

Radiation Therapy Oncology Group

RTOG PROCEDURE MANUAL

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Originally Issued: March 1978
Current Edition: October 2004

Supported by the National Cancer Institute Grant #CA21661

Division of Cancer Treatment, Diagnosis, and Centers

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I. INTRODUCTION

A. HISTORY

The Radiation Therapy Oncology Group (RTOG) was initially organized in 1968 under the direction of Dr. Simon Kramer 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 has grown considerably since the activation of its first study in 1968, an adjuvant methotrexate study for head and neck cancer. The methotrexate study employed combinations of radiation, methotrexate and surgery in the treatment of advanced head and neck cancer, and is considered a milestone in interdisciplinary clinical efforts. The over 700 patients accessed to this study formed the baseline for many of the clinical investigations in the area of head and neck cancer.

Since its inception the Group has activated 350 protocols and accrued a total of approximately 60,000 patients to cooperative group studies.

The RTOG is a multi-institutional cooperative organization, the principal objectives of which include: 1) increasing the survival of patients with malignant diseases in which control of the local-regional tumor is a major determinant of outcome; 2) demonstrating the contributions of new modalities to the therapy of cancer, adjunctive to the established modalities of surgical resection, radiation therapy and chemotherapy; 3) improving the quality of life of patients by preserving structure and function while maintaining or increasing survival, and providing palliation and preserving dignity for patients who are not cured; 4) preventing second and subsequent malignant tumors among patients cured of cancer, and 5) seeking greater understanding of the biology of several types of cancer.

The Group provides an infrastructure for clinical investigators from the United States and Canada to seek more effective treatments for cancer. Radiation, surgical and medical oncologists, pathologists, laboratory scientists and diagnostic imaging specialists seek to expand knowledge of basic biology and clinical manifestations of cancer, and thereby find means to increase survival, decrease morbidity, and relieve symptoms among those afflicted. As the Group has pursued studies a decade or more ago that have resulted in treatments that are considered standard today, so it is striving to identify new therapies which can be transferred to the community as standard for the 21st century. This transfer is facilitated by the interaction of clinicians and laboratory scientists from academic medical centers with postgraduate training programs and oncologists in the private practice of medicine. An important by product of this interaction is a common understanding of quality assurance requirements to achieve the most effective care throughout the general medical community for standard as well as new modalities. Results from therapeutic efforts have permitted new understandings that can be brought to bear on the prevention of second and subsequent tumors in cured patients at high risk; pilot studies in single institutions suggest great promise and provide the basis for group wide investigations of chemoprevention.

The RTOG has established mechanisms to assure compliance with protocols in all aspects of radiation therapy, dose prescription and delivery. The Group emphasizes day-to-day quality control in patient registration procedures, radiation therapy treatment

review, data management, pathology review, medical oncology review and surgical review.

RTOG is an active coordinator of and participant in Intergroup studies. Over the years the Group has participated in over 50 Intergroup trials and has coordinated almost 20 of those Intergroup studies, thereby broadening the Group's research efforts and patient population to the greatest number of participants possible.

The Group Headquarters and Statistical Unit are located at the offices of the American College of Radiology in Philadelphia, PA. The Headquarters Office has been in Philadelphia since the Group's inception, while the current Statistical Unit was formed in 1982.

B. GROUP OBJECTIVES

1. To increase survival in common types of cancer afflicting citizens of the United States and Canada by effective integration of local-regional therapy with ionizing radiation and/or resection, and systemic therapy with cytotoxic drugs and hormones.
2. To evaluate new methods of delivery of radiation therapy and surgery (3-dimensional conformal radiation therapy and stereotactic radiosurgery) 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 encourage laboratory scientists not previously collaborating with cooperative groups to undertake cooperative investigations.
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 administrative support for Group functions, including:
 - a. Distribution of protocols to members.
 - b. Entry of patients into studies.
 - c. Assistance to each study chair, as required, through communication with individual members and the statisticians.
 - d. Compilation and distribution of all Group reports.
 - e. Arrangement of all Group and committee meetings; the 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 establish and maintain the database required by the statistical unit for analysis of RTOG studies.
6. To coordinate the Group's quality assurance program.
7. To provide administrative support for RTOG committees such as the Pathology, Medical Oncology, and Surgery Committees as well as Membership Evaluation, Publications, etc.
8. To monitor Group grant awards and expenditures including the reimbursement of Group members for case accrual, data management activities and scientific contributions.

II. GROUP ORGANIZATION

A. OVERVIEW

The Group Constitution and Bylaws define organizational structure, committee responsibilities, membership rights and membership responsibilities. Standardized membership approval and performance criteria are applied to all RTOG participants. Publication and Protocol Guidelines have also been established. The Group Bylaws and established guidelines can be found in the appendices.

B. CHAIR, VICE-CHAIRS & DEPUTY CHAIR

1. Group Chair

Walter J. Curran, Jr., M.D. became Group Chair in July 1997. He has been a member of the Group since 1986 and prior to assuming the Group Chair was Deputy-chair and Chair of the Brain Committee. The Chair, elected by a majority vote of the Full Member institutions, serves a term of four years and may be re-elected twice. As Chair, Dr. Curran provides scientific and administrative leadership for the Group. He works closely with the Vice-Chairs and other Committee Chairs as well as the Headquarters and Statistical Unit to develop and achieve the Group's goals.

2. Vice-Chairs

The Vice Chairs for Membership Evaluation, Publications, and Disease Sites, will be elected by a majority vote of eligible votes cast by Full members at the Group meeting. The remainder of the Vice Chairs will be appointed by the Group Chair with the approval of the Executive Committee. Each Vice Chair will serve a term of four years and may be re-elected/reappointed to a second four-year term.

Each of the eight Vice-Chairs serves on the Executive Committee and Steering Committee.

The Vice-Chair for Membership Evaluation, Jay S. Cooper, M.D., is the Chair of the Membership Evaluation Committee and is responsible for the semi-annual review of all Full Member participants, evaluation of all new member applicants, and the continuing refinement of the Group's membership review criteria.

The Vice-Chair for Publications, William T. Sause, M.D., is the Chair of the Publication Committee and is responsible for identifying potential publications, promoting their timely development, coordinating the review of all proposed RTOG publications by Publication Committee members and revising the publication guidelines as necessary.

The Vice-Chair for Disease Sites, oversees disease site committees, seeks to encourage protocols in areas of particular need, and helps set priorities for best use of patients, data management, and statistical center resources. This position seeks to coordinate common research themes and initiatives among the disease site committees.

The Vice-Chair for Translational Research, directs the Translational Research Program, comprising the Tumor Biology, Pathology, Time/Dose and Tumor Repository Utilization Committees. The information developed in this joint effort feeds into the modality and site committee programs.

The Vice-Chair for Prevention and Cancer Control oversees all cancer control efforts including CCOP protocol development and the activities for the CCOP program. Also oversees the Chemoprevention and Late Effects Subcommittees.

The Vice Chair for Medical Oncology oversees all RTOG Medical Oncology efforts including the coordination of activities of the Brain, Gastrointestinal, Genitourinary, Head and Neck, Lung, and Medical Oncology Quality Control Subcommittees to bring new ideas and developments into the Group.

The Vice Chair for Surgical Oncology oversees all RTOG surgical efforts including the coordination of the activities of the Gastrointestinal, Head and Neck, Neurosurgical, Surgical Quality, Thoracic, and Urology Surgical subcommittees to bring new ideas and developments into the Group.

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 and Headquarters and Statistical Unit 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.

C. COMMITTEES

1. Executive Committee

The Executive Committee consists of the Chair, the Deputy Chair, the eight Vice-Chairs, the immediate Past Chair, the Chairs of the New Investigators, Quality Control, CCOP Evaluation, CCOP PIs, Medical Physics, Special Populations, Research Associates, Pathology, Tumor Biology, Time Utilization, Patient Advocate Committees, the Group Statistician, 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 shall consist of the Group Chair, the Vice-Chairs, Deputy Chair, and the Group Statistician. It will carry out necessary Executive Committee

activities between meetings of the Executive Committee and will report 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 Statistical Center, the disease site committees chairs and the other scientific core committee chairs. It meets twice at 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. Standing and Site 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, Research Strategy and Executive Committees, are appointed by the Group Chair and reviewed by the Executive Committee. The Standing Committees are defined in the Group's Bylaws and are responsible for setting the scientific and administrative goals of the Group. The specific site committees assist the Standing Committees in developing and monitoring protocols and publications.

D. HEADQUARTERS RESPONSIBILITY AND STAFF

The RTOG Headquarters is based in Philadelphia under the direction of the RTOG Chair. Day-to-day RTOG operations are administered by the Administrative Director for Clinical Trials, Director of Protocol Development, and Director of Radiation Oncology Quality Assurance. The RTOG Headquarters is organized in three functional units: 1) administration; 2) protocol development and regulatory compliance and 3) radiation oncology quality assurance. Historically the Data Management Unit has been funded through the Headquarters budget. However, it is considered to be a part of the Statistics and Data Management Center and its functions are described in that section.

1. Administration

The administrative unit coordinates correspondence and contact with the National Cancer Institute. The unit, headed by the Administrative Director for Clinical Trials, maintains the membership roster and all other group records and files. The Administrative Director is responsible for the fiscal management of the group, the preparation of all group progress reports and the development of all funding applications.

Administrative staff schedules all group meetings, prepares meeting agendas, coordinates the scientific sessions and records and distributes all meeting minutes. Scientific reports, abstracts and manuscripts submitted for publication utilizing RTOG data are monitored by and distributed to the appropriate committees and individuals for review and approval. The evaluation of new Affiliate membership applications is carried out in Administration under the direction of the Membership Committee, as is the scheduling of membership site visits to evaluate prospective

Provisional Members. In addition, the staff coordinates the continuing review of current members.

2. Protocol Development and Regulatory Compliance

Protocol development is coordinated by the Director of Protocol Development. Developing protocols are routed to the appropriate committees within the RTOG and to the Statistical Unit and Headquarters Staff. After committee and Group Chair approval, protocols are submitted to NCI for review and after NCI approval, distributed to the membership. Data collection forms and other tools necessary for protocol management are developed by Headquarters Research Associates' staff in concert with the Statistical Unit and the Deputy Chair. The Director of Protocol Development acts as a liaison with the ACR Institutional Review Board to ensure that all RTOG protocols receive central IRB approval prior to activation.

Responsibilities also include randomization of patients to studies, facilitation of industry and cooperative group liaison, and management of the Institutional Audit Program. OHRP-approved assurances and IRB approvals and sample consent forms are reviewed by the Director. Computer programs to provide these functions have been developed.

3. Radiation Oncology Quality Assurance

The Radiation Oncology Quality Assurance Unit coordinates the radiation oncology treatment review process for cases accessed to RTOG protocols. This is accomplished using a two-step procedure defined as the Initial and Final Review Procedures. The Initial Review is performed at the initiation of treatment, for the purpose of ensuring compliance with protocol specifications. Cases are randomly selected for the Initial Review following proven ability to comply with protocol stipulations.

The sampling procedure reviews the first five cases per study for each institution; if all cases are compliant, only one out of the next ten cases is "sampled for review." If any one case is scored as non-compliant, the procedure reverts back to the next five cases for initial review.

Upon completion of the treatment a Final Review is performed to document the treatment administered relative to the study requirements. Variations in treatment are categorized and used in the statistical analysis. Each review process is done in conjunction with the respective Study Chair and the staff dosimetrist.

The Radiation Oncology Quality Assurance staff is responsible for: the review of developing protocols; design of treatment forms and data collection for approved studies; development of quality assurance procedures; preparation and coordination of the Initial and Final Reviews, and compilation and distribution of review results to RTOG members, committees, and Intergroup offices.

E. STATISTICAL UNIT CENTER RESPONSIBILITIES AND STAFF

Statistical support for RTOG is provided by the Statistical Unit, located together with the Headquarters Office at the American College of Radiology in Philadelphia.

The objective of the Statistical Unit is to collaborate with RTOG investigators in defining the optimum role of radiation therapy, either alone or in combination with other modalities, in the management of patients with cancer: to improve local control, enhance the quality of life, extend survival and ultimately cure of disease.

To achieve these aims, the unit is involved in all aspects of the RTOG. The statisticians interact with the Site Committees in the design and feasibility of proposed protocols, prepare randomization schemes and procedures related to treatment assignment for each study and monitor protocol treatment delivery.

Analyses of all studies open to new patient entry are prepared for each semi-annual meeting. These analyses are aimed at detecting major difficulties with protocol execution that may require study revision, or in revealing toxicity problems or poor patient accrual, which may warrant the discontinuation of a study. These results (except for "efficacy") are published in the pre-meeting book. For randomized trials, the RTOG Data Monitoring Committee reviews the interim statistical analyses at times specified in the protocol. Additionally, they review efficacy results, blinded to treatment assignment, to detect extreme early treatment differences. Based on these results, the Data Monitoring Committee recommends to the Group Chair a possible future course for the study. For non-randomized studies, there is no Data Monitoring Committee to monitor efficacy. The study chair, responsible statistician, and responsible disease/modality chair examine it as specified in the protocol. Studies closed to new patient entry are reported only if there is new information available.

After a study has accrued the required patients and the targeted number of events (e.g. deaths) in the protocol have occurred, a detailed statistical analysis is prepared for use in presentations at scientific meetings, and in publications regarding treatment results. Some protocols are designed to address quality of life or correlative laboratory measurements in addition to treatment. These are 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 whenever possible. These analyses have to be approved formally beforehand by the RTOG secondary analysis and review committee.

F. DATA MANAGEMENT UNIT

The primary responsibility of the Headquarters Data Management Unit 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 a Headquarters Research Associate who then plans and carries out the various processes and tasks necessary for study management, such as the creation of the eligibility check, design of the study data collection schedule, participation in data collection forms design and creation of special procedures needed to monitor the study.

The Data Management Unit creates, maintains, and monitors the computer file that contains the clinical information utilized by the statistical staff and the Study Chair. Because data forms and other required material impact on the analysis file, early and close involvement of the Data Management staff with the studies, with study chairs and the data set is important.

Headquarters research associates are organized into two teams with each team responsible for several disease sites. Additional responsibilities such as institutional orientation, forms requests, intergroup studies, etc., and other general or project specific tasks are assigned among the teams. Each team consists of a number of junior research associates and a senior RA who is responsible for supervision of team efforts. Teams are assisted in their day-to-day activities by a unit secretary and by a data assistant. Senior Research Associates are supervised by the Assistant Director of Data Management. *The Assistant Director participates in the orientation of new departmental staff.* Under the direction of the Director of Data Management, the data management staff coordinates the Headquarters effort with regard to the clinical aspects of the protocols. The Assistant Director of Data Management assigns new protocols to the appropriate team. A research associate from the team is assigned as the study coordinator. Cases within a study may be assigned to several team members. 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 interactions with Study Chairs, statistical staff, radiation therapy quality assurance monitors, and administrative staff. Individual case problems not resolved by the Headquarters Research Associate or study problems that indicate a need for protocol modification are referred to the appropriate person, i.e., study chair, modality chair, protocol administrator. Periodic reviews with Study Chairs are conducted at which time data are examined and institutional compliance with respect to treatment delivery are assessed. The Data Management Unit coordinates modality reviews of medical oncology, surgery and other systemic agents.

The Headquarters 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 the problems handled daily.

III. MEMBERSHIP

A. TYPES OF MEMBERSHIP

The RTOG has four membership categories: Full, Provisional, Affiliate, and CCOP.

1. Full Membership

Full membership can be held by an institution and their affiliates, which meets the criteria found in Appendix III. Full Members are responsible for placing 25 cases on RTOG studies each year. Full Members must also maintain adequate data quality scores as defined in Appendix IV.

To become a Full Member an institution must successfully complete a trial period as a Provisional Member. An Affiliate Member may request Provisional Member status

after accruing 25 patients on RTOG studies during a 12-month period and undergoing a satisfactory site visit by the Membership 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 Appendix IV.

2. Provisional Membership

Institutions wishing to become Full Members of the Group are required first to become Affiliate Members, and after enrolling 25 patients on studies during a 12 month period may apply for Provisional membership.

Application for Provisional membership is 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. Provisional Members are no longer affiliated with a Full Member, once they have achieved Provisional Member status.

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, and if the institution fully assumes the responsibilities outlined in Appendices III and IV, 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 which 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 in Appendix III.

Application for Affiliate membership should be made to the Headquarters office. The parent institution must first review the institution and application and sign off on both the administrative and physics portions of the application. All applications for Affiliate membership are also reviewed and finally approved by the Headquarters office and the Group Chair.

4. CCOP Membership

CCOPs 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 Affiliate Member institutions, as described in Appendix III. CCOP membership applications are reviewed by Headquarters and/or the CCOP Membership Evaluation Committee, and their progress is reviewed semi-annually by the CCOP Membership Evaluation Committee. CCOPs are required to place ten patients on study annually, five of which must be enrolled in cancer control studies.

B. CONTINUING MEMBERSHIP CRITERIA AND EVALUATION

Membership is reviewed and evaluated semiannually. Full and Provisional Members are reviewed by the Membership Evaluation Committee; Affiliate Members are reviewed by Headquarters, and CCOP Members are reviewed by the CCOP Membership Evaluation Committee. The evaluation is based upon patient accession and data quality.

1. Case Credit for RTOG Studies

Below are the minimum accrual requirements for continued RTOG membership:

	<u>Treatment or Cancer Control Credits Required Per Year</u>
Full	25
Provisional	25 in first 12 months (to achieve Provisional Membership status)
Affiliate	5 treatment and/or cancer control
CCOP	10 (5 treatment, 5 cancer control)

2. Case Credits for Intergroup Study Participation

If an RTOG institution accrues patients through another cooperative group to Intergroup studies in which RTOG participates, joint case credit may be given. The Intergroup study must not be managed by the RTOG. It is the institution's responsibility to notify Headquarters in writing of cases so accrued (patient name, RTOG study number, other group study number, case number, date of entry, group) on an RTOG Case Credit form, obtainable from RTOG Headquarters. Credit for these cases will appear on the yearly case accession report labeled as "Other Group Cases." Notification must be received at Headquarters by the end of the calendar year for which the patient was randomized.

3. Case Credit for Cancer Control and Complementary Studies

Institutions participating in RTOG sponsored Cancer Control and Complementary studies will receive Cancer Control and Ancillary credits for these cases instead of treatment protocol case credit.

4. Data Quality and Timeliness

All institutions are required to submit complete, accurate and timely data for all study patients. Institutions are reviewed semi-annually for data submission, timeliness and data quality according to the guidelines in Appendix IV.

C. FUNDING

All funding is awarded by the RTOG through a grant from the NCI. All institutions are funded on a per case basis. Additional funds, when available, are also awarded to

institutions meeting the requirements for full membership and to institutions with investigators making scientific or administrative contributions to the Group (e.g., protocol or committee chairs). The funding schedule for 2003-2004 is as follows:

Follow-up Form Submission - All Members (*except CCOP members*)

\$50.00 per form

Per Case Reimbursement - All Members (*except CCOP members*)

Phase III Studies	\$	2,000
Phase I, II, I/II Studies		2,000
Cancer Control		1,000
Quality of Life		400

Scientific/Administrative Contributions - All Members

Additional funding is provided at the end of the year, if funds are available, to institutions with investigators involved in the following activities: Group Chair, Vice-Chair, Deputy Chair, Committee Chair, Protocol Chair, and first author of manuscript.

Per case reimbursement funding is paid when the case has been determined to be eligible for the study after review of the submitted Initial Evaluation Form (I1).

Per case reimbursement on a monthly basis. Credits given for Intergroup study participation (see III.B.2 above) count toward the required five case credits.

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

Support for any activity may or may not be provided depending on the availability of funds at the time application is made.

IV. PARTICIPATION REQUIREMENTS

A. ASSURANCE DOCUMENTATION

1. Types of Assurance Applications

Completion of Assurance Documentation is required by the Federal Government and cooperative groups to ensure that institutions participating in cooperative group trials are in compliance with the Department of Health and Human Services (DHHS) regulations for the use of human subjects and research. The institution completing this assurance certifies that the institution and its investigators will comply with the Code of Federal Regulations (45 CFR 46). The institution also certifies that the composition of its Institutional Review Board (IRB) is in compliance with the regulations and that the IRB will follow the federal regulations when reviewing and approving cooperative group studies. The Assurance document must be filed with the Office for Human Research Protections (OHRP) and approved by OHRP. A copy

of this document must be on file at RTOG Headquarters before the institution is allowed to enter patients on any group study.

There are three different types of assurances: Multiple Project Assurances (MPA), Cooperative Project Assurances (CPA) and Single Project Assurances (SPA).

- a. The Multiple Project Assurance (MPA) is used by institutions which have numerous projects funded through DHHS.
- b. The Cooperative Project Assurance (CPA) is used by an institution, which has no Multiple Project Assurance on file with OHRP and is a member of any OHRP-recognized Cooperative Protocol Research Programs (*i.e.*, RTOG, SWOG, ECOG, etc.).
- c. The Single Project Assurance (SPA) is for an institution who has submitted to DHHS a single project for funding and currently has no assurance on file with DHHS. Most RTOG institutions will use an MPA or CPA Assurance rather than a Single Project Assurance.

2. Instructions for Application

To apply for an Assurance, the institution must first determine its proper category as detailed above. Headquarters can provide the required forms and/or instruction. The complete application with the necessary signatures is submitted to RTOG Headquarters for processing, membership verification, and submission to OHRP for acceptance and approval. Once the application is approved the institution is notified by OHRP via a letter of acceptance and assigned a number for use whenever correspondence is submitted regarding human subject review.

If an RTOG investigator is a member of his Institutional Review Board, the investigator on that committee cannot participate in the review process of RTOG protocols. The investigator may be available for questions by the other members of the committee, but must leave the room when RTOG protocols are under discussion. The IRB chairperson must either footnote the IRB roster or attach a separate letter to the assurance application stating that the RTOG investigator will not participate in the RTOG protocol review process.

Headquarters keeps on file a copy of the Assurance application, the IRB Roster, a list of the Member/Affiliate institutions and investigators, and a copy of the assurance approval by OHRP containing the expiration date and assurance number.

It is the institution's responsibility to notify OHRP and Headquarters of any changes that would affect the current assurance application (*e.g.*, composition of IRB, primary contact, etc.).

3. Renewal

Headquarters will notify the institution of the upcoming expiration date of its assurance. The institution must contact Headquarters for the appropriate procedure for assurance renewal.

B. IRB APPROVALS

1. Initial Approval

Before an institution may participate in an RTOG study, the institution's IRB must review and approve the protocol and certification of that approval must be submitted to Headquarters. This can be done by completing the HHS 310 form.

The following information must be provided:

- Section 1: Specify initial or continuing review
- Section 2-3: Not Applicable to RTOG Protocols
- Section 4: Title of the Protocol/Project (to include RTOG protocol number)
- Section 5: Name of Principal Investigator
- Section 6: Assurance and IRB Identification Numbers
- Section 7: Date of IRB review and approval. Only Full Board review and approval will be accepted by RTOG.
- Section 8: Not Applicable to RTOG Protocols
- Section 9: Not Applicable to RTOG Protocols
- Section 10: To include the RTOG institution's name, address and RTOG identification number.

Section 11-16: Pertains to the IRB Chairperson or Institutional Official

The HHS 310 form and a sample study-specific consent form must be submitted to Headquarters when an institution's IRB initially reviews and approves the protocol. Patient entry will not be permitted unless a valid approval is on file at Headquarters. 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.

2. Renewal

Headquarters will notify RTOG institutions of the upcoming expiration dates of their IRB approvals. Case entry will not be permitted after the IRB's approval has expired. Protocols must be reviewed at least once per year during the data collection phase and renewals must be submitted to RTOG annually. Renewals going beyond 12 months will be considered a deviation in OHRP procedures. Continuing review of permanently closed protocols in the follow-up phase may be expedited.

C. MODALITY REQUIREMENTS

1. Medical Oncology

a. Participation

Participation in studies that require the administration of chemotherapy drugs is permitted only for institutions that have registered the name of a Medical Oncology Representative with RTOG Headquarters.

Specifically, no case may be entered into a study using chemotherapy unless the Principal Investigator for the institution has submitted to Headquarters the name, address, telephone number, and the *curriculum vitae* of a medical oncologist who represents medical oncologists administering RTOG protocol treatments to RTOG registered patients enrolled by the member institution. This representative is the liaison for this modality and is responsible for resolution of treatment and data issues that cannot be resolved by the site research associate and the treating medical oncologist. Ideally, this should be a physician who is expected to participate in the RTOG clinical trials at that institution.

b. Review of Representatives

The Principal Investigator must have reviewed with the responsible medical oncologist the Medical Oncology Quality Control Guidelines (see Section IX, B.2) and affirms that the responsible medical oncologist is in agreement with the requirements.

Reaffirmation of the Medical Oncology Representative is periodically required upon request by Headquarters.

c. Investigator Responsibilities

It is the responsibility of the Principal Investigator to notify Headquarters of changes in representatives. The Principal Investigator must see to it that protocols involving chemotherapy in which the institution participates are distributed to their Medical Oncology Representative and the treating medical oncologist prior to patient entry. 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 appears to be a problem or if the protocol regimen will not be followed by the attending physician despite requests by the Principal Investigator and the Medical Oncology Representative, the patient should not be entered on study.

The Medical Oncology representative should receive from the institution's Clinical Research Associate or RTOG Principal Investigator notice of each

patient enrolled who is assigned chemotherapy. The name of the treating medical oncologist must be provided to the register.

Problems with treatment compliance or data submission for study patients will be referred to either the Principal Investigator or the Medical Oncology Representative for resolution. Problems that persist will be referred to the RTOG Medical Oncology Quality Control Chair and/or to the Group Chair.

2. 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. RTOG receives a copy of the institutions 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 thermoluminescent dosimeter (TLD) 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 Medical Physics Committee, the 3-D QA Center or the Radiological Physics Center (RPC) and is required to submit specified information to Headquarters, 3-D QA Center, and/or RPC about RT equipment and dosimetry.

3. Stereotactic Radiosurgery/Radiotherapy Studies

A Stereotactic Radiosurgery/Radiotherapy Physics Survey Form, available in the protocols, must be completed and are on file in Headquarters prior to enrolling patient onto RTOG protocols that use these modalities. The physics information provided on the survey form is used in the radiation therapy quality assurance review and verification of the radiosurgery/radiotherapy studies. The questionnaire was designed to document that each institution has adequate committed facilities for participating in clinical trials of this modality and to provide physics and quality assurance data.

4. Radiolabelled Isotopes

All RTOG institutions participating in radiolabelled isotope studies must comply with the Nuclear Regulatory Commission's (NRC) regulations concerning the use and handling of radiolabelled isotopes. Institutions must receive the permission prior to the start of patient entry.

5. Brachytherapy Studies

Prior to enrolling any patients on protocol, each institution must submit a complete RTOG Brachytherapy questionnaire to RTOG Headquarters for review and approval by the Radiation Physics Center.

6. 3D-CRT Studies

A 3-D CRT QA Facility Questionnaire must be completed and submitted to the RTOG 3-D QA Center located in The Mallinckrodt Institute in St. Louis before any patients can be enrolled onto any 3-D CRT protocol. The data helps assure the RTOG 3-D Quality Assurance Center that each institution has the capabilities and committed the proper facilities and personnel to enroll patients on any 3-D CRT studies and that the patients are treated in an appropriate manner so that high quality data is available for analysis.

D. LIMITED PARTICIPATION STUDIES

Only a defined set of institutions may enter patients on a limited participation study. If a protocol is designated as a limited participation study, 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 either requires unusually strict monitoring of the participants, uses special equipment or treatment techniques, or because 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.

E. DRUG PROCUREMENT

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

Unless the study drug is commercially available, the investigator should make sure that the specific agent is available prior to the time it will be needed. Approval, if required, special processing and shipping will generally take about three weeks. However, unusual circumstances have created delays of six weeks; thus, an adequate lead-time must be planned.

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 NCI for use in a CTEP-approved protocol must have an identification number issued by the Investigational Drug Division. To obtain a number, the investigator must complete Form 1572, "Statement of Investigator." This form may be obtained from NCI's Drug Management and Authorization Section (301/496-5975). 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. As a general rule, NCI discourages secondary shipment; direct shipment from NCI to satellites and affiliates is preferred and is highly recommended.

Investigational drugs supplied by NCI must be requested on the NCI Clinical Drug Request Form, NIH-986. The completed form is sent directly to NCI.

The following guidelines should be observed when completing Form NIH 986.

- a. The form must be typed. Handwritten forms are unacceptable.
- b. The investigator's identification number (assigned by the Investigational Drug Division) must be recorded on the request.
- c. All requested information must be complete. Specific drug information (NSC number, dose formulation, etc.) can be found in Section 7.0 of the protocol. The form will be returned if any items are left incomplete.
- d. Request a sufficient quantity for approximately eight weeks. Current inventory, if applicable, must be stated.
- e. The shipping label must be completed with the requester's name and address. Supplies will be shipped only to investigators with an NCI identification number.
- f. Retain a copy of the request.
- g. When requesting double blinded drugs, care should be taken not to unlabel the treatment assignment through the drug request.

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 NCI 2564. Drug inventories and receipts must be maintained according to NCI guidelines as outlined in the manual available below.

Supplies may also be obtained by calling the NCI Drug Management and Authorization Section at (301) 496-5725 and registering for the electronic drug ordering system. The Electronic Clinical Drug Request (ECCR) System may be used in place of, or in addition to, the NIH-986 form. The ECCR System requires the use of an IBM-compatible personal computer equipped with a modem.

Orders for investigational agents may also be transmitted by fax (301) 480-4612. Normal processing time will be two working days. A return/reply fax number must be included on the order form. Telephone (301) 496-5725 to confirm receipt of orders requesting next day delivery.

2. Investigational Drug Resource Manual

A handbook for practitioners who use NCI investigational drugs is available upon request from the:

Pharmaceutical Resources Branch
National Cancer Institute
Executive Plaza North, Suite 818
Bethesda, MD 20892
Phone: (301) 496-8774
FAX: (301) 496-8333
<http://ctep.info.nih.gov>

3. Drug Accountability

Drugs provided to an investigator by NCI 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 requirements, NCI has developed a standardized Drug Accountability Record. This form must be used for each agent supplied by NCI. A pamphlet entitled "Investigational Drug Accountability" (OMB No. 0925-0240) may be obtained from:

Drug Management and Authorization Section
Investigational Drug Branch/Cancer Therapy Evaluation Program
National Cancer Institute
Bethesda, MD 20892

This pamphlet provides details and examples of the accountability records for routine and special record keeping as well as detailed instructions regarding primary and secondary drug accountability records.

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 (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 be identical to the NCI-approved form including the number and expiration date assigned by the Office of Management and Budget.
2. There must be a valid audit for all data entries. This must include electronic entries of who, what and when. Corrections of any previously entered data require a new entry and not modifications of 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.

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

4. Storage of Drug Supplies

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

5. Transfer of Investigational Drugs

An investigator may 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. Copies of these forms and instructions for their completion are found in the pamphlet, "Investigational Drug Accountability."

6. Return of Unused Drug

Investigators are required to return drugs if 1) the study is completed or discontinued; 2) drugs are outdated; or 3) the drug is damaged or unfit for use (*e.g.*, loss of refrigeration). Unused drug must be returned to the supplier unless stated otherwise by the protocol. A return receipt should be requested and the Drug Accountability Form must be updated to reflect returned drugs.

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 main objective of the study. Three distinct "phases" — phase I, phase II, and phase III — have evolved over time. The endpoints used in phase I and II trials of radiotherapeutic modalities are often long term endpoints such as late toxicities and local regional control at one year in contrast to the usual short-term endpoints of acute toxicity and initial tumor response, which are typically, used with chemotherapeutic phase I and II trials. Therefore, the sample size requirements for a radiotherapeutic trial with a long term toxicity endpoint are generally three to five times larger than a chemotherapeutic trial with a short term toxicity endpoint because not all patients entered into the radiotherapeutic trial will survive beyond the latent period for late toxicity and be at risk a sufficient time after the latent period. In

addition to phase I, II, and III studies, RTOG also supports cancer control and companion studies.

2. Phase I Studies

The objective of a phase I study is to determine the maximum tolerated dose by evaluating toxicity. In chemotherapeutic trials, the toxicity to be evaluated is short term or “acute” since the typical study population will have failed all conventional therapies. In radiotherapeutic trials, the toxicity to be evaluated can be either acute less commonly or long term more commonly depending upon the modality being evaluated. Trials investigating radiosensitizers employ acute toxicities as their principal endpoint to determine the maximum tolerated total dosage for such a drug. Trials investigating new radiation fractionation schemes such as hyperfractionation employ late toxicity as their principal endpoint to determine the maximum tolerated total dose.

3. Phase II Studies

The primary goal of a phase II trial is to determine whether the overall response rate of a particular treatment regimen with acceptable toxicity warrants a large scale phase III trial. Ideally, a phase II study is initiated to evaluate the activity of a selected regimen following successful determination of maximum tolerated dose in a phase I trial. In phase II chemotherapeutic trials, the principal endpoint to measure activity is the extent of tumor reduction, either partial or complete. This endpoint can be measured relatively early. Although radiation oncologists frequently use initial tumor response as an end point, loco-regional control of the tumor at some specified time point is often a more relevant measure of anti-tumor activity.

The endpoint of loco-regional control requires longer patient follow-up than the endpoint of initial tumor response. Because of the late endpoints used in the evaluation of morbidity and anti-tumor effect, the RTOG designs and conducts studies, which look at both endpoints simultaneously and are designated as phase I/II studies.

Phase I/II “dose searching studies” are generally designed as randomized studies with patients randomized between a previously untested higher dose and a previously tested lower dose. The rationale for this randomization is to guard against the investigators selecting only the poor risk patients for a previously untested higher total dose because of their perception that the higher total dose is probably too toxic. With some patients randomized to the lower total dose, it is possible to determine whether any increase in the morbidity observed with the higher total dose is due to the type of patient entered or due to the treatment itself.

4. Phase III Studies

Phase III trials are a randomized prospective comparison of one or more experimental regimens that have already gone through phase I and phase II testing with a standard regimen. Phase III trials are conducted with patients who generally have had no previous treatment for the cancer site under study. Phase III trials typically require much larger numbers of patients than phase I or phase II studies. The endpoints in phase III studies, such as response duration and survival, are long term in contrast to

the acute toxicity and initial tumor response endpoints used in phase I and II drug studies.

5. Laboratory Correlates Studies

These studies are generally included within a treatment protocol. Flow cytometry, angiogenesis, p53 markers are some examples of investigators that have been done in addition to the basic central pathology review to standardize the diagnoses. Fixed and frozen tissue is also banked for future work.

6. Cancer Control

Cancer control studies evaluate an intervention to lessen the symptoms or side effects of cancer or its treatment. Quality of life, cancer prevention, and late effects are also under investigation.

7. Randomized vs. Non-Randomized Studies

RTOG routinely uses randomization in studies where patients can be assigned to one of two or more treatment regimens. Randomization minimizes the selection bias on the part of the clinical investigator entering the patients on a particular study. With randomization, the clinical investigator knows that the patient being entered onto study must be able to receive any of the protocol's treatment regimens because the investigator will not know beforehand which treatment regimen will be assigned. In addition, randomization balances out the distributions of prognostic factors among the patient groups assigned to each treatment regimen. Finally, randomization gives the results increased credibility among other clinical investigators and hence, greater acceptance because the assignment of treatments is done by computer and without prior knowledge of the participating investigators.

8. Intergroup Studies

Intergroup studies are those that two or more cooperative groups have agreed to: 1) enroll their eligible patients and 2) not conduct a competing study. One cooperative group is designated as the group responsible for administration, data management, quality assurance and statistical analysis, i.e., the Coordinating Group. The rationale for undertaking an Intergroup study is to recruit patients as quickly as possible so that an important question can be answered or to study uncommon tumors. In addition, to decrease the number of competing protocols among the groups, an Intergroup study may be conducted when several groups have the same research interests. RTOG participation in any proposed Intergroup study must be approved by the RTOG Research Strategy Committee.

B. PROTOCOL DEVELOPMENT

All protocols must be 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) concept approval; 2) review and approval of the protocol among the group members; 3) Headquarters review; 4) NCI review; 5) protocol activation; and 6) protocol revisions.

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 site committee. The proposed protocol 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 protocol in a timely fashion, a concept sheet (Appendix VI) is prepared by the Study Chair following discussion with the Statistical Unit and Site Committee Chair and submitted to the Headquarters Protocol Administrator. The Protocol Administrator assigns a developing study number to the concept, enters the study specifics into the computer database (*i.e.*, study name, site, modality, responsible committee, status, etc.) and sends an accrual survey to all RTOG investigators. As the surveys are returned to Headquarters, they are entered into the computer and the results of the survey are distributed to the Group Chair, Study Chair, appropriate Disease Site Committee Chairs and the Group Statistician. The Disease Site Chair will present the concept to the Research Strategy Committee for consideration. Based upon the results of these surveys, the group then decides whether the proposed research is feasible and worthy of the group's efforts. If the group decides to proceed, a Study Chair is charged with writing the protocol.

2. Group Review

After the group approves the protocol concept, the Study Chair writes a draft of the protocol according to the Protocol Guidelines (see Appendix V) with input from the Statistical Unit and the Site Chair and submits it to Headquarters. Study Co-Chairs are assigned according to guidelines found in Section C.3. The Protocol Administrator distributes the protocol to the assigned reviewers for each involved committee. In addition, the draft protocol is also distributed to Headquarters for internal review. Each reviewer examines the protocol paying particular attention to his specialty area and submits his comments, requested revisions, etc. to the Protocol Administrator. The comments are reviewed by the Group and Study Chairs for incorporation into the protocol.

This extended review process ensures that the protocol is a consensus of the group's objectives and that a clear, well thought-out document reflecting the current standards of the group is sent to NCI for review.

3. Internal Review

As part of the protocol development procedure, the Group Chair, a senior statistician, research associate, dosimetrist, and Protocol Administrator review and comment on all protocols.

a. Statistics

The statistician initially reviews the design and assesses 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 addressing gender and minority issues. The statistician also reviews the eligibility criteria, the study's endpoints and study requirements for feasibility.

b. Data Management

The assigned research associate reviews the data items to be collected relative to the protocol's eligibility criteria and the endpoints along with the data submission schedule. A check of the pre-treatment and the follow-up section is made to verify that this will satisfy the specific data requirements. During the review process, the development of the data collection forms is begun as a joint effort by the Forms Committee, which includes the disease site chair, the statistician, the dosimetrist, and the headquarters research associate. The research associate 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 these adequately define the required study population. If the study involves chemotherapy or other chemical modifiers, the research associate 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.

c. Radiation Oncology Quality Assurance Review

The radiation oncology component of each developing protocol is reviewed by the Radiation Oncology Quality Assurance Staff to ensure that the treatment specifications are explicitly identified. Particular attention is given to the method of radiation dose specification, target volume definition, treatment planning requirements, total dose and time of delivery to the primary, nodes and critical structures, and adherence to quality control modality guidelines. This consistent attention to radiation therapy detail is intended to eliminate the potential for variation from the intent of the protocol.

The Radiation Oncology Quality Assurance Staff is responsible for the following quality assurance tasks in connection with study activation: treatment forms development; identification of radiation therapy items for collection; development of procedures to facilitate the radiation therapy review process; and, implementation of computerized collection systems for radiation therapy review materials.

d. Protocol Administrator Review

The Protocol Administrator ensures that the protocol is in the proper format and contains all necessary information and documentation (i.e. consent form, pathology review guidelines, registration procedures, drug distribution procedures, staging and the toxicity criteria, etc.). The Protocol Administrator 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.

e. IRB Review

All RTOG protocols must be approved by the ACR IRB prior to activation. The Protocol Administrator prepares a Human Subjects Questionnaire and presents the protocol to the ACR IRB which reviews the questionnaire, the protocol and the consent form. Any required revisions are incorporated into the protocol and consent form by the Protocol Administrator. Subsequent protocol revisions are submitted to the IRB for review and approval. The Protocol Administrator also ensures that all active protocols have both initial and yearly approval from each member institution's IRB.

4. NCI Review

Phase II trials with investigational drugs must be submitted to NCI as a Letter of Intent (LOI). This is done by the Protocol Administrator. CTEP approval of the LOI reserves a spot for the protocol for up to two months while the protocol is finalized. A concept sheet, a brief 1-3 page summary, for phase III protocols must be submitted to NCI for review prior to submission of the full protocol. This is done by the Protocol Administrator while the draft document is undergoing Group review.

After the protocol review is completed at the Headquarters level, it is submitted by the Protocol Administrator to NCI for review. 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 Administrator to the Group Chair and Study Chair and the response is coordinated and resubmitted to the NCI by the Protocol Administrator.

5. Activation

Once NCI approves the protocol, the Protocol Administrator ensures that all administrative procedures and tools necessary for activation of the protocol are in place. The Protocol Administrator updates the computerized study file and makes sure that the eligibility, data collection and stratification requirements have been reviewed, approved and entered. Any special procedures must be documented (*i.e.*, drug ordering for double-blinded studies, special institutional requirements, data flow for intergroup studies, etc.). When the study is activated, it becomes available to the membership on the RTOG website.

6. Revisions

All changes to active studies are coordinated by the Protocol Administrator. Amendments and revisions must be submitted to the Protocol Administrator from the Study Chair in writing. If there are co-chairs on the study, the revisions should be discussed and agreed upon. Amendments are distributed to the member institutions and filed with NCI. The Protocol Administrator notifies the membership of protocol status changes.

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

7. RTOG Web Site

All protocols coordinated by RTOG are on the web site (<http://www.rtog.org>) for on-line viewing and/or printing. Revisions, if any, are summarized in each protocol's Revision History section. Additional features of the site include member only information such as updates (activations, closure, meetings, etc.), Adverse Event Reporting Guidelines, Toxicity Tables, and Forms.

Further information available to both members and non-members consists of Protocol Summaries, 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 institutions in good standing within RTOG.
- 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 should be reviewed regularly by the 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 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

The specific duties for a Study Chair are:

- a.* 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 research associates to develop the appropriate data collection forms and other tools or procedures necessary to activate the study.
- b.* Monitor the progress of the study. This includes 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 quality assurance staff. In addition, cases may undergo modality review by the applicable study chair or co-chair (*i.e.*, final dosimetry review or medical oncology review). The first of such reviews should be undertaken as soon as an adequate 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. Interdepartmental modality reviews are performed at Headquarters generally when accrual has reached approximately 25 to 50 patients in large studies and for small studies when accession has reached approximately 15-20% of required accrual. The review process allows the chair to clarify procedures in the protocol and to evaluate compliance with the protocol specifications.

When an RTOG study chair reviews the primary endpoint of an RTOG study, and the study chair wishes to change the data on a case report form concerning the primary endpoint, the Disease Site Vice Chair will arbitrate between the study chair and the institution to reach a conclusion in a timely manner. If the Disease Site Vice Chair is not available or is the study chair requesting the change, then the issue will be referred to the Deputy Chair.

- c. Patient entries are restricted to those fitting the eligibility criteria in Section 3.0 of each protocol. Requests for exceptions to these requirements are not permitted by NCI unless they are done as a protocol revision to include other patients fitting this description. The Group Chair also cannot override the stated eligibility criteria. Protocol ambiguities should be addressed by a documented correction to the official protocol and filed with NCI.
- d. Collaborate with statistical, data management, and quality assurance staff. Close collaboration with the Statistical Unit staff is needed during the development of the study and during the preparation of the interim and final study reports. Ongoing collaboration with the data management and quality assurance staff is needed during the accrual and follow-up phase to identify any problems with treatment delivery, toxicity, data collection or monitoring. Subsequent monitoring for development follow-up should be undertaken.
- e. Prepare a manuscript reporting the final results of the study using only the RTOG database information; a "local" database is not permitted.

3. Assignment of Study Chairs

- a. Each protocol will have one Study Chair who is responsible for the development, conduct and initial analysis of the protocol.
- b. A Chair will be appointed for each treatment modality found in the protocol that is not represented by the Chair.
- c. If a central pathology review is planned for the study, a Pathology Chair will be named.

D. RELEASE OF STUDY DATA

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

1. The study chair is reviewing charts for the study for his/her study.
2. An individual other than the study chair has a project that has been approved by the RTOG Secondary Publication. Requests must be made in writing to the RTOG Publication Chair stating the data which is needed and the purpose for which it will be used. In certain circumstances, it may also be necessary to receive ACR IRB approval as well.

3. Data that is to be used for reporting purposes, *i.e.*, publications, abstracts, etc. must be prepared and/or reviewed by the study statistician prior to being released to a study chair or other approved individual.

VI. PATIENT ENTRY PROCEDURES

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed and dated 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. Computerized Registration and Randomization

All RTOG studies have computerized eligibility and registration/randomization.

After information is provided to the computer to verify a patient's eligibility for a given protocol, as stated in Section 3.0 of every study, the treatment and the protocol case number are assigned. A computerized record is finalized and may not be changed. If an error was made at the time of registration, a note will be included in the patient's file at Headquarters; however, the computerized registration record will not change and the treatment assignment will not change.

