Manual of Operations
For RTOG Foundation Trials

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I. INTRODUCTION

A. History

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

As an NCI-funded cooperative group, the Group activated over 500 protocols, accrued more than 110,000 patients to cooperative group studies, and published over 1,000 papers reporting the results of its findings. The Group was the leading multicenter research organization systematically testing novel radiotherapy approaches against cancer and pursuing fully integrated translational research to support and further this effort. The Group's research was directed towards evaluating new evidence-based approaches to patients with solid tumors of the brain, upper aero digestive tract (head and neck), lung, gastrointestinal system, and genitourinary tract (prostate and bladder) with focused efforts directed within the working groups in breast cancer, gynecologic cancer, sarcoma, and symptom management.

RTOG Foundation, Inc. (RTOG or Foundation)

The RTOG Foundation had its origins in 1997 when the RTOG Fund under the auspicious of the American College of Radiology, the grant holder for the Group, was created for the purpose of receiving and allocating corporate and private donations to allow the Group to sustain and expand important activities critical to its research mission. In August 2013 the RTOG Foundation incorporated as a non-profit foundation in the Commonwealth of Pennsylvania and in July 2014 RTOG Foundation, Inc. received its 501(c)(3) non-profit status from the Internal Revenue Service.

The RTOG Foundation continues the NCI-funded research of the Radiation Therapy Oncology Group through its membership in NRG Oncology. In addition, it has developed a portfolio of industry-funded research partnerships that seek to further our understanding of effective therapies to improve the survival and quality of life of patients with cancer.

RTOG Foundation has maintained its relationships with the core members from the legacy Radiation Therapy Oncology Group and is able to access new members through its membership in NRG Oncology. Today RTOG is a dynamic multidisciplinary research organization with vigorous participation by physicians and other investigators at many of NCI's designated cancer centers, major community centers, and the major academic and regional centers of Canada. RTOG also has a strong international presence with access to sites on four continents. This participation includes leadership from medical oncologists, surgical oncologists, pathologists, and laboratory scientists as well radiation oncologists.

The RTOG Foundation Operations and Statistics & Data Management Centers continue to be located at the offices of the American College of Radiology in Philadelphia, PA.

NRG Oncology (NRG)

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

NRG became the successor LPO for RTOG's NCI-funded treatment protocols as of March 2014. NRG is a collaborative venture of the RTOG, GOG and NSABP Foundations, formerly the Radiation Therapy Oncology Group, the Gynecologic Oncology Group (GOG), and the National Surgical Breast and Bowel Project (NSABP).

This manual details how RTOG Foundation research is conducted. It is also important to note that research conducted by the RTOG Foundation is outside of the NCI pathway and does not utilize any of the NCI infrastructures.

B. RTOG Foundation Objectives

1. Improve the survival outcome and quality of life of adults with cancer through the conduct of high-quality clinical trials.
2. Evaluate new forms of radiotherapy delivery and test new systemic and targeted therapies in conjunction with radiotherapy in the context of clinical research.
3. Participate as one of three member organizations in the activities of NRG Oncology Foundation.
4. Develop and conduct practice-changing clinical trials for the NCTN through RTOG Foundation's membership in NRG Oncology.
5. Develop and conduct industry-supported clinical trials that are important to RTOG Foundation's research mission.
6. Provide funding for basic, clinical, and translational investigators to collaborate with RTOG Foundation in the development of both biologic and biophysical targeted therapies.
7. Support young investigators from many disciplines within the Foundation research enterprise through fellowships, travel awards, and access to educational and research opportunities.

II. RTOG FOUNDATION ORGANIZATION

OVERVIEW

RTOG Foundation, