will not be considered adequate source documentation. Documentation of drug administration must be included in the patient’s record independently of RTOG data forms.

Prior to leaving the facility, the auditor(s) conducts an “exit interview” with the investigator and staff, at which time any discrepancies or problems identified during the audit are discussed. This is an educational time for questions and suggestions. If significant noncompliance with regulatory requirements, major problems with data verification, or suspected data fabrication/falsification are identified during the audit, RTOG shall notify NCI immediately by telephone.

4. Reporting of Results

The audit report is entered in to the NCI Audit Information System (AIS) Database. A copy of this audit report, along with a formal cover letter, is sent electronically to the Principal Investigator (with a copy to the Lead Research Associate).

Each audit is assigned an overall evaluation score: 1) Acceptable, no response is required; 2) Acceptable-needs follow-up, requires a written corrective plan; 3) Unacceptable-poor overall quality, requires a written corrective action plan and a re-audit; or 4) Unacceptable-suspect scientific misconduct, findings suggestive of scientific misconduct, fraud or intentional misrepresentation of data and/or disregard of regulatory safeguards. If significant noncompliance with regulatory requirements, major problems with data verification, or suspected data falsification are identified, RTOG shall notify NCI immediately by telephone.

A report of all audit site visits and results are provided to the RTOG Quality Control Committee at each RTOG semiannual meeting.

5. Misrepresentation of Data

At its semiannual meetings, RTOG provides seminars from time to time in medical ethics training and monitoring of data quality to ensure adherence to high standards of research integrity in clinical trials. If there is any evidence of fraud discovered during an audit, RTOG will notify the Clinical Trials Monitoring Branch of CTEP at NCI immediately by telephone. The institution’s accrual is suspended until appropriate action can be taken including a second site visit for a comprehensive study of all cases. If fraud is confirmed, the institution’s membership is terminated and its data are purged from the RTOG database. Any previous analyses are redone. Journal editors are notified immediately if results were previously published, and a reanalysis would be submitted for publication.

Investigative and reporting procedures for possible misconduct in science are detailed in the RTOG Procedures for Investigating and Reporting Possible Misconduct in Science (see Appendix I for link). All RTOG members are required to sign the RTOG Affirmation of Integrity of Research Data (see Appendix I for link).
X. STATISTICAL ANALYSIS

A. INTERIM ANALYSES

The Department of Statistics prepares summary reports for each RTOG semiannual meeting on all studies open to patient entry or in follow up until the initial publication (abstract or manuscript) of the primary endpoint. These reports focus on accrual (while the study is still open to accrual), patient characteristics, study execution and safety, and the results are reported to the entire Group. No efficacy data are presented in these reports. In each semiannual interim report, the following information is included:

- Projections for completion of patient accrual based on the rate observed over the entire study and the last 6 months (until study closed to accrual).

- Patient accrual by institutions.

- Case status for all the cases entered into the study. Cases included in analyses are those considered eligible as confirmed by the on-study pretreatment study data and having some post-baseline information. These cases are called "analyzable". Patients who are determined to be ineligible or did not receive any protocol treatment (for phase I and non-randomized phase II studies only) are excluded from all analyses of protocol treatment. Frequency of reasons for exclusion are provided.

- Distributions of stratifying variables used in randomization and/or other important demographic and prognostic variables for each assigned treatment regimen.

- A summary of reported adverse events presented by type, severity, and attribution for each assigned treatment regimen.

- An analysis of delivery of each treatment modality relative to the protocol prescription by assigned regimen.

Each interim report is reviewed before its external distribution to the Group. This review is performed by the disease site team, (senior statistician, the study research associate, study dosimetrist, and the protocol associate) and then by a second statistician.

The RTOG Data Monitoring Committee (DMC) reviews phase III and randomized phase II trials with a comparison to a standard of care within the trial treatments semiannually that RTOG is conducting for accrual and adverse events semiannually. The DMC also reviews the results of the protocol-specified formal interim efficacy analyses and other studies with problems identified. Based on their review, the DMC recommends to the Group Chair a possible future course for each study. The DMC can make one of five possible recommendations: 1) continue the study as it is; 2) revise the study because of adverse events or accrual issue problems; 3) close the study before it has realized its accrual objectives because of insufficient patient accrual; 4) close the study and report early because a high significant advantage is observed on one of the arms; or 5) close the study and report early because the interim analysis has found statistically significant evidence of futility.