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 on file at RTOG. In addition, RTOG may have special requirements for participation in a particular study such as the completion of modality-specific physics forms or study chair approval. Institutional attributes are stored on 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 will result in subsequent exclusion of participation in the study, *i.e.* no additional cases can be enrolled in the study by the institution. (See Section VII, I)

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 concerning eligibility must be addressed to Headquarters personnel. Specifically, questions related to eligibility must be addressed prior to case enrollment by a telephone call to the Headquarters research associate for the study. In addition to eligibility

information, the Study Chair and statistician often determine that other information concerning the patient is needed at the time of registration/randomization in order to make sure that treatment assignments are evenly distributed among various patient characteristics or to classify patients on the basis of predetermined prognostic factors. The stratification variables can be found on the schema and in the Statistical Considerations section of the protocol. Institutions must complete the eligibility Checklist for each patient prior to calling the Randomization Secretary. This will speed the process and help ensure the patient's suitability for the study.

3. Multiple-Step Studies

The design of some studies requires that at some point while the patient is on protocol, the treatment will change. For example, all patients on a given protocol may receive a standardized induction therapy. At some specified time the patient is re-evaluated, and if eligible, is assigned to a subsequent therapy. A second example would be a protocol where all patients are randomized at the time of registration, undergo their assigned protocol therapy and if at some specified time they are found not to have responded to the therapy they are "crossed over" to another protocol therapy. In both instances, a second phone call to the Headquarters randomization desk must be made before a new treatment can be assigned to establish a patient's eligibility for the secondary treatment. In multiple step studies, the subsequent registration process is necessary to update the statistical file. Failure to follow multiple step registration guidelines is considered a major protocol deviation by the investigator. Failure to contact the registrar for the subsequent registration will also result in an incorrect data collection calendar and accumulation of delinquent items. If it is necessary for a second registration phone call, directions can be found in Section 5.0 of the protocol.

4. Intergroup Studies

RTOG also participates in studies that are coordinated by another cooperative group. If the institution wishes the patient to be considered an RTOG case and to receive RTOG reimbursement, the patient must be registered onto the study through RTOG Headquarters. RTOG will collect the eligibility and stratification information and relay it to the coordinating groups' registration desk. If the patient is eligible for the study the coordinating group will assign the treatment and an intergroup case number. RTOG will then phone the registering institution and inform them of this information. If special procedures are required for the protocol concerning data submission, drug ordering, quality control reviews, etc., they will be detailed in the protocol or in the accompanying forms package. Information about receiving RTOG case credit for cases entered through another group can be found in Section III B.2. Different case numbers will be assigned by both the coordinating group and the participating group. Both numbers must be recorded on all material and data submitted. Questions regarding eligibility treatment or study specific procedures in intergroup protocols not coordinated by RTOG must be directed to the coordinating Group. Do not call the RTOG Study Chair regarding eligibility. S/he cannot make decisions on a non-RTOG study. To register a case through RTOG on non-RTOG coordinated studies requires that you fax a completed eligibility checklist to the registrar by 4:00 PM ET. The eligibility check must be the current version and must include a telephone

number and the name of the contact person at the institution. Questions about eligibility must be resolved before the eligibility check list is faxed to RTOG.

B. CONFIRMATION

Following a successful registration, the computer generates a printout of the information, the treatment assignment and case number. This confirmation form is mailed to the investigator along with a copy of the eligibility questions answered, a copy of the data collection forms needed for the study, a calendar listing forms due and their due date, and patient-specific bar coded labels. The Headquarters' Randomization Secretary 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 may be initials, name or whatever the institution requires to track the case to the individual. 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 case placed on study, the institutional principal investigator enrolling the case 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 case continues as long as the patient is alive and the case status is designated as "open" or until a study is "terminated." When the patient has expired and all outstanding data have been submitted to Headquarters, the case will be "closed". An exception to terminal follow-up may be found in some Cancer Control and correlative studies where survival may not be a study endpoint. In this example, follow-up is terminated when the endpoint of the study is reached and the data collection section of the protocol indicates a finite follow-up duration. Review the protocol for this information in Cancer Control studies. Very old studies that have undergone final analysis will be reviewed periodically to assess whether secondary or subsequent analysis will be carried out. If it is determined that this is not probable, the study will be terminated. 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. Periodic requests for data from resigned facilities will be made. If an institution reapplies for RTOG membership, the current investigator seeking membership will resume the obligation for all the delinquent data in unterminated studies on previously entered cases. The RTOG institution number for membership identification will remain the same.

C. GENERAL GUIDELINES

- All information on study patients (data forms, films, reports, slides, response to inquiries, regardless of origin) is mailed to the following address:

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

- Do not submit case information to a specific person or to a department unless specifically requested to do so. Failure to follow this advice will delay processing of the material. Do not address envelopes containing data forms to the Data Management unit or submit a query response to a particular Headquarters research associate.
- Facsimile submission of routine data forms is not acceptable and credit for submission will not be given. Exceptions: Adverse Event Reporting Forms and items specifically requested to be submitted by fax.
- Each item submitted to Headquarters must contain the RTOG study and RTOG case number. Institution ID and patient ID (supplied at registration)
- Intergroup study cases must contain both the RTOG and coordinating centers study/case numbers. Improperly identified items will be returned. As of August 1997, case-specific bar-coded labels have been provided for each study patient enrolled through RTOG Headquarters. This label contains the required case identification and replaces manual recording of this information. The labels must be applied to each page of material submitted on study patients. The omission of the labels will result in the return of the item to the institution. See section F for specific instructions on the application and use of the bar-coded labels.
- Patients enrolled through the RTOG in intergroup studies for which the RTOG is not the “coordinating group” will be assigned a study and case number by the coordinating group and by the RTOG. Both the RTOG’s and the coordinating group’s study and case numbers must be recorded on all pages of the material.
- 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. That is, submission of a current evaluation will not automatically lead to the assumption by Headquarters that earlier outstanding evaluations were not done. It is assumed that the investigator will follow the patient at the time points specified by protocol and submit data for these time points. Missed assessments will result in accumulation of delinquent forms that when tabulated may adversely affect institutional evaluation, *i.e.*, missed evaluations that are required by protocol may not be dismissed or suppressed regardless of the reason not done.
- Revisions must follow acceptable guidelines: use a single line to cross through the information being changed, initial the revision and date. Mark the page “revision” or use the revision box, if available. Be sure the revision is clearly identifiable. Do not use whiteout or totally obliterate the original information. Only items 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 returned to the institution for correction.**

- Data forms and all communication that includes patient information must be signed and dated by the investigator or the person responsible for submission of the information.

D. DATA CALENDAR

A case specific data collection calendar is issued for each patient placed on an RTOG protocol. See Figure II. 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 protocol may require the submission of additional material applicable to specific events or circumstances, *e.g.*, if the patient undergoes surgery, the submission of an operative report may be required. This conditional material specified by protocol will be required without prior notification sent to the institution and the Headquarters case calendar will be updated to include the specified item(s).

Data submission requirements for patients in multiple registration studies (See Section VI. A.3) may change once the patient undergoes reregistration. 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.

Although a data calendar is mailed to the investigator on the next working day following case registration at RTOG, mail delays may prevent its arrival before the first data items are due. The investigator should check the Data Collection Section of the protocol for submission requirements. It is recommended that an investigator have a set of forms on hand for each study with IRB approval. This is especially important for studies with a Quality of Life component

All items on the calendar must be submitted or notification sent when an assessment or item is not available. Except for “Requests for Information,” and “Adverse Events Reports” items due after the date of death are automatically suppressed. If a patient expires while under treatment, Headquarters should be consulted regarding the data requirements for the case. Generally, all data items required by protocol including those due at the completion or termination of treatment become due on the patient's date of death. The appropriate data form in the study that reports death information will also become due.

Intergroup Studies

RTOG provides calendars for non-RTOG coordinated studies; however, each and every item is not listed. Check the protocol for complete information.

E. DATA FORMS

Data forms 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, General Communication memoranda must be signed. Unsigned data forms, instructions to revise information, and requests to excuse forms are returned to the institution or destroyed if Headquarters is unable to identify the source of the submission.

Material gathered as source documentation should not be routinely mailed to Headquarters unless required by the study, e.g., pathology, operative reports, radiotherapy record, etc., or unless a specific request for documentation is made. Unsolicited source documentation is not reviewed or routinely retained in the Headquarters case records. When submitting source documentation, all pages must include 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.

Site-specific data collection forms are utilized in RTOG with general forms (drug flow sheets, pathology submission form, etc.) added to the data set when applicable. The form title is identified in the heading (top) and in the lower right corner of the data form. This information can be matched to the "key" column on the data calendar. See Figure III. A forms packet is mailed to the institution as each patient is placed on study with additional forms sent upon request. The forms packet may be used for any case in that particular study. If forms are modified or changed in any way, the date and version letter is updated. New packets will contain the most recent version of the form and 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 is distributed to investigators.

Forms labeled for one protocol cannot be used for another study.

Laboratory results must be reported in US equivalents unless specified otherwise. Required reports: pathology; surgical reports, etc., must be in English unless specified otherwise on RTOG data forms are reported as mm/dd/yy.

Quality of Life forms are reviewed in the RTOG Quality of Life Guidelines. A copy of this module may be obtained from RTOG Headquarters Data Management Department.

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. Flow sheets, replies to memos, request for study information replies, general communication memos must be signed unsigned data forms, instructions to revise information, requests to excuse forms are returned to the institution or destroyed if headquarters is unable to identify the source of submission.

Studies Coordinated by other Co-operative Groups

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 indicated 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, therefore, before making assumptions regarding eligibility or data submission, check the protocol for specific instructions. If the protocol

does not address the concern or question, the coordinating center may need to be consulted.

F. USE OF BAR-CODED LABELS AND PREPARATION OF DATA FOR SUBMISSION

RTOG uses an imaging system to process incoming data. This method has required some changes in preparation of data at the institutional level. All case specific material, e.g., data forms, reports, memos, treatment records, dosimetry calculation, films, etc., submitted on cases registered to RTOG studies must contain case-specific bar-coded labels. Labels are distributed for each newly registered case and may be obtained on old cases by faxing a request to the RTOG data management department. Requests will not be taken over the telephone. The request must list the study and case numbers, the institution name, the RTOG institution identification number, and the name and telephone number of the person submitting the request.

- All pages of data forms, reports, etc., must contain a label, have all the required identifiers recorded (study numbers, case numbers, institution number, patient ID), or the inter-group study and case number must be included, if applicable. Multiple occurrence forms, e.g., follow-up forms must contain the evaluation data on each page if more than one evaluation is submitted concurrently.
- Labels replace manual recording of case identifiers. Therefore, this information needn't be recorded when using labels. Labels may be placed in the banner section of data forms, or where they will not obscure data. For example, do not obscure report dates and dates of procedures.
- It is recommended that a master follow-up form be made for study cases with each page labeled. This master can be used to make copies. A first generation copy (one made from a form containing an original label) should be readable by the scanner.
- 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. Always record the form ID code for non-form items. Non-form data items received at Headquarters without ID codes are labeled "miscellaneous source documentation" and are not credited until someone reads the report and determines what it is. Credit for submission can be delayed or missed entirely.
- Do not include a cover page when you send forms except when one is part of the data form. Cover pages are discarded and only deplete your label supply.
- Avoid sending two-sided forms.
- Avoid attaching "post-its". 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.
- 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. Only use highlighter to underline or circle the information of interest.

G. REQUEST FOR STUDY INFORMATION - DATA MANAGEMENT

When forms are found incomplete or contain conflicting information, a Request for Study Information (*i.e.*, clarification or Z1) (Figure IV) will be sent to the institution. The form generating the request may be held from entry into the computerized database for analysis until the deficiency is resolved. Therefore, requests for information should be treated with urgency. While awaiting a reply, the institution is credited with having submitted the data form. If a reply to the request is not received within 45 days, a computer-generated reminder (second request) is sent to the institution. A third reminder is generated if no reply is received in 70 days. If a reply is not received after a total of 13 weeks, the form(s) that necessitated clarification is returned to the institution for correction. When a form is returned it is deleted from the database and is considered delinquent. Once a form has been returned to the facility, it must be resubmitted to receive submission credit.

Occasionally a response to the Request for Information and the reminder notifications will cross in the mail. If a notice is received at the institution after a reply has been submitted, the notice should be disregarded. If a subsequent notice is received, it should be marked "This was sent to you on (date)" and returned to Headquarters. The original request must be returned with the written response or explanation in order for the receipt credit to be given. All responses to requests for study information must be signed and dated. When inquiring about a request, use the 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 see that all questions have been properly completed before submission to Headquarters. Forms with numerous omissions, with a significant number of conflicts, without the assessment date or an obsolete version will be returned for correction. Submission credit will not be assigned until an acceptable form is resubmitted.

Intergroup Studies

Respond to requests from the other groups promptly. Copies of replies must be submitted to RTOG.

H. REQUEST FOR STUDY INFORMATION - RADIATION ONCOLOGY QUALITY ASSURANCE

Within one week of initiation of treatment, the radiation therapy data and films must be submitted to the Radiation Oncology Quality Assurance Unit in the Headquarters Office. The receipt of the materials is immediately logged into the database. All cases are tracked for the receipt of the Initial RT materials, and outstanding items will generate a

reminder notification to the facility. If the Initial RT materials are not received within 24 days from the start of RT, the case is considered delinquent, and the participant is notified. For those cases that lack sufficient information for completion of the Initial Review, memoranda (Z2) are sent identifying the items required to bring the review to completion. If no response is received within the 16 days from the date of request, the Initial Review cannot be completed.

In addition to the standardized RT materials identified for submission at study activation, supplemental items/films and clarifications may be required. These items are identified during the preparation for the Final Study Chair review by the dosimetrist, and are requested via memoranda (Z4). Two such memoranda will be posted if necessary, and if no response is received the case will be scored as non-evaluable at final review.

Reminder Letters to Institutions

Reminder letters are computer generated and run on the computer in the evenings.

Time Sequence for Computer Generated Reminder Letters

	DAYS	
1st Reminder	0 to 4	Usually (0 to 3)
2nd Reminder	8	(+3)
3rd Reminder and Final	16	(+3)
Delinquent*	24	(+3)

* (T9) RT Initial Review Form is computer generated on the 24th day automatically.

All data received for Initial Review (T2, T3, T4) must be entered in the Computer System on or before the 23rd day from the due date.

I. FORMS REQUESTS

Requests for outstanding forms, films and other case specific material are sent to the institution minimally twice yearly. The purpose of the Forms Request is to encourage prompt reporting so that current data is available for analysis. The request also provides an opportunity to resolve discrepancies between the institution's records and the Headquarters file. The memorandum that accompanies the Forms Request provides specific instructions regarding the management of discrepancies. **A Forms Request is not to be used to document patient information or to request suppression of data.** Data or communications submitted in this way is discarded. A copy of the Forms Request is mailed to both the institutional Principal Investigator and to the institutional Research Associate. Only the most current Forms Request should be used and each subsequent Forms Request nullifies all earlier versions.

J. INELIGIBLE PATIENTS AND TREATMENT REFUSAL

When a patient is deemed ineligible for study, written notification is sent to the responsible investigator. Ineligible patients 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 s/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 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 may withdraw consent to continue treatment or wish to discontinue follow-up at any time. The **investigator** must first determine what the patient's wishes are and based on this, should provide adequate explanation to RTOG. Both the patient and the investigator must agree on expectations regarding study data.

1. 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.
2. If the patient decides to discontinue follow-up with the RTOG investigator, this too is acceptable; however, 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, (s)he should be informed that failure to provide survival status, and information about treatment toxicity may adversely affect the explanation by the investigator, 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 differ among institutions.

3. If the patient refuses all contact, this decision must be documented, signed by the investigator and submitted to RTOG headquarters data management. At RTOG, the patient record will be changed to a “lost” patient status but the case will remain “open” as patients may change their decision and return for follow-up. The V5 Form ID (Survival Update) will remain on the patient’s calendar as a reminder that the case has not been closed. The institution need not respond to the V5 form unless submission of new information is permitted.

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. 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. SURVIVAL UPDATE

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 Headquarters. When a case is verified as “lost to follow-up” by Headquarters, the case will not be closed, but periodic survival updates will be requested. When the patient’s status is lost, all subsequent follow-up requests are deleted and replaced with a V5 (survival update). This is not a form but serves as a reminder that the case is open. The V5 will show up on the institutions forms requests. 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 information is obtained that documents the patient’s death. When survival is updated, the appropriate data form in the study (Follow-up form, Death form, if applicable) is submitted with the new information. If survival cannot be updated, the original V5 remains 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 a plan to avoid additional lost to follow-up occurrences.

L. DATA PROBLEMS

1. Data Management

If you have persistent problems with invalid requests for data or you wish to discuss a data-related problem, call the **Data Management Unit at 215/574-3214** and ask to speak with a Research Associate. Data Management should be able to help with eligibility, non-radiation therapy treatment questions, data forms, toxicity reporting procedures and protocol interpretation.

2. Radiation Therapy Quality Assurance

For problems related to submission of radiotherapy quality assurance material call **215/574-3219**. Questions regarding radiation oncology treatment planning should be referred to **215/574-3209** or **215/574-3228** or **215/574-3181** or **215/574-3229**. The

FAX number is **215/928-0153**. The most common dosimetry items include the following:

RADIATION THERAPY ONCOLOGY GROUP

RT QA STAFF

ELIZABETH MARTIN, DIRECTOR	(215) 574-3209
DARLENE HERD	(215) 717-0853
LORRAINE QUARLES	(215) 574-3181
DENISE MANFREDI	(215) 574-3219
JULIE MCILVAINE	(215) 574-3229
JOANNE HUNTER	(215) 574-3222

RT QA ADMINISTRATIVE ASSISTANT

TAMMY ROGERS	(215) 574-3219
FACSIMILE	(215) 923-1737 (215) 928-0153

DOSIMETRY FORMS

INITIAL REVIEW DATA

T2 - PROTOCOL TREATMENT FORM
 T3 - LARGE LOCALIZATION FILM
 T4 - DOSE CALCULATION FORM

Z2 - REQUEST/ADD'L INITIAL DOSIMETRY

FINAL REVIEW DATA

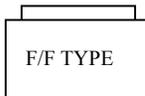
T5 - DAILY TREATMENT RECORD
 T6 - ISODOSE DISTRIBUTION
 T7 - PHOTO - POLAROID
 T8 - BOOST FILMS
 TL - SUPPLEMENTAL DOSE CALCULATION

FILMS

TP - SUPPLEMENTAL LOCALIZATION FILMS

Z4 - REQUEST/ADD'L FINAL DOSIMETRY

SMITH, JOHN
 RTOG 0001 Case 0001 ECOG 0001/0001
 0000 University Hospital



MR - MRI FILM
 ME - MRI REPORT
 C1 - PRE-RX CT SCAN
 C2 - FOLLOW-UP CT SCAN
 C3 - CT SCAN REPORT
 C4 - DIAGNOSTIC FILM
 C5 - PRE-RX BONE SCAN
 C6 - FOLLOW-UP BONE SCAN
 C7 - BONE SCAN REPORT
 PS - PRE RT PERFUSION LUNG SCAN
 PR - PERFUSION LUNG SCAN REPORT
 T0 - AP/LATERAL INTRACAVITARY
 BT - BRACHYTHERAPY TREATMENT FORM
 I9 - INTRACAVITARY DOSE FORM
 RP - RADIOSURGERY PLACEMENT FILMS
 RS - RADIOSURGERY CALCULATIONS
 TM - PRIOR RADIOTHERAPY MATERIAL

- PLEASE USE THE CASE SPECIFIC BAR-CODED LABELS PROVIDED.

- INCLUDE CONTACT PERSON'S NAME AND PHONE NUMBER.

M. TRANSFER OF A PATIENT TO ANOTHER FACULTY

To transfer a protocol patient to another RTOG institution, the investigator who originally enrolled the patient must submit a written request to the RTOG Administrator. See Patient Transfer Form. The request must include the following information: the name and RTOG institution number that registered the case, the study and case number, patient registration ID, the name and RTOG institution number of the recipient institution and the name of the recipient Principal Investigator. The transfer form or letter must include signatures of both Principal Investigators. All information must be provided so that the case file and the institutional record can be corrected. Documentation of IRB study approval by the recipient investigator must be on file at RTOG HQ before case/institution transfer can be made.

If the case has been registered through the RTOG to a non-RTOG intergroup study, the RTOG administrator will submit notice of the transfer to the appropriate Group Office.

Transfer of cases from the 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 using the mechanism described. Transfer from one Group to another is discouraged except in unusual circumstances. Transfer between Cooperative Group requires a written request to the RTOG administrator. This transfer can be made only by administrators at the Group Offices and not by institutions.

If the study includes patient specific drug distribution, the appropriate documentation, e.g., pharmacy registration information must be included with the transfer documentation.

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 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.

Patient Transfer Form

Complete this form to notify RTOG that an individual patient has transferred from one RTOG institution to another. Transfers between cooperative groups are not permitted except under unusual circumstances. Contact the RTOG Group Administrator. This form must be signed by the institutional Principal Investigator at the institution where the patient was originally enrolled to study AND by the Principal Investigator at the recipient institution. The completed form is submitted by the original PI to the RTOG Project Administrator. Before transfer is completed, both investigators should review the caveats to transfer, described in the RTOG Procedure Manual and IRB approval at the recipient institution must be on file. Upon receipt of the form, the RTOG records and database is changed to reflect that the recipient institution is responsible for the case. Upon completion of the transfer, the RTOG Administrator signs a confirmation of the change with a copy sent to each investigator. A set of labels and a new data collection calendar is sent to the recipient PI.

Patient Name/ID: _____

RTOG Protocol #: _____ **RTOG Case #:** _____

Coordinating Center Protocol #: _____ **Coordinating Center Case #:** _____

If multiple cases are being transferred from one institution to the same institution, a list of cases may be appended.

Transferring Institution Name/RTOG Number: _____ / _____

Name of Transferring Principal Investigator: _____

Signature of PI: _____ **Date:** _____

*******Recipient Information*******

Recipient Institution Name/RTOG Number: _____ / _____

Name of Recipient Principal Investigator: _____

Signature of PI: _____ **Date:** _____

*******RTOG Information*******

PLEASE RETURN FORM TO LINDA BOMBA IN CLINICAL TRIALS ADMINISTRATION
1818 Market Street, Suite 1600, Philadelphia, PA 19103

RTOG Administration Name: _____

Signature: _____ **Date:** _____

Copies: File, Transferring PI, Recipient PI, Data Management, Statistics

Figure II - Data Collection Calendar

CONFIRMATION CALENDAR

Page 1 of 2
Date: 01-Mar-02

RADIATION THERAPY ONCOLOGY GROUP

STUDY: 9517 BREAST:BRACHYTHERAPY FOR STAGE I AND II CARCINOMA

CASE: 101 PATIENT: TEST1 PHYSICIAN:

OPTION: 1 LDR 45 GY

INST. : 9999 Test Institution DATE LAST ASSESSED: 1/16/01

STATUS: OPEN-ELIGIBLE PATIENT: ALIVE

DATE TREATMENT COMMENCED: 01/17/01

Date of Death/Off Study:

ID#:	STATUS CHANGES			
Date	Patient	Init	Case	Init
	1. Alive		7. Open Eligible	
	2. Dead		8. Open Ineligible	
	3. Lost		9. Open No Pro Tx	
	4. Off St		15. Open Cancelled	

FORM DESCRIPTION	KEY	DUE	ASSD	SEND	REC	REVIEW	DE	DE	DE	DELETIONS/ COMMENTS
ELIGIBILITY FORM	A0	01/16/01	1/16/01	1/16/01	1/16/01					
"HQ" SURGERY REVIEW	S4	01/22/01	1/22/01		1/22/01					
DEMOGRAPHIC FORM	A5	01/31/01								
INITIAL EVALUATION	I1	01/31/01								
MAMMOGRAM REPORT	I2	01/31/01								
-PATHOLOGY REPORT-	P1	01/31/01								
SURGERY FORM	S1	01/31/01								
-SURGICAL REPORT-	S2	01/31/01								
-SURGICAL PATHOLOGY-	S5	01/31/01								
-BRACHYTHERAPY TX	BT	04/18/01								
INTRACAVITARY/EXT	T0	04/18/01								
RADIOTHERAPY FORM	T1	04/18/01								
FOLLOW-UP FORM	F1	07/18/01								
*SUPPLEMENT FU	FS	07/18/01								
PT COSMESIS EVAL	PQ	07/18/01								
RAD ONC EVALUATION	QP	07/18/01								
FOLLOW-UP FORM	F1	10/17/01								
FOLLOW-UP FORM	F1	01/16/02								
*SUPPLEMENT FU	FS	01/16/02								
PT COSMESIS EVAL	PQ	01/16/02								

**Figure III -
Sample Data
Collection Form**

TO VIEW A SAMPLE OF A FORM LOG ON TO:

<http://www.rtog.org/members/forms/9913/9913f1.pdf>

Figure IV - Request for Study Information

Instructions: Please complete/supply: a) Information as Requested b) Area Circled on Attached Form
Please make a copy and retain with your files. Return to RTOG Headquarters. Forms cannot be processed until all information has been received.

Radiation Therapy Oncology Group
 American College of Radiology
 Other (Specify): _____

Z1

1818 Market Street • Suite 1600 • Philadelphia, Pennsylvania 19103

REQUEST FOR STUDY INFORMATION

TO:	<u>GROUP/</u>	M.D.	<u>COPY PAGE</u>	<u>DATE OF</u>
_____	INSTITUTION	<u>FORM</u>	_____	<u>1st</u> Request
_____	STUDY #	<u>FORM</u>	_____	<u>2nd</u> Request
_____	CASE #	<u>FORM</u>	_____	<u>3rd</u> Request
	<u>NAM</u> <u>E</u>	<u>FORM</u>	_____	_____

REQUEST/PROBLEM: (Please type in box below)

REPLY: ALL CORRESPONDENCE MUST BE SIGNED. Check here if original attachments are included []. Staple **ONLY** information related to this request before returning.

Check here if you attach **previously unsubmitted/new data forms** related to this request []. Specify form type: _____

Figure V - Forms Request

**RADIATION THERAPY ONCOLOG GROUP
FORMS DUE REPORT
REPORTING FROM 01/01/2001-12/31/2001**

SAMPLE FORMS DUE FOR INST 9999, STUDY 9517

GROUP: 22 RADIATION THERAPY ONCOLOGY GROUP

INST: 9999 Test Institution

STUDY: 9517 BREAST: BRACH

Patient Name	Patient ID	Case Case Status	Patient Status	Last Assd Dt /Dt of Death	Form Due	Due Date	Verify Physician Inter #
Test 1		0101 Open-El	ALIVE	01/16/2001	A5 DEMOGRAPHIC FORM	01/31/2001	
					S1 SURGERY FORM	01/31/2001	
					S2 -SURGICAL REPORT-	01/31/2001	
					I1 INITIAL EVALUATION	01/31/2001	
					I2 MAMMOGRAM REPORT	01/31/2001	
Test 2		0102 Open-EL	ALIVE	01/16/2001	A5 DEMOGRAPHIC FORM	01/31/2001	
					I1 INITIAL EVALUATION	01/31/2001	

VIII. Toxicity/Adverse Event Reporting

ADVERSE EVENT REPORTING GUIDELINES

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

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event though present at commencement of treatment becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

Definite	The adverse event <i>is clearly related</i> to the treatment/procedure.
Probable	The adverse event <i>is likely related</i> to the treatment/procedure.
Possible	The adverse event <i>may be related</i> to the treatment/procedure.
Unlikely	The adverse event <i>is doubtfully related</i> to the treatment/procedure.
Unrelated	The adverse event <i>is clearly NOT related</i> to the treatment/procedure.

B. Grading of Adverse Events

Unless specified otherwise, the NCI Common Toxicity Criteria (CTC) v2.0 is used to grade severity of adverse events. Protocols approved prior to March 1998 will use one of several different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol document for the appropriate rating system.

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines are to be observed. The guidelines apply to all RTOG studies. When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines. A protocol may stipulate that specific grade

4 events attributable to treatment are expected and therefore may not require the standard reporting, however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.
2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution requires telephone notification within 24 hours of discovery.
3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.
 - a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.
 - b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.
5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).
6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.
7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).

8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if so specified by protocol. Documentation must include an assessment of attribution by the investigator as previously described in section B.
9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.
10. All neuro-toxicity (=> grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair and to the Study Chair within 10 days of discovery.

D. Adverse Event Reporting Related to Radiation Therapy

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.
2. All grade 4, (CTC v2.0 and RTOG/EORTC Late Effects Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.
- 3 All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

E. Adverse Event Reporting Related to Systemic Anticancer Agents

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe, life-threatening (grade 4) or fatal even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents

	Grade 4 or 5 Unexpected with attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE ¹	Hospitalization During Treatment ²	Secondary AML/MDS ³
FDA Form 3500 ^{4,5} within 10 days	X	X	X	
NCI/CTEP Secondary AML/MDS Form within				X

10 days of diagnosis ^{4,5}				
Call RTOG within 24 hrs of event ⁷	X ⁶			

- 1 Any increased incidence of a known AE
- 2 Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTC Grade 3,4,5 which precipitated hospitalization must be reported regardless of the requirements or Phase of study, expected or unexpected and attribution.
- 3 Reporting required during or subsequent to protocol treatment
- 4 Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
- 5 Copy to RTOG Data Management labeled: Attention-Adverse Event Report
- 6 All grade 5 Known toxicity.
7. Call RTOG Data Management (215)574-3214. To leave a voice mail message when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the Phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, <http://ctep.info.nih.gov> for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

After January 1, 2001, all expedited reports on RTOG protocols for which NCI is the supplier of an investigational agent are made using the AdEERS process.

A list of protocols for which this reporting applies can be found on the CTEP web page noted above under the "protocol selection" window.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any Phase of trial (1,2,3). An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any Phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any Phase of trial (1,2,3).

RTOG will use "decentralized" notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For the few institutions that don't have Internet access, contact RTOG Data Management (215/573-3214) to arrange for AdEERS reporting for their cases. In these instances, the appropriate Adverse Event Expedited Report template (Single

or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instructions manual, i.e., all mandatory sections completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigator’s reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

If the AdeERS report is for a study coordinated by another cooperative group or center, follow the instructions specified by the coordinating center for the study.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied upon faxed request from the RTOG Registrar (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field. For studies coordinated by other groups, follow the group’s policies.

AdeERS reporting does not replace or obviate any of the required telephone reporting procedures.

Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate Arms: **An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).**

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agene(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents unless the event preceded administration of the investigational agent.**

For example, if treatment includes a commercial agent followed by investigational agent and the event occurs prior to administration of the investigational agent, report as required for the commercial agent. If the event occurs subsequent to administration of the investigational agent, report the event as for an investigational agent.

b. Expedited Reporting for Phase 1 Studies

Unexpected Event		<u>Expected Event</u>	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution

Grade 2 -Expedited report within 10 working days. Grade 3 – Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. Grade 1 – Adverse Event Expedited Reporting Not require.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of last does of treatment with an investigational agent.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last does of treatment with an investigational agent.
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- 1 Report by telephone to RTOG Data Management (215)574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
- 2 Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

<u>Unexpected Event</u>		<u>Expected Event</u>	
<u>Grades 2-3</u> Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Expedited report within 10 working days. (Grade 1 – Adverse Event Expedited Reporting Not required)	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited including Grade 5 Aplasia in leukemia patients within 10 working days. Grade 4 Myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

1. Report by telephone to RTOG Data Management (215)574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.

2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

F. Reporting Of AML/MDS In Patients On NCI Protocols

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) diagnosed on or subsequent to 7/1/95 that received treatment on NCI/CTEP sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form. See Appendix VIIc.

For cases registered through RTOG that are diagnosed with AML/MDS during or subsequent to protocol treatment, the Secondary AML/MDS Form will be completed within 30 days of AML/MDS diagnosis. The form must be mailed to NCI/CTEP to the address specified on the form. A copy of the form that includes the RTOG study and case number must be sent to RTOG Headquarters.

G. Reporting Of All Secondary Cancers Following Treatment On RTOG Protocols

Monitoring for and reporting of all second and secondary cancers is extremely important in all RTOG sponsored studies regardless of attribution. Forms in most RTOG studies provide for the reporting of this information.

If data collection forms in the study do not provide for reporting a diagnosis of a new primary tumor, this information may be reported by appending a completed Med Watch Form to the follow-up data form or by noting details about the new primary tumor in the remarks section of the follow-up data form. Include the site of the new primary, the date diagnosed and the histology. The RTOG study and case number must be recorded on all adverse event and special report forms, e.g., Med Watch submitted to RTOG. The diagnosis of AML/MDS should be reported on the applicable data form described in **Section F** and on the RTOG data form for the study in which the patient is enrolled.

H. Toxicity Criteria

Standard toxicity criteria are available for studies containing drugs (anti-neoplastic chemotherapy, Radiosensitizers, radioprotectors, radio-biologics, biological agents, etc.) and for radiotherapy. Radiation therapy toxicity criteria include a table for acute effects and a table for “late” treatment effects. RTOG protocols utilize the NCI Common Toxicity Criteria (CTC) for grading effects from systemic agents.

Protocols approved on or after March 5, 1998 utilize a new version of the NCI Common Toxicity Criteria (CTC). The new CTC (Version 2.0) incorporates the RTOG acute Effects Criteria; therefore, the CTC are used to score acute effects from all modalities including radiation therapy. Do not use the CTC version 2.0 unless this is cited as the applicable table. For all protocols approved prior to March 5, 1998, check the protocol for the appropriate toxicity table for the study.

IX. QUALITY CONTROL

A. PATIENT ELIGIBILITY

RTOG employs a sophisticated system of computerized checks to ensure that all patients entered on protocol meet the requirements for eligibility. Section IV, Requirements for Patient Entry, and Section VI, Patient Registration and Randomization, outline these procedures. If, subsequent to initial entry, the patient is found to be ineligible, Headquarters will notify the institution. Data on the patient continues to be collected, a tally of ineligible patients is kept for each institution and a less than 95% score for eligible patients results in a disciplinary action.

B. TREATMENT DELIVERY

2. Radiation Oncology 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:

- I. Credentialing and monitoring (by Medical Physics Committee, RPC, 3-D QA Center)
- II. Assure the clarity, consistency, and accuracy of the treatment specification for each specific protocol (protocol review).
- III. Prevent or minimize potential variations from the protocol treatment guidelines (initial review).
- IV. Categorize any variations from the protocol treatment prescription that do occur so that they can be considered in a statistical analysis (final review).
- V. Compile and report the review results for statistical analyses.
- VI. Educate 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 QA office, Chair of the Medical Physics Committee and the 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. For detailed description. See Appendix V, Section 6.

b. Initial Radiation Oncology (RT) Review

The initial RT review is a process by which dose prescription, field placement and calculated dose are reviewed by a radiation oncologist and dosimetrist for compliance with the protocol requirements at the initiation of radiation therapy. The objective of this review is to enable modifications at an early phase of the treatment to achieve a high standard of compliance throughout protocol activation. This requires the use of the RTOG data monitoring and reminder system to ensure the timely submission of the required information.

When a patient is entered into a study, the RTOG RT Quality Assurance Unit is notified and the previously mentioned data calendar showing the required information (films, dose prescription and calculations) specific to that study and treatment arm is mailed to the research associate at the institution registering the patient. Within one week of the initiation of treatment, the required data and films is sent directly to the RTOG RT Quality Assurance Unit in the Headquarters office. Direct receipt of the information by RTOG eliminates delays in the initial review process.

Immediately upon receipt of the required treatment data, these items are logged into the RTOG computer database. If the required data is not received within 31 days from the start of treatment, the case is considered delinquent, and this result is communicated to the facility. Since a major portion of treatment has been administered any protocol treatment variations identified are too late to correct to prevent deviations from the protocol.

After computer logging of the RT materials received, a computerized random sampling program identifies those cases that require an initial review, based upon the previously demonstrated ability of the institution to comply with a given protocol. A facility is deemed compliant if five consecutive cases adhere to the protocol RT requirements. A score of non-compliance or delinquency will negate the sampling program and require that each of the institution's subsequent cases be reviewed.

Case data submitted within this time frame and identified for sampling, are then reviewed by the radiation oncologist for field placement, planned course of treatment, and dose specification. A form (T9) is completed for each case indicating the results of the review and the timeliness of data submission. If protocol deviations are identified, the reviewer makes a telephone call to the treating radiation oncologist to request changes or to clarify the dosimetry information on hand. This telephone call is followed in writing by a memorandum to the institution's research associate. For those cases that lack sufficient information for completion of the initial review, memoranda (Z2) are sent requesting the necessary data. If this information is not received in the RTOG RT Quality Assurance Office within 16 days, the case becomes ineligible

for initial review. Initial review results are entered into the RTOG database on a weekly basis.

c. Final Review

The second case review procedure of the RTOG RT Quality Assurance Program is the retrospective Final RT review. The purpose of the final RT review is to confirm the treatment delivered and define protocol compliance for the statistician. The final Phase I and Phase II review is an overall evaluation of protocol compliance, and is limited to all cases in randomized phase II and phase III studies and is performed by the RT study chair and staff dosimetrist. Some phase I and phase II non-randomized studies may receive a final review.

To complete the final review, additional information is required from the treating facility including: simulation and portal verification films of all fields treated, any additional calculations performed, an isodose distribution at the level of the tumor and a copy of the daily radiation therapy treatment record. These items and the date on which they are due are specified in the previously mentioned data collection calendar.

Upon receipt of this information, the dosimetrist compiles all treatment data and films, and completes a dose summary form (V2). This form provides the Study Chair with a summary of radiation administered, and is used in conjunction with the localization and portal films of all fields treated at the final review session. The dosimetrist is also responsible for the completion of dose recalculation of all fields treated on those cases selected by the random sampling program. Agreement in dose delivery must be maintained at 5% or the sampling mechanism is negated. Machine calibration data are forwarded to the RTOG RT Quality Assurance Unit from the Radiological Physics Center (RPC) thus allowing the dosimetrist to perform the dose recalculations.

The radiation oncology study chair, at the final review session, works in close collaboration with the staff dosimetrist in completing an evaluation form (V1) for all cases reviewed. The Summary of the radiation treatment delivered available through form V2 in conjunction with the Simulation and portal films of all treated fields are used in the review process. The staff dosimetrist works closely with each study chair to develop and maintain protocol specific evaluation criteria. These compliance criteria are designed to ensure consistency in scoring each case and are derived from the protocol stipulations.

The primary tumor, regional nodes and critical structures are evaluated at final review with respect to: field border placement, total dose delivered, applied fractionation and total elapsed days of treatment. Since the review form has been standardized with descriptions appropriate to each primary tumor site, a review of radiation therapy data from several different studies of the same treatment site can be easily accomplished. The data from these forms are entered into the RTOG database upon completion of the final review and utilized by the statistician in the study analysis.

d. Reporting of Results

Similarly, the final review results, as defined by the Study Chair, are reported to the participant and statistician. The dose summary form prepared by the dosimetrist and verified by the Study Chair is made available to the statistician as each final review is completed. A Final Review Summary of the number of cases reviewed, the timeliness of data submission, and the results of the review are sent to each member and clinical trial group on a semi-annual basis.

Full member institutions that receive > 10% Major RT Variation Score at final review receive a notification of failure to comply with protocol stipulations. Clarification or study amendments may be necessary if the review process identifies compliance difficulties.

The headquarters dosimetry staff interacts with the statistical unit and the study chair during the interim analysis of studies when preparing reports on a semi-annual basis prior to the group meeting. Before the final study chair reviews, the staff works by collating, preparing and reviewing cases in anticipation of the interim analysis. The compliance rate of the treatment delivery relative to the protocol is collected and reported. The treatment related questions that arise during this reporting time period are resolved. Any questions that may arise from the statistical unit are also addressed.

All outstanding treatment problems must be resolved and the final review of the treatment delivery on each patient must be completed by the study chair, before the final analysis begins. The dosimetrist, research associate and statistician work with the study chairs to complete the final review prior to a final protocol analysis. Additional clarifications as needed are addressed prior to publication of results.

e. Educational Research Associates Orientation Programs in Radiation Oncology

The previously mentioned Research Associates Orientation include a presentation by the Headquarters Dosimetrist and a Dosimetry Orientation Booklet was developed for the purpose of providing:

- an overview of radiation oncology as a modality;
- specific description of RT items for submission and how the items relate to the review process; and,
- clarifications for specific protocols.

The RT Quality Assurance staff interacts on a daily basis with facility research associates by answering radiation oncology related questions.

f. Radiological Physics Center

In 1968 the Radiological Physics Center (RPC) under the auspices of the American Association of Physicists in Medicine was established at the M.D.

Anderson Cancer Center to evaluate the accuracy of the delivered dose from any treatment equipment through calibration and phantom measurements. All participating RTOG members must agree to be visited by the RPC. RTOG receives a copy of the machine calibration data, which is entered into the RTOG computer system and utilized in the verification of the radiation dose. All RTOG members are expected to participate in the RPC ongoing TLD program as an interim check mechanism.

g. Brachytherapy Quality Assurance

The RTOG has reviewed the recommendations contained in ICRU Report 38, Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology, and in Report 58, Dose and Volume Specification for Reporting Interstitial Therapy and incorporated selected recommendations for specific brachytherapy protocols. The RTOG has developed extensive guidelines for high dose rate intracavitary brachytherapy with the goal of incorporating this modality into future protocols. It has also developed new concepts of evaluation of target volume for its first prostate brachytherapy study. Consideration is given to establishment of a credentialing process in the development of each brachytherapy protocol. Forms have been developed to document that institutions planning to enroll patients onto the studies within this modality have adequate resources and facilities for participating in these trials. Before placing a patient on protocol, each institution must complete an application form available in the protocols and a benchmark case and submit it to RTOG Headquarters. The RT Quality Assurance staff and the Chair of the Medical Physics Committee review the information and upon approval, only then can an institution enroll a patient on a Brachytherapy study.

h. Stereotactic Radiosurgery/Radiotherapy Quality Assurance

In 1993, the RTOG published its Stereotactic Radiosurgery/Radiotherapy QA Guidelines, which represented the culmination of two years work by an ad hoc multidisciplinary committee. The Guidelines had three purposes: (1) to insure that institutions participating in RTOG radiosurgery protocols have the proper equipment and appropriate techniques to administer radiosurgery; (2) to outline a standard set of physics data to assess compliance of each radiosurgically treated patient with protocol requirements; and (3) to define minor variations and major deviations from protocol treatment. The committee also outlined a standard set of clinical data to assess treatment efficacy (including failure patterns) and treatment toxicity.

To accomplish the first goal, an RTOG Radiosurgery Facility Questionnaire was developed. Before entering a patient on an RTOG radiosurgery protocol, an institution must complete the questionnaire, which is then reviewed by Drs. Michael Gillin and Robert Kline from the RTOG Medical Physics Committee. They decide whether the institution has the technical ability capability to perform stereotactic radiosurgery. As of October 2000, over 90 institutions have been credentialed (representing just under 20% of all radiosurgery facilities in the United States) and approved for participation in RTOG stereotactic radiosurgery (SRS) protocols. Twenty-four institutions are in the review process and likely to

be approved, and four have been rejected (personal communication, Dr. Michael Gillin, 10/00)

To accomplish the second goal, the SRS committee developed a Radiosurgery Form to summarize the physics data for radiosurgically treated patients on protocol. Two ratios were devised to help quantify homogeneity within the radiosurgical treatment volume (MD/PD) and conformity of the prescription isodose volume to the tumor volume (PIV/TV). MD/PD is the ratio of the maximum dose within the treatment volume to the prescription dose. The PIV/TV is the ratio of the prescription isodose volume to the tumor volume.

To accomplish the third goal, a set of rigorous definitions of compliance with protocol prescribed radiosurgical treatment, i.e., minor variation and major deviations, were developed. These are based on the following three parameters: 1) adequacy of coverage of the target volume by the prescription isodose line evaluated on serial axial or orthogonal CT or MRI images; 2) the MD/PD ratio; and 3) the PIV/TV ratio.

i. 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. IGRT includes, but is not limited to, 3-D conformal radiation therapy (3-D CRT), Intensity Modulated Radiation Therapy (IMRT), Stereotactic Radiosurgery (SRS), and brachytherapy. Each institution planning to participate in RTOG 3-D CRT and IMRT protocols must submit specific information and data to the 3-D QA Center in St. Louis before enrolling patients in the IGRT protocols. (The RTOG will expand this requirement to include SRS and brachytherapy after DICOM RT is established.) For example, for 3-D CRT studies such as RTOG 98-03, documentation of the accelerator model, beam energies, and description of the collimation system to be used to define conformal fields (e.g., multileaf or cerrobend blocks) are required. Documentation of the isocenter accuracy for the gantry, the collimator, and the couch rotations must be provided. A description of the type of immobilization repositioning system to be used and any patient motion studies (set-up uncertainty, organ movement) are also submitted. The treatment verification system to be used, e.g. film, on-line imager, must also be described. Most important, a complete description of the 3-D planning system to be used must be submitted to the 3-D QA Center.

Institutions must be able to exchange digital data with the 3-D QA Center. The RTOG Data Exchange specification (includes CT, contours, beam modality/geometry specification, 3-D dose matrix, fractionation, digital film images, and dose-volume histograms) is required, and all data submitted must conform to the specific treatment protocol requirements.