The Data Safety Monitoring Board (DSMB) which reviews all phase I, randomized phase II trials where all arms are experimental, and non-randomized phase II trials meets semiannually. The DSMB also reviews a specific trial outside the RTOG semiannually meeting whenever a major toxicity issue arises. Their reviews primarily focus on adverse events and protocol-specified interim analyses which usually involve morbidity. Based on their review, the DSMB recommends to the Group Chair a possible
future course for each study. The DSMB can make one of three recommendations: 1) continue the study as it is; 2) revise the study because of accrual and/or adverse events; 3) close the study because rate of accrual and/or adverse events is unacceptable.

The DMC and DSMB also review specific trials outside the RTOG semiannual meeting report schedule as needed for any major study issue.

B. FINAL ANALYSES – INITIAL TREATMENT RESULTS

The primary endpoint analysis is performed by statistician when the protocol-specified follow-up time on every patient or number of events has been realized. Before this analysis can begin, all outstanding data errors and inconsistencies must be resolved and the final review of treatment delivery for each patient must be completed by the study chair and co-chairs. The headquarters research associate, dosimetrist, and statistician work with the investigators to accomplish these tasks. The usual components of this analysis are:

- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion
- Patient accrual rate
- Institutional accrual
- Distribution of important baseline prognostic variables by treatment arm
- Frequency and severity of adverse events by treatment arm
- Observed results with respect to the endpoints described in statistical considerations section of the protocol (Section 13.1)

All eligible patients are used in the primary endpoint analysis as long as some follow-up information is available. Patients who are determined to be ineligible and did not receive any protocol treatment (for phase I and non-randomized phase II studies only) are excluded from protocol analyses.

The primary endpoint analysis is reviewed by a second statistician before it is sent to the study chairman to form the basis of an abstract and subsequent manuscript. After reviewing the results from this analysis, the study chair then discusses the need for further analysis with the responsible statistician. The study chair drafts the abstract/manuscript reporting the study results based on the statistician's analysis. The section on statistical methods in the abstract/manuscript is prepared by the statistician. It describes the randomization scheme, sample size parameters and calculations, test statistics, and procedures for estimation used in the analysis.

C. SECONDARY ANALYSES

The analysis and publication of the primary endpoint result for a study takes precedence over any other analyses using data from the same study. Once it is published, analyses of the unreported secondary endpoints in the protocol can be performed. Requests to use the RTOG database for analyses not specified in the protocol have been designated as secondary analyses. All such requests are submitted to the Publications Committee on a standardized form. All requests are initially reviewed by the disease site team with respect to the amount of work that needs to be done and if it can be completed by the meeting listed on the form. This information is then sent to the disease site chair for their input. Each proposal is scored by the members of the Publications Committee with respect to scientific value and contribution to the field. The
scores are reviewed by a subcommittee of the Publications Committee. This consists of the Vice Chair for Publications, Group Chair, and Group Statistician. This subcommittee accepts or rejects each proposal based upon the score.

D. RELEASE OF STUDY DATA

RTOG personnel will give non-Headquarters personnel access to patient charts and data only under the following circumstances:

- The study chair is reviewing individual patient charts for the study.
- An individual other than the study chair has a project approved by the RTOG Publications Committee or is developing a translational research project that has been discussed with the TRP Committee Chair. Requests must be made in writing to the RTOG Publications or Translational Research Committees via headquarters stating the data which is needed and the purpose for which it will be used. In certain circumstances, it may be necessary to receive ACR IRB approval as well.
- Data that is to be used for reporting purposes (e.g., abstracts, manuscripts) must be prepared and/or reviewed by the disease site senior statistician prior to being released to a study chair or other approved individual.

XI. MEETINGS

A. SEMIANNUAL

The RTOG meets twice yearly, in January/February and June/July, to discuss the progress of existing studies, protocol modifications, design of new studies, results of completed studies, new methods of treatment, and other business. At each meeting, scientific sessions are held to inform members of developments in other disciplines and pertinent topics not covered in general sessions. In addition, educational workshops are held to update members on treatment planning and delivery techniques.