In all external beam IGRT studies, the GTV, CTV, PTV, and normal tissues required by the protocol must be contoured on all CT slices and planned using beam's-eye-view display.

External beam 3-D CRT studies require that first-day port films or portal images of each field be submitted. Thereafter twice-weekly port films or portal images of orthogonal views (anterior to posterior and lateral projection) are required for review by the treating physician.

The 3-D QA Center reviews all PTV, CTV, GTV, and designated critical structures on, at a minimum, the first five cases submitted by each institution. After the institution has demonstrated compliance with the protocol, future cases may be spot-checked only.

The 3-D QA Center staff reviews the first placement films of the initial fields on all patients, comparing them with the digitally reconstructed radiograph from the treatment planning program, or alternatively, simulation verification radiographs. After the institution has demonstrated compliance with the protocol, future cases may be spot-checked only.

The 3-D QA Center reviews the DVHs and isodose distributions for the plans submitted to verify correct interpretation and conversion of the digital patient and dose data.

Special QA tests may be required for all participants to participate in a particular IGRT protocol. For example, for the RTOG IMRT Oropharyngeal protocol, the RTOG Medical Physics Committee, together with the RPC, has developed an IMRT treatment verification phantom. This phantom will confirm the dose delivered to specific points in the phantom and will also verify the general dose delivery pattern. This is especially important for this new treatment approach, which will be delivered by many different types of systems from step and shoot tomotherapy.

2. Medical Oncology Quality Control

a. Requirements for Participation

- i.* Prior to participation in a medical oncology study, the institution is required to submit the name of a medical oncology representative to Headquarters. Details are found in Section IV. C.1.
- ii.* 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.
- iii.* At the time of registration, the facility must provide the name of the responsible medical oncologist and may be required to provide the patient's current weight, height and body surface area (m²).
- iv.* The 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

- i.* 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.

To insure timely submission of medical oncology treatment information, a drug submission form or flow sheet is generally required to be submitted with on-study information due within two weeks of registration. In addition to pre-registration laboratory results, details of the administered initial chemotherapy treatment must be recorded on this first drug data form when initial treatment includes chemotherapy delivery.

- ii.* If chemotherapy is not given, written notification, including the reason, must be submitted in writing without delay.
- iii.* When RTOG is the coordinating center for a study, the site clinical research associate will provide the treating medical oncologist with the "standard RTOG flow sheets" or treatment summary form used in the study and instructions regarding the required submission schedule. When another co-operative group is the coordinating center, the clinical research associate will provide the treating medical oncologist with appropriate flow sheets 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.

- iv.* 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 flow sheets. All modifications in dosage or in the interval between treatments including termination, refusal or delays in therapy must be clearly documented on the flow sheets. The reasons for all modifications must be reported in the remarks. If treatment is discontinued prior to completion, the reason must be documented.
- v.* 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 VII for general guidelines.

c. *Review of Treatment*

- i. 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 telephone or by written inquiry and clarification or correction will be sought. Documentation of modification is required.
- ii. 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. In studies where the computerized medical oncology information uses summarized data, i.e., an abstracted summary is created by Headquarters research associates from the submitted flow sheets, the modality study chair is required to review both the original flow sheets or data forms, and the summarized data, preferably the printed summary. The reviewer completes and signs the Final Medical Oncology Evaluation Form, and printed summary, making corrections to the summary and requesting clarification as needed. The evaluation form documenting the review is entered in the computerized medical data files where it is available for use in statistical analysis.

- f. 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*

The following standard guidelines are used in the evaluation of treatment compliance of chemotherapy administration. If additional or different guidelines are necessary, they must be identified prospectively and included in the protocol.

Per Protocol - indicates following the protocol, including dose modifications (escalations and dose reductions), based on toxicity. A margin of variation of 15% for each drug from the protocol guidelines is considered to be acceptable for this definition with non-protocol treatment delays of less than 7 days.

Minor Variation Acceptable - Greater than 15% but less than 30% dose modification for any one or more drugs not stipulated by the protocol. Failure

to escalate dosage per protocol. Omission of a treatment that comprises = 15% of the total number of treatments required per protocol. Non-protocol delays in therapy totaling less than 2 weeks.

Major Variation Acceptable - More than 30% non-protocol dose variation in total drug delivery of one or more drugs required per protocol. Omission of any treatment after the first chemotherapy cycle comprising more than 15% of the total amount of treatment required per protocol. Treatment delays totaling more than 2 weeks.

Major Variation Unacceptable - Failure to administer one or more drugs required by the protocol. Failure to give the first cycle of chemotherapy within the guidelines stipulated under “minor variations.” Addition of anti-neoplastic therapy other than that specified in the protocol.

Not Evaluable for Chemotherapy Review - Incomplete chemotherapy flow sheets and required laboratory parameters for determination of drug dose modifications.

Incomplete Chemotherapy - Failure to complete chemotherapy to $\geq 85\%$ of total number of cycles specified due to death, patient or physician refusal or other nonspecified reason, in the absence of apparent drug-related toxicity.

Overall case evaluation ratings are specified in institutional quality control reports as: Per Protocol; Variation, Acceptable; Violation, Unacceptable; Not Evaluable; Incomplete. A summary of cases evaluated within a calendar year is sent to the institutional principal investigator yearly. A copy is submitted for review by the modality quality control chair.

3. Surgical Oncology Quality Control

With the introduction of surgical procedures as an intrinsic part of RTOG protocols, processes have been developed by the various surgical site subcommittees in order to standardize surgical technique and to evaluate surgical procedures for protocol compliance. When surgery is part of the therapy, every effort is made by the surgical study chair to clearly specify 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 standard surgical evaluation form has been developed and approved for use. This form requires study specific customization by the study chair with regard to specification of variations and study endpoints. A sample of the standard form and examples 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.

Surgical checklists which enumerate protocol specific requirements may be required for studies that include specific surgical procedures. The checklist must be

completed and submitted by the operating surgeon. This form becomes a component for review of protocol compliance.

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

1. Review of Submitted Data

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 is received, it is screened by the assigned research associate for accuracy, consistency and completeness. Discrepancies and missing data are clarified through the use of query letters, 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 VII). Unusual events are computer tagged for special review at a later date by the Study Chair.

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

1. Introduction

The two aims for central pathology review are to confirm the diagnosis, which is a quality control aspect, and to evaluate the histologic parameters for their prognostic value with respect to response or survival, which is a scientific question.

The RTOG has performed and analyzed such special studies in glioma, head and neck, lung, prostate cancers, and bladder cancers.

2. Pathology Material Submission Form

When a study requires the submission of pathology material, a “Pathology Material Submission Form” is included in the forms packet for that study. This form must be submitted to the RTOG Tissue Bank at LDS Hospital 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 of the protocol. Appropriate pathology reports, clearly photocopied to include patient name, slide numbers and diagnosis must accompany any slides or blocks. Pathology slides and block numbers must be identical as those on the reports. All materials must be labeled with the RTOG study and case numbers.

3. Materials Preparation

Slides and blocks must be clearly marked with surgical pathology accession number. Care must be taken when packing the slides to minimize the chance of breakage. Slides should be packaged in plastic slide cases taped closed so the material will not fall out and break during shipment. Do not use cardboard containers, as the risk of breakage during shipment is greater when these containers are used. The plastic slide cases should be shipped in a standard mailing cylinder or padded envelope. Do not ship slide cases in a regular envelope. Your pathology department can provide you with the proper mailing containers.

4. Shipment of Specimens

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

LDS Hospital
Department of Pathology
E. M. Laboratory
8th Avenue and C Street
Salt Lake City, UT 84143

Shipping labels are available from RTOG Headquarters.

5. Return of Pathology Material

Slides and blocks submitted for review are not routinely returned to the institution but will be preserved in the RTOG Tissue Bank at LDS Hospital for access during future studies.

E. INSTITUTIONAL AUDITS

1. Purpose

All member facilities are audited once every three years with all facilities at risk yearly. New full member institutions are audited within 18 months of becoming full members. New affiliate members are audited within 18-36 months based on patient accrual. The scope of this program is to audit investigators for the purpose of: 1) corroborating 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 at risk for audit even if their membership in RTOG is withdrawn or terminated.

2. Institutional Preparation

The institutions are notified up to two months in advance of the visit; a case list, from which specific cases (up to 20 cases) will be reviewed is sent to the investigator 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. A set of instructions as to the specific material that will be needed is available from the Protocol Office. All patient information must be available even if maintained at a location other than the institution; *i.e.*, referred cases or patients receiving some treatment elsewhere. The following records should be available for each case: informed consent document, radiation oncology department chart, hospital chart, physician and research notes, outpatient and clinic records, simulation and portal films, and medical oncology records. The institution is instructed to flag all relevant documents to expedite the site visit process.

3. The Survey

The survey team will consist of an RTOG quality control auditor, and/or a physician, and occasionally, an NCI representative. The team visits the institution and reviews all institutional records, which pertain to the cases selected. The material reviewed includes films, reports, laboratory records, and medical oncology files when applicable. Source documents should be independently verifiable. Copies of RTOG data forms will not be considered adequate and the use of RTOG flowsheets as sole documentation of drug administration is strongly discouraged. Documentation of drug administration must be included in the patient's record independently of RTOG data forms. If RTOG flowsheets are used as source documentation, they must be signed and dated.

Major categories for review are patient consent, eligibility, treatment compliance, treatment toxicity, response assessment, and overall record keeping. In addition, IRB approval letters or minutes and drug accountability records as well as specific radiotherapy procedures (film verification, special calculations, time of treatment,

etc.) are examined. IRB records are checked for full board review and approval both initially and at least annually. Consent forms must be study specific and dated and signed prior to registration and treatment start. Records of NCI-supplied investigational drugs and their storage areas are inspected for compliance with NCI requirements.

Prior to leaving the facility, the auditor(s) conducts an “exit interview” with the investigator at which time any discrepancies or problems identified during the survey are discussed. The auditor(s) fax a preliminary audit report to the NCI within 24 hours of completing the site visit. If discrepancies cannot be answered during the interview, the investigator is asked to respond by submitting relevant documentation to the Protocol Office at Headquarters within two weeks. 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 team submits its report to Headquarters along with the survey material (Case Questionnaires, Drug Survey Form, IRB Control Form, and sample consent forms, etc.). The report is reviewed by the Audit Coordinator and is entered into the NCI Audit Database. This report is also submitted to the Quality Control Committee for review, evaluation and recommendations for action. Copies of the reports, including the Committee’s and institution’s response, are sent to NCI within six weeks of the audit. Each audit is assigned an overall evaluation score: 1) Acceptable, few minor deviations; 2) Acceptable-needs follow-up, requires a written corrective plan; 3) Unacceptable-poor overall quality, requires group action including reaudit; 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.

If serious deficiencies are found during the site visit, the Quality Control Committee may suspend the patient registration privileges, order a re-site visit, require the institution to submit copies of documentation not normally required (*i.e.*, signed consent forms, and drug inventory logs) or require any other appropriate remedy.

5. Misrepresentation of Data

At its semi-annual 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 would be 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 Appendix XI. The RTOG Affirmation of Integrity of Research Data is specified in Appendix XIII.

X. STATISTICAL ANALYSIS

A. INTERIM ANALYSIS

Statistical Unit prepares reports for each RTOG semi-annual meeting on all studies open to patient entry or requiring new data analysis. While a study is open to patient entries, these reports focus on accrual, study execution and safety, and the results are reported to the entire Group. No efficacy data are presented on open, accruing studies. The statistician responsible for the study prepares the interim analyses with input from the study chairs. The research associate and the dosimetrist assigned to the study assist in preparing the analysis. Before each semi-annual RTOG meeting, the senior statisticians review the patient accrual rate for each open study and identify those which are failing to meet the targeted accrual goals for consideration by the Research Strategy Committee.

In each statistical report, the following information is generally included:

1. Projections for completion of the patient accrual phase based on the rate observed over the entire study and/or for the last year.
2. Patient accrual to the study by institution.
3. Disposition of all the cases entered into the study with respect to analysis. Those cases typically included in all the analyses are those considered eligible as confirmed by the on-study pretreatment study data and some follow-up information. These cases are called "analyzable". Ineligible patients excluded from analysis are identified by their unique case number and reasons for their exclusion are generally provided.
4. Entry characteristics are determined. Distributions of stratifying variables used in randomization and/or other important prognostic variables for each assigned treatment regimen.
5. A summary of reported toxicity presented by type and severity for each assigned treatment regimen. Details of major toxicities are included.
6. An analysis of delivery of each treatment modality relative to the protocol prescription by assigned regimen.
7. An analysis of the completeness and the timeliness of the submitted data. A summary of the study progress to date.

Each interim report is reviewed before its external distribution to the Group. This review is performed by the Group Chair (or Group Deputy Chair), the Group Statistician, the headquarters research associate, RT quality assurance staff (where appropriate), the

protocol administrator, and the study chair. The Group Statistician's studies are reviewed by another senior statistician.

Semi-annual reports are published in a pre-meeting book that is distributed to members of the RTOG at each meeting. Many of these analyses also are presented orally at the meeting, usually by the study chairs. The study statistician meets with the study chairs and with the disease site committees to discuss these reports during the meeting.

For randomized trials, the RTOG Data Monitoring Committee also reviews the usual interim report at times specified in the protocol. They also review other studies with major problems, which have been identified by the statistical unit or DMC member. Additionally, they review efficacy results blinded to treatment assignment in order to detect extreme early treatment differences. Based on these results, the Data Monitoring Committee recommends to Group Chair a possible future course for the study. The committee can make one of five possible recommendations: 1) continue the study as it is; 2) revise the study usually because of toxicity or execution problem, or 3) close the study before it has realized its accrual objectives because of insufficient patient accrual, or, 4) close it because of a highly significant advantage is observed on one of the arms, or 5) close it because the conditional power of eventually observing a significant improvement for experiment arms given what has been observed is extremely low. For nonrandomized studies, there is no Data Monitoring Committee to monitor efficacy. The study chair, responsible statistician, and responsible disease/modality chair examine it as specified in the protocol.

B. FINAL ANALYSES - INITIAL TREATMENT RESULTS

A comprehensive analysis for reporting study results is done by the statistician for the study chair when there is sufficient follow-up information. The duration of follow-up for a phase I/II study is usually shorter than for a phase III study, but it also depends on the tumor type. For example, regardless of whether it is phase I/II or phase III study, the follow-up time is usually 1 year in a high grade brain protocol because of the high death rate. In contrast, a phase III protocol for stage C prostate cancer may require 5 or more years of follow-up after the last patient is entered.

Before the final analysis can begin, all the outstanding data problems must be resolved and the final review of the 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.

In addition what is usually included in the interim analysis as described in last section, final analysis examines all the protocol efficacy endpoints. For a phase III trial, these are overall survival, disease-free survival, local-regional recurrence, and distant metastasis. Information about treatment delivery is regularly included. All eligible patients are used in the final analysis as long as some follow-up information is available. All the ineligible cases are excluded, but they are listed along with the reasons for exclusion.

The study analysis is reviewed by a second statistician before it is sent to the study chairman to form the basis of a 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 usually writes most of the manuscript reporting the study results based on the statistician's analysis. Generally the section on statistical method in the manuscript is prepared by the statistician. It describes the randomization scheme, test statistics, and procedures for estimation used in the analysis.

In addition to the eventual publication of the abstract and the manuscript in the medical literature, the results with the supporting data are summarized for publication in the semi-annual RTOG premeeting book.

C. SECONDARY ANALYSES

1. Timing

As a general policy, the analysis for the initial report of the results from the treatment and the companion (QOL and laboratory correlative) studies in a protocol takes precedence over any other analyses. There have been an ever-increasing number of requests to utilize the RTOG database to look at questions other than those originally proposed in the protocol such as treatment comparison. These have been designated as secondary analyses. All such requests are submitted to the Publications Committee on a standardized form. Each proposal is scored by the members of the Publications Committee with respect to scientific value and contribution to the field. The scores are periodically reviewed by a subcommittee of the Publications Committee. This consists of the Vice Chair for Publications, Group Chair, Deputy Group Chair, and Group Statistician. This subcommittee accepts or rejects each proposal based upon the score and provides a priority for the accepted proposal.

XI. MEETINGS

A. SEMI-ANNUAL

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. A session on medical/legal ethics is presented from time to time. In addition, educational workshops are held to update members on treatment planning and delivery techniques.

Electronic mailings for the semi-annual meeting begin two-three months prior to the meeting. At that time, invitations, hotel reservation forms, and a tentative agenda are available on our web site at www.rtog.org. Approximately two months in advance, agendas are requested from the Committee Chairs for distribution at the meeting. A meeting book, containing meeting agenda, progress reports, minutes from prior meeting, committee reports and list of publications, is available at the meeting.

Minutes from each semi-annual meeting are distributed in the following meeting's meeting book.

B. COMMITTEES

All committees are requested to meet prior to or during the RTOG meeting. Additional Committee meetings and conference calls are also held during the year, if needed.

APPENDIX I

**RADIATION THERAPY ONCOLOGY GROUP
CONSTITUTION AND BYLAWS**

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Revised:	1/86
	2/90
	2/94
	6/94
	12/95
	10/97
	04/00
Updated:	03/02

1.0 RADIATION THERAPY ONCOLOGY GROUP

1.1 PURPOSE

- 1.1.1 To constitute a group of clinical oncology investigative centers dedicated to cooperative clinical trials and other studies to improve the management of patients with cancer.
- 1.1.2 To provide for the collection of long-term data on the results of radiation therapy and on radiation complications.
- 1.1.3 To integrate the programs of the Radiation Therapy Oncology Group with other oncology disciplines and cooperative groups for more effective treatment of patients with cancer.
- 1.1.4 To integrate radiobiological and other laboratory advances into new clinical radiation oncology research programs and protocols.
- 1.1.5 To establish quality control measures for surgery and chemotherapy combined with radiation therapy.
- 1.1.6 To establish standardized treatment parameters so that uniformity exists in treatment plans, dosimetry and reproducibility of outcome in participating centers.
- 1.1.7 To standardize, in conjunction with the Radiologic Physics Center, the definition and application of dose units and calibrations used in radiation oncology.
- 1.1.8 To define the radiation and ancillary equipment needed for the proper conduct of clinical trials.
- 1.1.9 To establish a 3D treatment planning center for quality control.
- 1.1.10 To enrich training programs in radiation oncology and related disciplines, including radiobiology and physics.

2.0 MEMBERSHIP

2.1 FULL MEMBERS

Full Membership may be held by any institution meeting the following criteria:

- 2.1.1 The institution shall have the potential ability and interest to participate in cooperative group activities. Full membership resides with the institution and not the Principal Investigator.
- 2.1.2 The Principal Investigator agrees with the goals of clinical trials and will participate fully. A Full Member Institution Principal Investigator must be a radiation oncologist.
- 2.1.3 A professional team of at least three full time radiation oncologists, full time physics and biology support and adequate technical support is necessary.
- 2.1.4 The institution shall provide a minimum of 25 evaluable cases per annum to the studies in which it participates in the RTOG. In addition, the institution shall make a meaningful contribution to RTOG in terms of protocol design and

development, participating in committees and in scientific reviews and publications.

- 2.1.5 The institution shall have adequate treatment equipment including linacs and electron units, simulators computerized treatment planning and adequate systems for patient data recording and retrieval.
- 2.1.6 Co-investigators may be appointed in member institutions who can be either radiation oncologists or other clinicians devoted to oncology, such as medical oncologists, surgeons, etc. Such co-investigators shall be proposed by the principal investigator of a member institution.
- 2.1.7 Prospective members shall apply to the Membership Evaluation Committee. All new members must first join the group as an affiliate of an existing Full Member institution as described in section 2.3.

2.2 PROVISIONAL MEMBERS

Any institution which fulfills the criteria set out under section 2.1 may apply for affiliate membership. When an affiliate member reaches an annual accrual rate of 30 patients, the affiliate may apply for provisional membership. Such an applicant may be accepted, as a provisional member of the group. Provisional membership is not to exceed two years following a site visit and approval by the Membership Evaluation Committee. If performance is satisfactory as judged by the Membership Evaluation and Executive Committees, the applicant will then be admitted to Full Membership by a majority vote of those given voting rights as described below.

Provisional members shall have no voting rights.

2.3 AFFILIATE MEMBERS

- 2.3.1 Applications for affiliate membership shall be made to the Membership Evaluation Committee. These applications will be reviewed and approved by the Chair of the Membership Evaluation Committee, Group Administrator, and Director of Radiation Therapy Quality Assurance Department.
- 2.3.2 Affiliate members must place a minimum of five treatment cases per annum on active group studies. Performance will be reviewed semi-annually by RTOG headquarters and/or the Membership Evaluation Committee.
- 2.3.3 Affiliate institutions which have participated in the RTOG for at least 12 months, have met the criteria in section 2.1, and are accessioning patients at a rate of 30 per year may apply for Full Membership. They will be required to be provisional members and meet the criteria of section 2.2 before approval of the Membership Committee and election to Full Membership.

2.4 COMMUNITY CLINICAL ONCOLOGY PROGRAM (CCOP) MEMBERS

- 2.4.1 National Cancer Institute (NCI) approved and funded CCOP institutions may apply for membership if RTOG is an NCI designated CCOP Research Base.
- 2.4.2 The CCOP may apply for Full Membership, if it meets the criteria outlined in section 2.1, or if as a consortium CCOP it in aggregate meets the requirements of section 2.2.

- 2.4.3 CCOP institutions not meeting the requirements for Full Membership will be considered as CCOP affiliate members and must place a minimum of 5 cases per annum on RTOG sponsored treatment studies and 5 cases per annum on RTOG sponsored cancer control studies. The CCOP Membership Evaluation Committee will review the participation of CCOP affiliate members twice yearly according to the group's evaluation procedures.
- 2.4.4 If the CCOP principal investigator is not a radiation oncologist, the CCOP will designate a radiation oncologist as co-principal investigator for the RTOG membership.
- 2.4.5 Applications for membership by CCOP's will be reviewed by Headquarters and the CCOP Membership Evaluation Committee. Those requesting Full Membership will also be reviewed by the Membership Evaluation Committee and approved by vote as previously described in section 2.2.

2.5 VOTING RIGHTS

- 2.5.1 Voting rights are assigned for votes to be held in the meetings of the Full Membership on such matters as are brought to the Full Membership for decision.
- 2.5.2 Each Full Member institution shall have one vote. The institution's vote is cast by the principal investigator or his/her designated representative. If neither the principal investigators nor the designated representative attends a Group meeting, the member's institution can vote by way of proxy. Proxies: Each Full Member institution which does not attend a Group meeting in person through its principal investigator or through a designated representative may appoint a proxy, through a written instrument, from among other full members. Such proxies must be delivered to and received by the Headquarters office no less than 24 hours prior to any Group meeting.
- 2.5.3 Voting can occur at Group meetings or by postal vote. Only Full Members institutions shall make policy decisions. Decisions regarding the election of new officers or amendments to the constitution and bylaws must be made at Group meetings. All other decisions, such as the acceptance of new protocols, elections of new members, arrangements for meetings, and actions arising from other committee meetings may take place either at Group meetings or may be determined via postal vote.
- 2.5.4 A majority of the Full Members institutions at the Group meeting shall constitute a quorum. All matters to be voted upon must be approved by a majority vote of all eligible votes cast.
- 2.5.5 For a vote, which has been conducted through the postal service to be effective, a majority of full member institutions must have voted on the issue. The result of such election is determined by the majority of votes actually cast.
- 2.5.6 The Group Statistician shall have one vote.
- 2.5.7 The Group Chair shall have one vote in the case of a tie.

2.6 TERMINATION OF MEMBERSHIP

- 2.6.1 Membership shall reside in an institution via the principal investigator. A membership may be terminated by resignation of the principal investigator on behalf of the institution.

- 2.6.2 A previous Full Member principal investigator joining a new institution (not an active Full Member) shall follow the routine for membership application as previously described in section 2.1 if the institution is a non-member and section 2.3 if it is an affiliate member.
- 2.6.3 If a Full Member institution fails to meet the criteria of Group participation as determined by the Executive and Membership Evaluation Committee it shall be placed on probation for one year. Probation may be extended for a second year if recommended by the Membership Evaluation Committee and approved by the Executive Committee. If a Full Member fails to meet the criteria of the Membership Evaluation Committee, even after extended probation, this Full Member will be asked to resign from the Group. If the reason for the request of resignation is due to patient accrual numbers, the Full Member will be allowed to change to affiliate status. Once so changed, this member will not be allowed to reapply for Full Membership for two years. If the reason for failing to meet membership criteria is due to poor data quality, falsification of data, or other such similar circumstances, affiliate membership will not be offered and membership will be terminated. Failure to meet the standards set for membership and for performance during the probationary period will lead to termination of membership.
- 2.6.4 If an officer or a committee chair leaves his/her institution, he/she shall resign that office or chair position if the new institution is not already an RTOG Full or Affiliate member or if the new institution does not apply for Affiliate membership within one year. In the case of the Group Chair and the Group Vice Chairs, the new institution must achieve Full Membership within three years. It is expected that through this mechanism the Group Chair and all Vice Chairs will be elected from or serve from Full Member institutions.

3.0 ORGANIZATION

- 3.1 The Group shall be operated by an Executive Committee and a group of standing committees. The scientific work of the Group will be performed by Site Committees and coordinated by the Research Strategy Committee.

3.1.1 Executive Committee: Members

The Executive Committee shall consist of the Chair, the Deputy Chair, the Immediate Past Chair, the RTOG Foundation Chair, the Vice Chairs, the Group Statistician, and the chairs of the following committees/subcommittees:

- New Investigators
- Quality Control
- CCOP Investigators
- CCOP Membership Evaluation
- Medical Physics
- Research Associates
- Pathology
- Translational Research Program

In addition, there shall be two members-at-large who will be elected by majority vote from the membership and will serve for three years. Each may be re-elected for a second term.

- 3.1.2 The Executive Committee executes group policy and resolves issues involving policy matters. Meetings will be conducted at the RTOG Semi-annual meetings and on an ad hoc basis as needed. It shall appoint a nominating committee to deal with vacancies on the Executive Committee when they occur.

- 3.1.3 Steering Committee: The Group Chair, the Deputy Chair, the Immediate Past Chair, the Vice Chairs, and the Group Statistician will make up the Steering Committee, which will carry out necessary Executive Committee activities between meetings of the Executive Committee and will report to the Executive Committee.
- 3.1.4 The Group Chair will be elected by a majority vote of all eligible votes cast by Full Member institutions in a vote at a group meeting. The Chair will be elected for a term of four years and may be elected to a second four year term. The Full Members may also, by a majority vote, allow the Group Chair to serve for a third four-year term. If the term of the Group Chair shall not extend for at least one year after the due date for the submission of a competitive grant renewal for the support of the group, then the Full Members may, on the recommendation of the Executive Committee, extend the term of the office of the Group Chair by up to eighteen months to assure continuity before the submission of an application, and for the defense of the group at a site visit.
- 3.1.5 The Vice Chairs for Membership Evaluation, Publications, and Disease Sites, will be elected by a majority vote of eligible votes cast by Full members at the Group meeting. The remainder of the Vice Chairs will be appointed by the Group Chair with the approval of the Executive Committee. Each Vice Chair will serve a term of four years and may be re-elected/reappointed to a second four-year term.
- 3.1.6 The Group Chair may appoint a Deputy Chair to supervise the headquarters, oversee protocol development, and represent the Group Chair at various meetings in his/her absence. The term of office of the Deputy Chair shall be for four years and renewable for additional four year terms.
- 3.1.7 Membership Evaluation Committee: The Vice Chair for Membership Evaluation will chair the committee and will develop criteria for membership in the RTOG, evaluate all new member applicants, develop criteria for continuing membership and periodically evaluate the members. This committee will:
- 3.1.7.1 Draft a set of guidelines for requisites to apply for membership in the Group.
- 3.1.7.2 Design specific forms, which will succinctly provide this information to headquarters from applicants.
- 3.1.7.3 Define types of memberships, which are allowed in the Group, and requirements and privileges for each one.
- 3.1.7.4 Review all applications of prospective Full Members and conduct site visits as indicated.
- 3.1.7.5 Make recommendations to the Executive Committee about qualifications of the applicants for Full Membership.
- 3.1.7.6 Evaluate each Full Member and Affiliate Member twice yearly for accrual and performance. Recommend warning letters and/or probation as needed.
- 3.1.8 Publication Committee: The Vice-Chair for Publications will identify potential publications from RTOG activities, promote their timely development, develop group publication guidelines and will receive all abstracts and manuscripts reporting on group matters or studies. The role of this committee is to promote and facilitate publication of studies. RTOG trials results in a timely manner, assure authorship lines are correct, review the science of abstracts and papers, assure

- timely reporting by assigning or reassigning responsibility and update publication guidelines as necessary.
- 3.1.8.1 The dissemination of information from RTOG trials (verbal or written) must comply with the guidelines developed and amended by the Publications Committee.
 - 3.1.8.2 The guidelines generally will be published in the RTOG Meeting Reports books at least once per year or at a minimum when amended. Guidelines for secondary publications will also be published.
 - 3.1.8.3 The Publications Committee is charged with the responsibility of monitoring compliance with Publications guidelines and recommending remedial and/or punitive action, as appropriate, to the Executive Committee for enforcement. Additional guidelines for Group publications may be developed by the Publications Committee and instituted with the approval of the Executive Committee.
 - 3.1.9 The Research Strategy Committee is composed of the Group Chair, the Deputy Group Chair, the Vice-Chairs, the Group Statistician, senior members of the Statistical Center, the disease site committee chairs and the other scientific committee chairs. It meets twice at 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.
 - 3.1.10 The Vice Chair for Sites will develop research strategy for each of the major tumor sites covered by the RTOG. This chair will develop research strategy as appropriate, will review protocol development, will identify deficiencies and opportunities for site oriented protocol development and will closely coordinate site applications of new treatments developed within the modality committees. The Vice Chair for Sites will co-chair the Research Strategy Committee.
 - 3.1.11 The Vice Chair for Translational Research will coordinate the introduction of basic sciences both into the modalities and into the sites. This individual will also develop educational programs, and manage the tissue repository.
 - 3.1.12 The Vice Chair for Cancer Control is in charge of overseeing all cancer control efforts including CCOP protocol development and the activities for the CCOP program, the Chemoprevention, and Late Effects Subcommittees.
 - 3.1.13 The Vice Chair for Surgery is in charge of overseeing all RTOG surgical efforts including the coordination of activities of the Gastrointestinal, Head and Neck, Neurosurgical, Surgical Quality, Thoracic, and Urology Surgical Subcommittees to bring new ideas and developments into the Group.
 - 3.1.14 The Vice Chair for Medical Oncology is in charge of overseeing all RTOG Medical Oncology efforts including the coordination of activities of the Brain, Gastrointestinal, Genitourinary, Head and Neck, Lung and Medical Oncology Quality Control Subcommittees to bring new ideas and developments into the Group.
 - 3.1.15 The Vice Chair for Outcomes is in charge of overseeing all RTOG outcomes efforts including coordination of Quality of Life, Epidemiology and Special Populations.

- 3.1.16 Nominating Committee The Executive Committee will, as needed, will nominate candidates for vacancies in elected positions on the Executive Committee.
- 3.1.17 The Nominating Committee shall have at least four members, of which one is Chair, broadly representative of the diversity of the RTOG membership.
- 3.1.18 Approximately two months prior to a planned election, the Nominating Committee will prepare a preliminary list of candidates for nomination, after consultation with the Group Chair, and based on recommendations from the Full Member Principal Investigator's site/modality committee chairs and other relevant sources.
- 3.1.19 The Nominating Committee will evaluate this preliminary list for the most suitable nominees and submit to the Group Chair, approximately one month prior to the election, a final list of up to four nominees who have agreed to serve, if elected. This list, if approved by the Group Chair, will be circulated to the Principal Investigator's at least two weeks prior to the election.
- 3.1.20 For some positions, as an aid to the voting Principal Investigators, the nominees may be asked to write a précis describing their perception of the requirements of the position and in what manner they will perform the required duties.
- 3.1.21 At the Full Member Principal Investigator's meeting, ballots containing the names of the nominees will be distributed for a closed vote by the voting members of the committee. At this time, candidates not nominated by the Nominations Committee can be nominated from the floor or written in on the ballot.
- 3.1.22 A member of the Nominating Committee can be considered as a nominee for a vacant position, if he or she is willing to serve, but must abstain from Nominating Committee deliberations concerning nominees for that position.

4.0 OTHER COMMITTEES

- 4.1 Each committee chair and co-chair will be appointed by the Group Chair for four years and may be reappointed for one additional four year term. All committee and subcommittee chairs must be appointed from Full and Affiliate member institutions and must resign if their institution does not maintain Full or Affiliate status.
- 4.1.1 Other Committees: Subcommittees and *ad hoc* committees may be formed as the need arises. These subcommittees and *ad hoc* committees will aid the standing committees in accomplishing their specific tasks.
- 4.1.2 Outside consultants may be members of the standing and *ad hoc* committees without vote.
- 4.1.3 Complementary Studies Committee: This committee shall be divided into Late Effects and Quality of Life subcommittees. These subcommittees will conduct studies and supervise protocols in these two areas.
- 4.1.4 CCOP Evaluation Committee: This committee will develop criteria for CCOP membership and evaluate CCOP members.

- 4.1.5 Constitution and Bylaws Committee: This committee will be charged with the responsibility for keeping the Constitution and Bylaws of the Radiation Therapy Oncology Group current with the practice of the Group.
- 4.1.6 Data Accession and Retrieval Committee: This committee will deal with problems related to data accession and retrieval.
- 4.1.7 Research Associates Committee: The Research Associates Committee will coordinate the activities of the RTOG research associates and their training.
- 4.1.8 Medical Oncology Committee: This committee will provide advice to the RTOG regarding the integration of chemotherapy into RTOG studies and will oversee the quality control of the chemotherapy of such studies. This committee will provide a liaison with the other multi-modality cooperative groups, keep RTOG abreast of recent developments in medical oncology, eliminate undue duplication between cooperative groups and provide input into the design of any potential combined modality protocols within the RTOG.
- 4.1.9 Medical Physics Committee: This committee will participate in protocol design and will ensure appropriate statements for the manner in which radiation therapy is to be administered and dose prescriptions specified. The committee will also be available to review the data relative to treatment administration and dosimetry calculations.
- 4.1.10 New Investigators Committee: This committee is charged with the responsibility of fostering increased participation in Group activities by qualified new investigators at RTOG institutions.
- 4.1.11 Pathology Committee: This committee will participate in protocol design and will be responsible for the review of all submitted slides as required by the various protocol studies.
- 4.1.12 Quality Control Committee: Its purpose will be to evaluate the performance of the individual cooperating institutions to ascertain that the research is maintained at an acceptably high level. This will involve interviewing individual senior investigators, reviewing their records, and rating their performance. In addition, the committee's finding will be reported at the semi-annual meetings of the Group and necessary steps taken to maintain the scientific quality. If necessary, groups performing unsatisfactorily may be put on probation or be asked to withdraw from the group.
- 4.1.13 Translational Research Program: This committee provides basic science input into the modality and site committees. They also organize educational symposia for the semi-annual meetings to familiarize the group with new modalities and inform them of possible studies that may be developed using these modalities.
- 4.1.14 Surgical Oncology Committee: This committee will perform the same function with the surgical clinical investigative groups as the Medical Oncology Committee does with chemotherapy.
- 4.1.15 The Data Monitoring Committee: shall be appointed by the Group Chair and Statistician plus two NCI representatives will be *ex officio*, non-voting members. The DMC periodically reviews the efficacy and the morbidity data on every phase III RTOG conducted trial to ensure that any decision made about future continuation of these studies are both scientifically sound and ethically responsible. The DMC makes recommendations to the RTOG Chair for his/her consideration and decision.

5.0 PROTOCOLS

- 5.1 Ideas for a new study may be submitted by any group member.
 - 5.1.1 Feasibility of a new study will be determined by the appropriate Site Committee and the Research Strategy Committee.
 - 5.1.2 If considered feasible, the appropriate Site Committee Chair in conjunction with the Group Chair will appoint a Study Chair.
 - 5.1.3 Study Chair: Each new study will be chaired by a Group member who typically would have been instrumental in the creation of this study. He/she may be aided by other group members to form a Protocol Committee for this study.
 - 5.1.4 The Study Chair and his/her Protocol Committee will assist the Headquarters Office and the Statistical Center in making the protocol development.
 - 5.1.5 The study protocol shall be proposed at the Group meeting and approved by the Research Strategy Committee.

6.0 MEETINGS

- 6.1 Plenary meetings of all participating members shall be held semi-annually. Presentation of ongoing studies will be made from the point of view of case accrual, clinical problems.
- 6.2 Notification of such meetings will be made by the Headquarters Office.
- 6.3 Attendance by at least one member from each participating institution is expected. The Principal Investigator will be expected to attend at least one meeting per year.
- 6.4 Quorum for the meetings demands that representatives from more than 50% of the participating institutions be physically present.
- 6.5 Committee meetings will be held at the time of semi-annual meetings and as often between times as needed.

7.0 AMENDMENTS TO CONSTITUTION AND BYLAWS

- 7.1 Amendments to the Constitution and Bylaws may be proposed by any Full Member institution. All such amendments must be passed by a majority of eligible votes cast.
- 7.2 Proposals: All proposals for amendments must be submitted to the Executive Committee four weeks prior to the next Group meeting at which time the amendment is to be discussed. A written copy of the proposal will be available to Group members prior to the balloting.

8.0 HEADQUARTERS

- 8.1 The Headquarters location of the RTOG shall be selected by the Executive Committee and approved by a majority vote of the Full Members. It will conduct all major organizational activities of RTOG and collect and analyze RTOG data. Emphasis will be placed on continuity and excellence.

8.2 Headquarters will not move when the Group Chair changes unless approved by the Executive Committee and a majority vote of the Full Members.

9.0 STATISTICAL CENTER

9.1 The statistical center location will be chosen by the Executive Committee. It will be geographically close to the Headquarters. The Group Statistician will be a voting member of the Group and Executive Committee.

APPENDIX II

PUBLICATIONS GUIDELINES

A. ROLE OF THE PUBLICATIONS COMMITTEE

1. Promote and facilitate publication of RTOG trial results in a timely manner.
2. Assure authorship lines are correct so that the appropriate contribution credit is recognized.
3. Review the science of abstracts and papers.
4. Assure timely reporting by assigning or reassigning responsibility.
5. Update guidelines as necessary.

B. GENERAL CONSIDERATIONS

1. Study Chairman has priority on the first report of a study. RTOG publications have adapted the *New Eng J Med* (NEJM) guidelines. However, the specifications will be used as suggestions, not requirements. The only time these specifications are required is when the paper is submitted to the *NEJM*.
2. There may be one Radiation Oncologist Co-Chairman when appropriate, a Medical Oncologist or Surgical Oncologist should be Co-Chairman where appropriate.
3. The Study Chairman (Institution) must contribute 5% or 10 patients (whichever qualifies) to his/her study to retain publication rights. If the Study Chair has accrued less than 5% or 10 patients, then the committee will review it on an individual basis.
4. Headquarters will identify those who have participated in reviewing a study so they appear on the authorline. The authorship line will include physicians and statisticians as appropriate. Data Managers will be recognized by acknowledgment when appropriate. The 1st author needs to request permission in writing when seeking to add additional people to the authorline.
5. The Publications Committee shall meet at each group meeting.
6. Study Chairman must have approval of their site/modality committees as necessary to begin to analyze and report a specific study. The Publications Committee will authorize the use of statistical services and formulate the authorship line with the Study Chairman at that time. The Study Chairman and the Publications Committee will agree upon a reasonable time for completion of the report.
7. The Publications Committee will review all abstracts and all publications before submission to a meeting or a journal. This review will be accomplished in one week for abstracts, one month for papers. No abstracts or manuscripts may be submitted without prior Publications Committee approval.
8. Initial papers reporting the primary endpoints of each protocol are routinely assigned to the Study Chair. These endpoints would be those that had been specified in the study initially. They might include not only disease endpoints but toxicity endpoints, quality of life endpoints and any other ancillary endpoints. Publication of these papers will follow the traditional

publication guidelines. This will be looked at beforehand to determine “up front” what initial endpoints are contained in a protocol.

9. Updated papers on the same endpoint analyses will be reviewed separately by the Publications Committee.
10. Secondary analysis follows additional guidelines as specified below:

A person is limited to 2 requests per calendar year. Members who have one set of data being worked on, and one pending, may *not* submit another request. All forms must be typed before submitting to headquarters. Handwritten forms *will not* be accepted.

- A. Secondary papers are those in which data are looked at for nonpredetermined endpoints and may cross several studies. These papers are identified by individual investigators with an idea and will be approved by a subcommittee consisting of the Group Chair, Deputy Chair, Vice-Chair for Publications and Group Statistician before Headquarters and Statistical Unit resources are allocated to the Project. Preference will be given to investigators who have contributed to the study and/or the RTOG in the past.
 - B. Secondary papers that are identified by the Study Chairman and/or Statistical Unit at the time the main paper is being written will be assigned to institutions with the largest accrual.
 - C. The authorship of secondary papers will be identified in advance and will include the investigators from the institutions with the largest accrual plus the original study chair.
11. A study cannot be reported until it is completed unless an exception is made by the Publications Committee.
 12. The first author of an initial treatment paper cannot give authorship rights to another person. Exceptions can be requested of the Publications Committee.

C. AUTHORSHIP

1. Contributors who register $\geq 10\%$ of the evaluable cases of a nonrandomized study will be listed as co-authors. The designated author is the choice of the institution's principal investigator. If fewer than three institutions contributed $\geq 10\%$ of the cases, then the top three accruing institutions will be listed.
2. Contributors who randomize $\geq 5\%$ of the evaluable cases on a randomized study will be listed as co-authors. The designated author is the choice of the institution's principal investigator. If an institution places a large number of cases on the study, that institution will get an additional co-author for every 10% of the patients accrued, not to exceed a total of three co-authors. (Two co-authors for $\geq 15\%$ accrual and three co-authors for $\geq 25\%$ accrual.) If $\geq 5\%$ of cases creates an author line that is too long, then the Publications Committee will revert to the 10% rule for case accession.
3. The authorship line of an overview paper will consist of the following: The first author, study chairs from each study, statistician, and the top three total accruers, appropriate site or

modality chair. The number of authors from the institutions depends on the percent of total accrual.

4. Membership and authorship representation rests with the institution. When an investigator leaves an institution, it is up to the Principal Investigator to assign someone to the authorship spot allocated for that institution. If a Study Chairman leaves an institution, he maintains his authorship rights with the permission of the Group Chairman and the Publications Committee if: 1) he has accessed patients to the study and 2) if he stays affiliated with RTOG and continues to place patients on the study and/or reviews the data within a reasonable time period.
5. If a statistician or reviewing pathologist has been involved with the study, he should be listed as a co-author.
6. If the Group Chairman or Associate Chairman has made a substantial contribution to a study their name may be included in the author line.
7. The order of authorship for an initial treatment paper for randomized studies will be: primary author, statistician, co-chairman contributing to data review and analysis, other modality chairmen e.g. pathologist (if applicable), and the institutional representatives. The remaining study co-chairmen not contributing to data review and analysis will be placed in an appropriate position as determined by the Publications Committee (if applicable).
8. Secondary analysis authorship lines will be identified as follows: 1st author (person who requested 2nd Analysis), statistician, study chair(s) (study databases used in analysis, by # of pts accrued in descending order), and site chair(s) who oversaw the conduct of the studies.
9. Every paper must include an appendix or table of all contributors to the study. (This does not apply to abstracts.)
10. Site or Modality Committee Chairmen may not publish a review article from material appearing in the RTOG minutes without the permission of the Study Chairman.
11. The Publications Committee will discuss their decisions on authorship with the principal author, but the Committee's decision will be final.
12. The RTOG Name and Study Number must appear in the title of every publication.
13. The authorship of any paper based totally on previously published RTOG data is left to the first author's discretion. It is recommended that RTOG authorship guidelines be followed, but it is not required. Any paper that publishes any new data (i.e. data that has not previously been published in a source that is suitable for reference and citation) must follow RTOG authorship guidelines exactly.
14. If a manuscript is overdue, that author loses authorship rights on that and any other pending manuscript and cannot take on new responsibilities within the Group.
15. An abstract approved for submission is only approved for a particular meeting. If it is rejected and the author wants to resubmit it to an alternative meeting, it must be treated as a new/separate issue.

D. INTERGROUP GUIDELINES FOR STUDIES RTOG COORDINATES

1. The authorship line will consist of the Study Chairman, RTOG Statistician, Study Co-Chairmen (all groups), institutional representatives contributing $\geq 5\%$ of cases ($\geq 15\%$ to get a second co-author) and additional Site/Modality Chairmen as appropriate. The order of authorship will follow the guidelines as stated above.
2. If $\geq 5\%$ of cases creates an author line that is too long, then the Publications Committee will revert to the 10% rule for case accession.
3. The paper must include an appendix or table of all contributing institutions.
4. Points of discussion for other groups studies will be considered at that time.

E. COMPLEMENTARY STUDY GUIDELINES

1. If Complementary Study information has been included in a study, then the Complementary Study Chair should be listed in the authorship line.
2. The Complementary Study Chair can write the Complementary attribute based paper following author guidelines but the Study Chair must be included.
3. Approval for publication of the Complementary Study information, prior to the first paper, has to be approved by the Publications Committee.