Electronic mailings for the semiannual meeting begin two to three months prior to the meeting. At that time, invitations, hotel reservation forms, and a tentative agenda are available on the RTOG Web site. Approximately two months in advance, agendas are requested from the committee chairs for distribution at the meeting. A meeting book, either printed or in electronic format, containing meeting agendas, progress reports, minutes from the previous meeting, committee reports, and a list of publications is available at the meeting.

RTOG protocol associates draft minutes from the Research Strategy Committee meeting at each semiannual meeting, circulate the drafts to the HQ disease site teams and the site chairs for review and feedback, and then distribute finalized minutes to the site chairs and teams. Committee chairs are responsible for submitting minutes of their committee meetings to the RTOG Administrator. Finalized minutes also are included in the following meeting’s meeting book and are available on the RTOG Web site.

B. COMMITTEES

All committees are requested to meet prior to or during the RTOG meeting. Additional committee meetings and conference calls are held during the year, as needed.
APPENDIX I: Web Site Links

RTOG Web Site Links

RTOG Bylaws
http://www.rtog.org/LinkClick.aspx?fileticket=G0GWDopb4-o%3d&tabid=99

Publication Materials
http://www.rtog.org/Publications/Welcome.aspx
- RTOG Publication Guidelines
- RTOG Secondary Analysis Guidelines
- RTOG Secondary Analysis Request Form
- Request for Data by Non-RTOG Investigators

Membership Materials
http://www.rtog.org/AboutUs/MembershipApplicationMaterials.aspx
- Membership Application & Instructions
- Requirements for Institutional Membership
- Criteria for Maintaining RTOG Membership
- Member Roster Update Form

Institutional Audit Materials
- RTOG Audit Manual
- CTMB Guidelines
- PMB Policy

Case Credit & Reimbursement Schedule
http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=335

Username & Password Application
http://www.rtog.org/AboutUs/RTOGPasswordApplication.aspx

Protocol Development Materials

Translational Research Program
http://www.rtog.org/Researchers/TranslationalResearchProgram.aspx

Data Monitoring Committee Materials
http://www.rtog.org/ClinicalTrials/DataMonitoringCommitteeDMC.aspx

Data Safety Monitoring Board Materials
http://www.rtog.org/ClinicalTrials/DataSafetyMonitoringBoard.aspx

Data Sharing Policy
http://www.rtog.org/LinkClick.aspx?fileticket=OP_9KyR_mOw%3d&tabid=95

Conflict of Interest Policy
http://www.rtog.org/Researchers/PoliciesManuals/ConflictofInterestPolicy.aspx

Affirmation of the Integrity of Research Data
http://www.rtog.org/LinkClick.aspx?fileticket=_tTku68wFBM%3d&tabid=103
Procedures for Investigating & Reporting Possible Misconduct in Science

Guidelines for Monitoring of Clinical Trials for Cooperative Groups
http://www.rtog.org/Researchers/PoliciesManuals/ScientificMisconductPolicy.aspx

Participant Form Calendar (password protected through the OPS tool)
https://silver1.phila.acr.org/Clinical_RTOG/pgCaseTrackingLogon.html;jsessionid=038f6cf50feb824c88d619db1cb92c09

General Communication Memo
http://www.rtog.org/LinkClick.aspx?fileticket=sQeEflph1Wc%3d&tabid=308

Patient Transfer Form

Non-RTOG Web Site Links

PMB Policy Guidelines for Investigational Agents
http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs

NCI On-line Agent Order Processing (OAOP) mechanism
https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx

NCI Central IRB
http://www.ncicirb.org/

CTEP AdEERS Tutorial

Office of Human Research Protections (OHPR)
- Assurance Application – Domestic & International
  http://www.hhs.gov/ohrp/assurances/forms/index.html

- IRB Registration Look-up
  http://ohrp.nih.gov/search/

- Registering an IRB (Initial or Update/renew)
  http://www.hhs.gov/ohrp/assurances/irb/index.html

Protection of Human Subjects
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

Advanced Technology Consortium
http://atc.wustl.edu