F. PRE-PUBLICATION PROCEDURES

1. PAPERS

- A. It is the responsibility of the 1st author to distribute a draft of the manuscript to all co-authors and obtain approval from them for submission of the manuscript to a journal.

Once all authors are in agreement and the manuscript is in the final version, it is to be submitted to the RTOG Publications Administrative Assistant (Lisa Morabito) at headquarters who will then send it to appropriate reviewer. This review will be completed within a one-month period. Once reviewed, headquarters will notify the 1st author of the next step. (i.e.: submission to journal or changes required.)

- B. Papers and abstracts may be submitted to journals or meetings only after publication review by the RTOG office.

2. ABSTRACTS

- A. It is the responsibility of the 1st author to distribute the draft of an abstract to all co-authors *and the site chair* and obtain approval from them before submitting to the Publications Committee for approval.

1/31/01

APPENDIX III

RADIATION THERAPY ONCOLOGY GROUP REQUIREMENTS FOR INSTITUTIONAL MEMBERSHIP

Full Members

1. PERSONNEL

- 1.1 Three full-time radiation oncologists. At least two of them must be certified in Radiation Oncology by the American Board of Radiology or equivalent, one of them having a minimum of three years of experience beyond completion of training.
- 1.2 There should be one staff radiotherapist for each 200-225 new patients treated per year.
- 1.3 Minimum one full-time Board-certified physicist. The staff should have the capability to perform periodic calibrations and quality control check output of all machines. There should be capability for doing multiport isodose summations and multiple point calculations on irregular field treatments.
- 1.4 Research staff in building desirable.

2. EQUIPMENT

- 2.1 There should be at least two megavoltage units (eg⁶⁰Co, 4 MEV x-ray linear accelerator or greater with isocentric treatment distance of 80 cm or greater) but at least one unit for every 300 new cancer patients treated per year. One of the machines should have the capability of obtaining field areas of 35 cm x 35 cm.
- 2.2 Equipment of diagnostic quality for localization and simulation purposes.
- 2.3 A treatment planning section able to plan and implement complex radiotherapy techniques is required. Computer capability for generation of isodose distribution is desirable.
- 2.4 Access to computer facility for treatment planning dosimetry.

3. CLINICAL MATERIAL

Fifty percent of the patients should be considered curable (not palliative XRT).

4. PHYSICS REQUIREMENTS

- 4.1 The institution must maintain routine dosimetry, calibration and treatment planning procedures recommended by the American Association of Physicists in Medicine (AAPM).

5. RECORDS

The record system of the institution must meet the following standards set by RTOG.

- 5.1 Initial evaluation (consultation note).
- 5.2 Anatomical drawing of lesion and staging.
- 5.3 Aim of treatment.
- 5.4 Daily treatment dose sheet.

- 5.5 Description of technical factors including patient diameter, RX distance, field size, beam energy, arrangement, depth dose, etc.
 - 5.6 Isodose distribution and irregular field point calculations when required.
 - 5.7 Drawings or photographs of treatment portals.
 - 5.8 Copy of pathology report.
 - 5.9 Progress note.
 - 5.10 Treatment summary.
 - 5.11 Follow-up notes.
 - 5.12 When patient receives multidisciplinary management, appropriate details should be part of the record (Applies to institutions wishing to participate in RTOG multimodality studies).
- 6. THE FOLLOWING ARE DESIRABLE ALTHOUGH NOT ESSENTIAL:**
- 6.1 Megavoltage equipment providing high energy photons and electrons (> 8 MEV)
 - 6.2 Dedicated treatment simulator.
 - 6.3 Training program is strongly recommended.

7. IRB AND ASSURANCE CERTIFICATION

The institution must have an Institutional Review Board (IRB) and an assurance approved by the National Institutes of Health (NIH) Office for Protection from Research Risks (OHRP).

02/01

REQUIREMENTS FOR INSTITUTIONAL MEMBERSHIP

Affiliate and CCOP Members

1. PERSONNEL

- 1.1 One full-time radiation oncologist, who must be certified in radiation oncology by the American Board of Radiology, the American Osteopathic Board of Radiology, or equivalent certification for participants from other continents, and who has a minimum of one year of experience beyond completion of training.
- 1.2 There should be one staff radiotherapist for each 200-225 new patients treated per year.
- 1.3 A part-time physicist is required. The staff should have the capability to perform periodic calibrations and quality control check of output of all machines. There should be capability for doing multiport isodose summations and multiple point calculations on irregular field treatments.
- 1.4 Institution must demonstrate the ability to handle the requirements of data management.
- 1.5 There must be representation of other oncologic disciplines in the institution, such as medical oncology, surgery and pathology, with commitment of full-time people to participate in RTOG.

2. EQUIPMENT

- 2.1 There should be one megavoltage unit (eg⁶⁰Co, 4 MEV x-ray linear accelerator or greater with isocentric treatment distance of 80 cm or greater). One of the machines should have the capability of obtaining field areas of 35 cm X 35 cm.
- 2.2 Equipment of diagnostic quality for localization and simulation purposes.
- 2.3 A treatment planning section able to plan and implement complex radiotherapy techniques is required. There should be capability for doing multiport isodose summations and multiple point calculations on irregular field treatments.
- 2.4 Access to computer facility for treatment planning dosimetry.

3. CLINICAL MATERIAL

- 3.1 A minimum of 250-300 new patients treated per year.

4. PHYSICS REQUIREMENTS

- 4.1 The institution must maintain routine dosimetry, calibration and treatment planning procedures recommended by the American Association of Physicists in Medicine (AAPM).

5. RECORDS

The record system of the institution must meet the following standards set by the Radiation Therapy Oncology Group:

- 5.1 Initial evaluation (consultation note).
- 5.2 Anatomical drawings of lesion and staging.
- 5.3 Aim of treatment.

- 5.4 Daily treatment dose sheet.
- 5.5 Description of technical factors including patient diameter, RX distance, field size, beam energy, arrangement, depth dose, etc.
- 5.6 Isodose distribution and irregular field point calculations when required.
- 5.7 Drawings or photographs of treatment portals.
- 5.8 Copy of pathology report.
- 5.9 Progress note.
- 5.10 Treatment summary.
- 5.11 Follow-up notes.
- 5.12 When patient received multidisciplinary management, appropriate details should be part of the record. (Applies to institutions wishing to participate in RTOG multimodality studies).

6. IRB AND ASSURANCE CERTIFICATION

The institution must have an Institutional Review Board (IRB) and an assurance approved by the National Institutes of Health (NIH) Office for Human Research Protections. (OHRP).

03/02

APPENDIX IV

CRITERIA FOR MAINTAINING RTOG MEMBERSHIP

I. PATIENT ACCESSION REGISTRATION

<u>Membership Category</u>	<u>Minimum RTOG Credits (per year)</u>
Full	25
Affiliate	5 treatment and/or cancer control case credits
CCOP	10 cases (5 treatment cases, 5 cancer control cases)

II. QUALITY CONTROL

	<u>Acceptable Minimum %</u>
1) Eligibility & percent of patients evaluable	80%
2) Percent complete forms - no additional inquiries	80%
3) Timeliness of forms submission (including pathology & chemotherapy flow sheets)	80%
4) Submission of initial treatment planning data (received within 24 days)	80%
5) Responsiveness to additional inquiries	80%
6) Submission of treatment data on completed cases	80%
7) Pathology and surgery	80%
8) Intergroup Data (non-RTOG Forms)	80%

Overall Score must be > 80% or a Warning Letter will be issued.

EVALUATION PROCEDURES

The RTOG Membership Evaluation Committee will review all Full and Provisional members and the CCOP Membership Evaluation Committee will review all CCOP members using the following procedures. Headquarters review of the Affiliate members will utilize the same criteria:

- 1) Full Member institutions with a new principal investigator must inform headquarters in writing and be approved by the Membership Committee (6/03).
- 2) Case credits must be as follows:

Full Member	25 cases per year
Provisional Member	See Paragraph #11
CCOP	10 cases; 5 treatment cases/year, 5 cancer control cases/year
Affiliate	5 treatment and/or cancer control cases
- 3) New RTOG member institutions (Full, Affiliate or CCOP) will be sent a letter clearly stating the requirements for continued membership (6/79). A new Affiliate Member institution must choose its formal activation date. After the usual Headquarters review of its application, a new institution will receive an acceptance letter and an institutional number assignment, but will not be able to place patients on study until a copy of the OHRP assurance is on file at Headquarters and at least one protocol has been approved by the institution's IRB. It will then be necessary for the new institution to notify Headquarters when it is ready to "start the clock." As of that date, the institution will be required to place five treatment cases on study per year. When possible, all affiliates' accrual will be measured on a calendar year basis to facilitate oversight by Headquarters. (3/02)
- 4) All members will be reviewed in July. Each institution will receive a statement regarding its performance. The statements will highlight one of the following categories: a) satisfactory, b) warning, c) probation, and d) request for resignation. The printouts used to evaluate an institution will be included with the letter and an institution will have 30 days to appeal the evaluation (6/03).
- 5) An institution will be given a warning if its case accession falls below acceptable levels. If the institution fails to meet its case accrual for the current year, the institution will be placed on probation. An institution can remain on probation for one year, but if it continues to have unacceptable accrual, it will be asked to resign. If the institution's performance improves to acceptable levels for an entire year (a minimum of 12 months), it will be removed from probation. If an institution does not meet the accrual requirements for two consecutive calendar years, the institution will be asked to resign without a further warning or probationary period (3/02).
- 6) An institution with poor data quality will be given a warning. If data quality is still not acceptable at the time of their next evaluation, the institution will be placed on probation. If at the time of their next evaluation, the problem is still not corrected the institution will be asked to resign (3/02 Revised).
- 7) Membership Evaluation Committee members must leave the room while their institution is being evaluated (1/80).

- 8) A minor deficiency category was created to call an institution's attention to areas in which performance is borderline. This will not replace the warning letter which will continue to be used for more serious problems (7/82).
- 9) At the Winter meeting all members will have entered the total number of patients required during the preceding four quarters (Full \geq 26, CCOP \geq 10, and Affiliate \geq 5 treatment and/or cancer control) and at the mid-year meeting they will have entered one-half the number of patients required in the preceding two quarters to be considered in compliance with the case accession criteria (06/03).
- 10) The Principal Investigator (or co-PI at a CCOP member institution where the PI might not be a Radiation Oncologist) at any RTOG institution shall be certified in radiation oncology by the American Board of Radiology, the American Osteopathic Board of Radiology, or equivalent certification for participants from other continents. (7/95)

Additional Criteria for Full Members

- 11) An institution wishing to become a Full Member must first join as an Affiliate Member. After the facility has accrued 25 case credits in one year, it may apply for Provisional Member status. This involves submitting a complete new application to the Committee, who will review it at their semi-annual meeting. If the application is in order, the institution will be site visited prior to the next Committee meeting, and if the site visitors' reports are then approved, the institution will be designated a Provisional member. Provisional Members may recruit affiliates. During the following year it must meet the requirements for Full Membership. If it meets these requirements, it will be awarded Full membership status. (6/03)
- 12) When an institution has been approved for a site visit, protocols and other pertinent information will be sent to the institution so that the study review process can be started (6/81).

Additional Criteria for CCOP Members

- 15) During the first six months of membership, each institution is required to complete any IRB details locally and complete the Research Associate Orientation. After 12 months of membership, the institution must have placed 50% of the yearly case requirement on study. Warning letters will be sent to all institutions not satisfying this standard. After 18 months, if tasks specified in warning letters are not fulfilled, the facility will be placed on six months probation with specific case accession tasks. After 24 months, the facilities on probation that do not fulfill their obligations will be asked to resign from RTOG.
- 16) Institutions that participate in more than one Cooperative Group can receive credit toward fulfillment of their membership requirements for patients placed on joint protocols through another group. This credit cannot exceed one-quarter of the membership requirement (3 cases are allowed).
- 17) A CCOP cannot be on probation more than once during a two-year period for the same deficiency. If, according to the Evaluation Criteria, an institution must be placed on probation for a second time the institution will be asked to resign.

Definition of an Affiliate Member:

An affiliate member is an institution with its own professional and technical staff which has petitioned and been accepted as an affiliate of a full or provisional member, which is responsible for its affiliate's data management. Each affiliate will be expected to contribute a minimum of five treatment and/or cancer control cases per year. Affiliates intending to apply for Provisional membership must place 30 cases on study in one year (see #11 above). Contribution and compliance of affiliate members will be monitored by the central office of the RTOG.

If an affiliate is dropped for not meeting its accrual objectives and wishes to become active in the Group at a later date, then reinstatement will require consideration by the Membership Evaluation Committee. An explanation of why the institution's membership should be reinstated and endorsement of the proposed parent institution will be required.

Definition of a Joint Center*:

A joint center consists of a Department of Radiation Oncology, which is located in more than one institution. Although each participating institution may have its own equipment and technical support, the physicians caring for patients in a joint center will be from a single group or faculty and will have privileges in all institutions that constitute the joint center. The joint center institution is covered under an Office for Human Research Protection (OHRP) Assurance. The radiation therapy facility must be approved by RTOG RT Quality Assurance.

*Note: The determination of a member as a joint center will be determined by review of the preliminary application.

Revised (10/02)

APPENDIX V

RADIATION THERAPY ONCOLOGY GROUP PROTOCOL GUIDELINES

Adherence to these instructions will result in faster protocol development. Contact the study statistician to confirm the study objectives (Section 2.0) and the statistical considerations (Section 13.0). A formatted RTOG Master protocol is available from Headquarters. Do not retype existing RTOG protocols - format deviations will cause protocol development delays. Submit a hard copy, as well as an e-mail copy, of the final document to the Protocol Office. All RTOG protocols will contain the information outlined in the following specifications. The information should appear in this order and be labeled according to the following criteria.

Title page: Will contain the following information.

- a. Full title (to include drug NSC number, if applicable)
- b. Study number assigned by RTOG Headquarters when study is received (1000 number) and changed to a year-sequence number when sent to NCI for approval prior to activation
- c. Study Chair name(s), telephone number(s), and fax number(s) for each modality
- d. Date activated (on final active version only).
- e. Date of current version

Index: 1.0 - 13.0 and Appendices

Schema: Will contain the following information:

- a. Stratification criteria.
- b. Arm(s) descriptions-radiotherapy (dose, fractions) chemotherapy (days, drug, dose, number of cycles).
- c. Eligible histology(s), stage(s), performance status.
- d. Diagram of treatment sequence (if applicable).
- e. Required Sample Size

Registration/Randomization Checklist: Will contain the following:

- a. Eligibility questions asked at time of patient entry.
- b. Stratification questions asked at time of patient entry.
- c. Demographic information.

1.0 Introduction: Should contain the history of the disease and current treatment. References to pertinent studies, and the rationale for the proposed modalities should also be presented.

2.0 Objectives: The questions to be answered by the study and the study end points will be stated.

3.0 Patient Selection:

Eligibility-specific laboratory values required at study entry should not be specified at values that exceed grade 0 toxicity level (CTC 2.0). The following information will be included:

3.1 Eligibility Criteria

- a. Histology, whether biopsy proof is required or cytologic or clinical evaluation is adequate.
- b. Sites

- c. Stage, most recent AJCC should be used; if AJCC not used, the system should be stated and included as an appendix. A statement should be made as to whether clinical or surgical staging is to be used.
- d. Age: The lower and upper (if necessary) limits should be stated.
- e. Karnofsky performance scale, the minimum value should be stated.
- f. Minimum and/or maximum laboratory values and other evaluations as applicable
 - Hematologic
 - Renal
 - Hepatic
 - Pulmonary
 - Cardiac
 - Neurologic (refer to appendix if needed)
 - Nutritional score (refer to appendix if needed)
 - Dental (refer to appendix if needed)
 - Other
- g. Informed consent requirements.

3.2 Ineligibility Criteria

- a. Prior treatment, radiotherapy, chemotherapy, surgery, other.
- b. Prior malignancy, indicate criteria for skin tumors (excluding melanoma) and other malignancies separately. If allowable, state disease-free interval.
- c. Hematologic, renal, hepatic, and other values, which preclude entry into study.

4.0 Pretreatment Evaluation:

Any mandatory pre-treatment assessment that is considered a requirement of eligibility must be included in the eligibility/ineligibility section of the protocol. **All** mandatory assessments are not routinely considered conditions of eligibility.

- a. History and physical.
- b. Diagram of lesion and nodes.
- c. Mandatory imaging studies and acceptable interval between study and patient entry.
- d. Mandatory laboratory studies and acceptable interval between study and patient entry.
- e. Other assessments such as dental & nutritional.

5.0 Registration and Randomization:

- a. Where and when to call.
- b. Information to provide at entry.
 - Patient's name.
 - Patient's identification or social security number.
 - The institution, and referring institution where applicable.
 - The person responsible for the eligibility reviews.
 - The medical oncologist's name where applicable.
 - Stratification criteria.
 - Eligibility criteria.
 - Demographics.

6.0 Radiation Therapy:

This section should contain a short paragraph outlining the relationship of each treatment to the other as well as the treatment sequence.

When radiation therapy is to be administered during treatment with another modality, “**concurrent treatment**”, the protocol must specify whether both modalities **MUST** or **NEED NOT** be administered on the same day. If the other (concurrent) modality cannot be given due to toxicity or technical reasons, the protocol must indicate whether radiation therapy **must be held or should proceed**.

If radiation therapy is to be **administered sequentially**, either preceding or following another modality, e.g. surgery, specify the minimum and maximum interval between the preceding modality and the **commencement** of radiation. When another modality is to follow radiation therapy, specify the minimum and maximum interval between the new treatment and the **completion** of radiation.

- a. Physical factors.
 - Equipment type
 - Energy
 - SSD
- b. Localization requirements
 - Simulation
 - Contrast material
 - CT scan/MRI
 - Port films
 - Verification films
 - Photographs
- c. Target volume, anatomically defined.
- d. Treatment planning requirements - External Beam.
 1. The general use of the words “should” and “shall” are understood to mean the following: “should indicates an advisory recommendation that is to be applied when practical and “shall” indicates a requirement of the protocol.
 2. The target volume (area) shall be described in terms of the patient's anatomy and physical dimensions. Please note that there may be several target areas.
 3. The maximum target dose is defined as the largest dose in the target volume (area) which is delivered to an area greater than 2 cm².
 4. The minimum target dose is the smallest dose delivered within the target volume (area).
 5. The specification of the target dose is in terms of a dose to a point at or near the center of the target volume.
 - I. Photon Beams - The following portal arrangements are specified:
 - a. For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
 - b. For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

- c. For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
- d. For a single beam: on the central ray at the center of the target area.
- e. For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.
- f. Other or complex treatment arrangements (excluding 3D-CRT): at the center of the target area (Note: there may be several target areas).

Comment: If the point of dose specification is the center of the target area, the protocol shall stipulate how the target area is determined clinically and how it is to be indicated on the treatment plan.

II. Electron Beams:

- a. The target dose shall be prescribed at the depth of maximum dose.
 - b. The energy and field size shall be chosen so that the target volume is encompassed within 90% (or other appropriate minimum dose) of the prescribed dose.
6. The allowed variation of dose across the target area shall be stated relative to the target dose.
7. The dose calculation point shall not be in a high dose gradient (e.g. within 2 cm of the edge of a photon field) and generally not in a blocked area. (several exceptions might be the cord dose under a cord block, or if a field reduction technique is used instead of compensators).
- e. Time/dose definitions and schedule, including the maximum and minimum doses in the treatment volume and acceptable variations to the fraction size and total dose to primary and nodal groups.
 - f. Modifications and toxicity criteria, maximum dose permissible to the critical structures.

7.0 Drug Therapy:

- a. Drug description, packaging and storage.
- b. How supplied.
- c. NSC# if it is an investigational drug ordered through NCI.
- d. Dose definition.
- e. Technique of administration.

If recommending or requiring a pre-treatment regimen, the protocol should indicate whether the investigator may or may not be permitted to substitute an institutional standard regimen.

- f. Duration of treatment.

When chemotherapy is to be given **concurrently** (during treatment with another modality), the protocol must specify whether **both** modalities **MUST** or **NEED NOT** be administered on the **same day**. For example, if chemotherapy, is given during radiation therapy and radiation cannot be given because of equipment failure, holiday, etc., must chemotherapy be held or may it be given?

If chemotherapy given in a concurrent chemo-radiation treatment plan is delayed and radiation is terminated or completed, the protocol should indicate whether or **NOT** the chemotherapy regimen should be completed. The protocol should also specify beyond what

point the chemotherapy should not be given, e.g., if the final course is delayed more than three weeks after completion of **radiotherapy**, treatment should be discontinued.

When chemotherapy is to be administered **sequentially**, either preceding or following another modality, a minimum and maximum interval between completion of the previous modality and the commencement of drug therapy must be specified in the protocol. When another modality succeeds chemotherapy, the minimum and maximum intervals between modalities should be specified.

- g. Toxicity, expected effects and approximate times that these effects will be seen.
Toxicity must be described using CTC Version 2.0 terminology, e.g. mucositis due to radiation v. stomatitis/pharyngitis.
Expected toxicity and severity grade may conflict with STANDARD NCI reporting guidelines. **To avoid unnecessary reporting**, the study chair should identify which adverse events and grades should be considered exemptions.
- h. Dose modification.
Modifications must be specified using grade levels and descriptions.
- i. Recommended maximum dose.
- j. Medical oncology quality control review procedures.
- k. Toxicity reporting requirements.

8.0 Surgery:

Death from any cause while the patient is receiving protocol treatment and up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management department within ten days of discovery.

Death from protocol surgery, regardless of the interval from surgery, must be reported by telephone to the RTOG Headquarters Data Management department within 10 days of discovery.

When surgery precedes registration, the maximum interval between surgery, registration and commencement of protocol treatment must be specified in the protocol. If the interval affects eligibility, this must be stated in the eligibility section of the protocol.

If protocol surgery is to be performed subsequent to another protocol modality, the maximum, minimum interval between the end of therapy and surgery must be specified.

If protocol surgery involves a site where “staged surgery” is commonly used, i.e., resection of the tumor is performed in more than one sequential procedure (Head & Neck – neck dissection performed subsequent to resection at the primary site; breast - re-resection of margins, the protocol should indicate the multiple sequential procedures are or ARE NOT acceptable. The timing intervals (registration, start of protocol treatment) should be included from the first or last procedure.

If details of surgery are specified, the protocol should include the requirements that will be considered “**unacceptable deviations**”.

- a. Staging procedures.
- b. Therapeutic procedures.
- c. Flaps and drainage.

- d. Surgical quality control review procedures. If no central quality control review state why.

9.0 Other Therapies:

Use of **preventive and supportive non-protocol treatment** may affect the assessment of protocol therapy and toxicity; e.g., G-CSF, amifostine, etc. Some agents have their own toxicity that may confound assessment of protocol effects. The protocol should specify whether and under what conditions such treatment may be administered, especially with regard to prophylactic use.

When possible, the protocol should specify what supportive therapy needs to be reported on the study data forms. To avoid unnecessary data collection, only treatment expected to affect the study objectives or to be addressed in analysis of the study endpoints should be specified for reporting.

10.0 Pathology:

- a. Preparation of submitted material
- b. Specify type of acceptable samples and fixation method.
- c. Specify if H&E or other staining of slides is required (i.e. mucin, keratin, etc.).
- d. Grading criteria - Specify grading scheme to be used. Give reference studies to be performed.
- e. Give reference studies to be performed.
- f. Fixed tissue bank requirements, are patients eligible for the Tumor Repository?
- g. Report previous other pathology studies, DNA, immunocytochemistry, etc.
- h. If central review is not required, state why.

11.0 Patient Assessments: Should contain the requirements for each assessment, e.g. primary tumor, nodal disease status, presence of metastatic diseases and radiation effects. The studies to be done and the follow-up times should also be graphically indicated in table form. Response criteria must also be listed.

12.0 Data Collection: This section should contain a list of all data items due, including treatment planning information, forms, pathology material and the specified times. This section should be in two columns, the left hand column indicating the data item, and the right hand indicating the time it is due after commencement of treatment.

13.0 Statistical Considerations: This section will be supplied by the study statistician and will include a discussion of the endpoint, the difference expected and the sample size required to detect this difference.

References

Appendices:

- Appendix I - Sample Consent Form
 - Appendix II - Karnofsky Performance Scale
 - Appendix III - Staging System
 - Appendix IV - Late Radiation Morbidity Scoring Scheme
 - Appendix V - Adverse Event Reporting Guidelines
- Other Appendices as needed:
- Diagram of Primary and/or Nodes

Implant Diagram
Neurologic Classification
Nutritional Assessment
Dental Assessment

APPENDIX VI

RTOG PROTOCOL CONCEPT SHEET

RTOG DEVELOPING PROTOCOL # _____

TITLE: _____

PHASE: ___I ___I/II ___II ___III ___Other

PARTICIPATION: ___Groupwide ___Limited, specify: ___ Managing Group _____

RESPONSIBLE COMMITTEE: _____

STUDY CHAIR: _____

SCHEMA:

S	R	R
T	A	E
R	N	G
A	D	o
T	O	r
I	M	I
F	I	S
Y	Z	T
	E	E
		R

OBJECTIVES:

PATIENT ELIGIBILITY:

PROTOCOL TREATMENT PLAN:

REQUIRED SAMPLE SIZE:

APPENDIX VII

ADVERSE DRUG REACTION REPORTING FORMS

Form A

DCT ADVERSE REACTION FORM FOR INVESTIGATIONAL AGENTS

Person Completing this Form _____ Date _____

Phone (____) _____

Physician Responsible for this Report _____

(Please print or type)

I. DEMOGRAPHICS

A. Patient Information

PT I.D.# _____ Age _____ Sex _____ Date of Initial Dx _____

Malignancy _____

Site of Primary _____ PS (at start of study) _____

Site(s) of Metastatic Disease _____

Concurrent Non-Malignant Disease and Non-Protocol Medications _____

B. Drug Information

Drug Name _____

Source of Drug: NCI _____ Other (specify) _____

Type of Reaction _____ Toxicity Grade _____

Date of Reaction _____ Date IRB Notified _____

NCI Protocol # _____ Attending Physician (Investigator) _____

Phase of Study _____ Institution _____ Phone (____) _____

Protocol Treatment (include all agents)

<u>Drug</u>	<u>Dose</u>	<u>Schedule</u>	<u>Route</u>
-------------	-------------	-----------------	--------------

Date First Course Started _____ Number of Courses _____

Date Last Course Started _____ Date of Therapy Associated with ADR _____

Prior Therapy (Drug, radiation, relevant surgery: Include dates of therapy)

II. DOCUMENTATION OF REACTION

A. Non-Myelosuppressive Toxicity and Previously Unknown Myelosuppression

1. Description of Reaction and Temporal Relationship to Investigational Drug Administration

2. Physical Findings and Laboratory Data (e.g., bilirubin, creatinine, including baseline, worst and recovery value) Documenting Toxicity

3. Treatment of Adverse Reaction

4. Past History of Organ Dysfunction

5. Rechallenge with Agent _____ No _____ Yes

If yes: _____ with reaction; describe _____
_____ without reaction

6. Patient outcome: _____ Recovered without sequelae
_____ Recovered with sequelae; describe _____
_____ Remains under treatment
_____ Died; From _____ ADR _____ Malignancy _____ Other _____
Autopsy date _____

B. Myelosuppression (Previously known or unknown)

1. Laboratory Data Documenting Myelosuppression

	<u>Baseline</u> Date/Value	<u>Nadir</u> Date/Value	<u>Recovery or Latest Value</u> Date/Value
WBC or PMN	_____/____	_____/____	_____/____
Platelets	_____/____	_____/____	_____/____
Hgb or Hct	_____/____	_____/____	_____/____

2. Complications, Treatment and Sequelae (e.g., infections/hemorrhage)

C. Grade of Toxicity and Reporting Requirements (Check one)

1. Previously Unknown Toxicities:
 - a. Fatal _____ or Life-threatening _____ (Report by telephone within 24 hours: 301-230-2330) Date _____
NCI contact _____
 - b. Grade I _____ II _____ III _____ (Send form within 10 days)
2. Previously Known Non-Myelosuppressive Toxicities:
 - a. Fatal _____ or Life-threatening _____ (Send form within 10 days)
3. Previously Known Myelosuppressive Toxicities:
 - a. Fatal _____ (Send form within 10 days)

Send Forms to: Investigational Drug Branch, NCI
Post Office Box 30012
Bethesda, Maryland 20824
FAX # 301-230-0159

D. Investigator's Assessment (If more than 1 investigational agent was used, give an assessment for each by writing the drug names on the appropriate lines.)

	IND Drug	Non-IND Drug	Disease	Action Taken:	Therapy Required:
Unrelated	_____	_____	_____	None _____	None _____
Unlikely	_____	_____	_____	Dose Reduced _____	Symptomatic _____
Possible	_____	_____	_____	Dose Withheld _____	Supportive _____
Probable	_____	_____	_____	Drug Discontinued _____	Intensive _____
Definite	_____	_____	_____		

E. I hereby certify that the information on this form is correct and complete to the best of my knowledge.

(Signature of Responsible Physician) M.D. _____
(Date)

Form B

TO VIEW OR PRINT A COPY OF THIS FORM LOG ON TO:

<http://www.rtog.org/members/forms/medwatch.pdf>

**Protection of Human Subjects
Assurance Identification/Certification/Declaration
(Common Federal Rule)**

POLICY: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting common rule (56FR28003), June 18, 1991) unless the activities are exempt from or approved in accordance with the common rule. See Section 101(b) the common rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional

Review Board (IRB) review and approval to the Department or Agency in accordance with the Common rule. Institutions with an assurance of compliance that covers the research to be conducted and should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency.

1. Request Type <input type="checkbox"/> Original <input type="checkbox"/> Followup <input type="checkbox"/> Exemption	2. Type of Mechanism <input type="checkbox"/> Grant <input type="checkbox"/> Contract <input type="checkbox"/> Fellowship <input type="checkbox"/> Cooperative Agreement <input type="checkbox"/> Other: _____	3. Name of Federal Department or Agency and, if known, Application or Proposal ID No.
---	---	---

4. Title of Application or Activity	5. Name of Principal Investigator/Program Director/Fellow/Other
-------------------------------------	---

6. Assurance Status of this Project (*Respond to one of the following*)

This Assurance, on file with the Department of Health and Human Services, covers this activity:
Assurance identification No. _____ IRB identification no. _____

This Assurance, on file with (*agency/dept.*) _____, covers this activity.
Assurance identification no. _____ IRB identification no. _____ (*if applicable*)

No assurance has been filed for this project. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph _____.

7. Certification of IRB Review (*Respond to one of the following IF you have an Assurance on file*)

This activity has been reviewed and approved by the IRB in accordance with the common rule and any other governing regulations or subparts on
(date) _____ by: Full IRB Review or Expedited Review.

If less than one year approval, provide expiration date _____

This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the common rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed and certification will be provided.	10. Name and Address of Institution
11. Phone No. (<i>with area code</i>) 12. Fax No. (<i>with area code</i>)	
13. Email:	
14. Name of Official	15. Title
16. Signature	17. Date

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APPENDIX VIII

RADIATION THERAPY ONCOLOGY GROUP (RTOG) DATA MONITORING COMMITTEE POLICY

STUDIES TO BE MONITORED

A single Data Monitoring Committee (DMC) will be established to monitor all phase III therapeutic clinical trials of the RTOG.

RESPONSIBILITIES

1. The primary responsibility of the DMC is to review interim analyses of outcome data (prepared by the study statistician) and toxicity data at times specified by the protocol and upon special request and to recommend whether the study needs to be changed or terminated based on these analyses. The committee also determines whether and to whom outcome results should be released prior to the reporting of study results at the time specified in the protocol.
2. The committee reviews major modifications to the study proposed by the study committee after activation (*e.g.*, termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size).

MEMBERSHIP

The RTOG has elected to establish an independent data monitoring committee consisting of six outside reviewers whose collective expertise is in the three treatment modalities, statistics, and ethics. *The RTOG Group Chair, RTOG Group Statistician, a NCI/CTEP appointed physician and a NCI/CTEP appointed statistician would serve as non-voting, ex-officio members of the DMC.* It is anticipated that outside expertise will be called upon in specific situations where required. Care will be taken to exclude anyone who might have a conflict of interest. The RTOG will follow the guidelines outlined in the American College of Radiology's "ACR Conflicts of Interest Statement" in obtaining outside expert reviewers. Experts from RTOG member institutions, except the study chair, will not be invited to participate in this exercise unless their contributions are considered to be unique. *The NCI/CTEP appointed physician and statistician will be free to attend all sessions both opened and closed executive sessions of the DMC.*

The Group Chair and Group Statistician will be present at the meetings of the DMC in order to clarify issues related to the Group's research strategy, experience and other subjects. They will be non-voting members of the DMC. In the event that either of them is named on a study under review, the Group chair will be replaced by the Deputy Chair, and the Group Statistician will be replaced by another RTOG Statistician.

MEETINGS

The DMC meetings will be held at least every six months, ordinarily immediately prior to the RTOG semi-annual meetings. The frequency of monitoring for a given study will be guided by the design of the study, which should clearly specify the planned interim analysis, including significance testing, in the protocol. Unplanned monitoring of a given study may be requested by the study chair, study statistician or disease committee chair. The DMC may also request that a study be reviewed. Data are

collected and analyzed about four weeks before the DMC meeting. A copy of all the analyses except for the efficacy results are mailed to the members seven to ten days before the meeting.

The review of each trial will include two parts. The first part will be an open session in which members of the study team and disease committee may participate either at their request or at the request of the DMC. The study chair/disease committee chair requesting review of the study by the DMC should provide the statistical office with a written report of their concerns to be distributed with other DMC materials. The statistician responsible for the study under review presents the analyses to the DMC. The efficacy results are shown on transparencies and blinded with respect to the treatment arm. The chair is present to make additional comments and answer any questions from the DMC. Following the open session there will be a closed executive session in which the DMC reviews interim outcome results by blinded treatment arm. At the closed executive session those present are limited to DMC members and the NCI/CTEP physician and NCI/CTEP statistician, who participate as non-voting members. All other ex-officio members are not permitted to attend the closed executive session.

RECOMMENDATIONS

The DMC will make its recommendations for each study to the Group Chair. Recommendations must be approved by a majority vote of the committee. These recommendations will be accepted unless the Group Chair disagrees, and then the issues will be discussed with the CTEP Director. The CTEP Director will be notified by the Group Chair of any decision to change or terminate the study.

CONFIDENTIALITY PROCEDURES

No communication of the deliberations or recommendations of the committee, either written or oral, should be made outside of the committee except as provided for in these policies and procedures. Outcome (efficacy) results are strictly confidential and should not be divulged to any non-member until the recommendation to report the results is accepted and implemented. No one will divulge the recommendations of the DMC until those recommendations are accepted.

RELEASE OF RESULTS

Any planned release of outcome data, either internal to the group, to NCI personnel not members of the committee, or external (e.g., paper presented at professional society meeting, seminars, papers, etc.) prior to the final approval of general dissemination of results as specified in the protocol must be reviewed and approved by the DMC.

CONFLICT OF INTEREST

Individuals invited to serve on the DMC will disclose to the Group Chair any potential real or perceived conflicts of interest. These will include professional interest, proprietary interest and miscellaneous interest considerations as described in the attached conflict of interest policy. The Group Chair, with the advice of an *ad hoc* committee, will review possible conflicts and determine whether there is sufficient basis to exclude the individual from serving on the DMC. Potential conflicts, which develop during the conduct of a trial, or during tenure on the DMC, should also be disclosed to the Group Chair for appropriate review.

INTERGROUP STUDIES

These guidelines will apply to intergroup studies where RTOG is the coordinating group.

APPENDIX VIII

**AMERICAN COLLEGE OF RADIOLOGY
PROCEDURES FOR INVESTIGATING AND REPORTING
POSSIBLE MISCONDUCT IN SCIENCE**

The following are the policies and procedures which are to be followed by the American College of Radiology (ACR) for investigating and reporting possible misconduct involving research or research training, applications for support of research or research training, or related activities that are supported with funds made available under the Public Health Service Act. The policies and procedures are adopted pursuant to the requirements of 42 CFR 50.101 et seq.

1. The ACR will inquire immediately into an allegation or other evidence of possible fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. An inquiry is not required for honest error or honest differences in interpretations or judgments of data. The inquiry must be completed within sixty (60) calendar days of its initiation unless circumstances clearly warrant a longer period. A written report shall be prepared stating what evidence was reviewed, summarizing relevant interviews, and including conclusions of the inquiry. The individual(s) against whom the allegation was made shall be given a copy of the report of the inquiry. If the individual(s) comments on that report, their comments may be made part of the record. If the inquiry takes longer than sixty (60) days to complete, the record of the inquiry shall include documentation of the reasons for exceeding the sixty-day period.
2. The ACR will seek to protect, to the maximum extent possible, the privacy of those who in good faith report apparent misconduct in science.
3. The individuals against whom the allegation was made shall be afforded confidential treatment to the maximum extent possible. The individual(s) shall also be afforded a prompt and thorough investigation, and an opportunity to comment on allegations and findings of the inquiry and/or investigation.
4. The College will notify the director of the Office of Scientific Integrity (ORI)¹ when, on the basis of the initial inquiry, the College determines that an investigation is warranted. The director of ORI will also be notified prior to a decision to initiate an investigation if any of the following conditions exist:
 - (a) there is an immediate health hazard involved;
 - (b) there is an immediate need to protect Federal funds or equipment;
 - (c) there is an immediate need to protect the interests of the person(s) making the allegation or of the individual(s) who is the subject of the allegations as well as his/her co-investigators and associates, if any;
 - (d) it is probable that the alleged incident is going to be reported publicly.

¹Pursuant to 42 U.S.C. § 289(b) the Office of Scientific Integrity was placed under the jurisdiction of PHS and renamed the Office of Research Integrity (hereinafter "ORI").

5. The College will notify the ORI within 24 hours of obtaining any reasonable indication of possible criminal violations, so that ORI may then immediately notify the Office of Inspector General of the Department of Health and Human Services.
6. Sufficient detailed documentation will be maintained of inquiries to permit a later assessment of the reasons for determining that an investigation was not warranted, if necessary. These records will be maintained in a secure manner for a period of at least three years after the termination of the inquiry, and shall be provided to authorized HHS personnel, if requested by them.
7. The College will undertake an investigation within thirty (30) days of the completion of the inquiry, if findings from that inquiry provide sufficient basis for conducting an investigation. The investigation normally will include examination of all documentation, including but not necessarily limited to, relevant research data and proposals, publications, correspondence, and memoranda of telephone calls. Whenever possible, interviews will be conducted of all individuals involved either in making the allegation or against whom the allegation is made, as well as other individuals who might have information regarding key aspects of the allegations; complete summaries of these interviews should be prepared, provided to the interviewed party for comment or revision, and included as part of the investigator file.
8. The College will secure the necessary and appropriate expertise to carry out a thorough and authoritative evaluation of the relevant evidence in any inquiry or investigation.
9. Precautions will be taken against real or apparent conflicts of interest on the part of those involved in the inquiry or investigation.
10. The ACR will prepare and maintain documentation to substantiate the investigation's findings. This document shall be made available to the director of ORI who will decide whether the office will either proceed with its own investigation or will act on the ACR's findings.
11. The College will take interim administrative actions, as appropriate, to protect Federal funds and insure that the purposes of the Federal financial assistance are carried out.
12. ACR will keep the ORI apprised of any developments during the course of the investigation which disclose facts that may affect current or potential Department of Health and Human Services funding for the individual(s) under investigation or that the PHS needs to know to ensure appropriate use of Federal funds and otherwise protect the public interest.
13. The College will undertake diligent efforts, as appropriate, to restore the reputations of persons alleged to have engaged in misconduct when allegations are not confirmed, and also undertaking diligent efforts to protect the positions and reputations of those persons, who in good faith, make allegations.
14. The ACR will impose appropriate sanctions on individuals when the allegation of misconduct has been substantiated.
15. The College will notify the ORI of the final outcome of the investigation.

Revised October 1994

APPENDIX X AMERICAN COLLEGE OF RADIOLOGY CONFLICTS OF INTEREST

The American College of Radiology depends to a great extent on the knowledge, expertise, and efforts of members who volunteer their services, and it is desirable that as many members as possible participate in its activities. The confidence that members of the profession and the public have in radiology and radiologists depends on the integrity of those who represent the College.

Chancellors, officers, committee or commission members, staff, volunteers, and all others representing or acting on behalf of the American College of Radiology should avoid conflicts of interest or the appearance of conflicts of interest. All decisions and actions considered or made by such individuals should be based solely on the best interests of the College and in accordance with applicable federal, state, and local laws and regulations. Personal considerations should not be a factor in any action or decision made on behalf of the American College of Radiology.

What Is a Conflict of Interest?

A conflict of interest occurs whenever an individual or a member of his or her immediate family has a direct or indirect interest or relationship, financial or otherwise, that may conflict or be inconsistent with the individual's duties, responsibilities, or exercise of independent judgment in any transaction or matter involving the College.

A conflict of interest does not necessarily imply that an individual is ineligible to serve on a College committee, commission, or task force or cannot represent the College in a specific situation, but it may indicate that participation in some matters should be avoided or limited. Questions relating to whether a conflict might arise should be referred to the chair of the Board of Chancellors or the College's executive director.

Reporting Conflicts of Interest

If an individual has an actual or potential conflict of interest relating to business or transactions before the College, he or she should immediately notify the chair of his or her commission, committee, or task force or the chair of the Board of Chancellors *and* the executive director of the College. Members of the College's staff should disclose potential or actual conflicts of interests to the executive director. The executive director should disclose his own conflicts of interest to the chair of the Board of Chancellors. In making the disclosure, the individual should reveal all material facts about the conflict of interest and explain his or her relationship to the transaction or matter at issue. In some circumstances, full disclosure of the conflict may in itself be sufficient to ensure the integrity of College operations.

If a conflict of interest arises in connection with the activities of a deliberative body, such as a commission, committee, or the Board of Chancellors, the conflict should be disclosed to the other members of the body and the individual should not participate in the consideration of the matter at issue. Any withdrawal by a member of a commission, committee, or task force and the reasons for it should be recorded in the minutes of the meeting. Councilors and alternate councilors with a conflict of interest relating to a policy matter before the Council may participate in de-bate on that issue after disclosing the conflict to the Council but should refrain from voting.

When a conflict arises from an individual's presentation or participation in a seminar, workshop, or other such event, or in connection with an individual's contributions to a College publication, the facts

giving rise to the conflict should be disclosed to other participants, attendees, or readers and the individual should clearly identify his or her statements or contributions as personal opinions.

**AMERICAN COLLEGE OF RADIOLOGY
CLINICAL RESEARCH CONFLICTS OF INTEREST
DISCLOSURE STATEMENT**

A conflict of interest may be considered to exist if an investigator is affiliated with, or has a financial interest in, commercial organizations that may have a direct or indirect interest in the research being conducted by the RTOG. A “financial interest” may include, but is not limited to, being a shareholder in the organization; being on retainer with the organization; or having research or honoraria paid by the organization. An “affiliation” may be holding a position on an advisory committee or some other role of benefit to a sponsoring organization.

The intent of this disclosure requirement is not to prevent a researcher with a conflict of interest from participating in the research study but to make known the relationship to the RTOG so the conflict can be evaluated and managed.

Please check those which apply:

_____ I do not have a financial interest, arrangement, or affiliation with a commercial organization that may have a direct or indirect interest in the clinical research study being conducted by the RTOG.

_____ I have a financial interest, arrangement, or affiliation with a commercial organization that may have a direct or indirect interest in the clinical research study being conducted by the RTOG, as described below.

Failure to report a conflict of interest could result in the imposition of administrative sanctions. Such sanctions may include oral admonishment, written reprimand, notification to the appropriate institutional official, suspension or termination from participation in the RTOG.

Name

Signature

Execution of this statement is a requirement of your participation in the RTOG. Return this form to: Thomas Wudarski, Administrative Director for Clinical Trials, 1818 Market Street, Suite 1600 Philadelphia, PA 19103.

APPENDIX XI

RTOG AFFIRMATION OF THE INTEGRITY OF RESEARCH DATA

1. I am either (1) a principal investigator at a member institution of the RTOG; (2) an RTOG vice-chair, committee chair or subcommittee chair; (3) a study chair, or (4) a consultant to the RTOG.
2. I recognize that the clinical research of the RTOG is a publicly supported endeavor that is critically dependent upon the trust of the American people. Scientific misconduct is scientifically abhorrent and cannot be tolerated because it can destroy the public trust that is necessary for successful clinical research. Submission of falsified data is a form of scientific misconduct.
3. I have received a copy of the ACR's policy on Scientific Misconduct. I have read this policy, understand it, and agree to abide by it.
4. I recognize that the penalty for submission of falsified data may include debarment from federal grant projects, including cooperative group activities, exclusion from federal advisory boards, repayment of federal grant funds or any other appropriate remedy.
5. If I suspect falsified data is being submitted, or has been submitted from my institution, I understand that I must immediately bring the matter to the attention of the Group Chair.

I declare under penalty of perjury that the foregoing is true and correct. 28 U.S.C. § 1746.

(Name)

(Date)

(Institution)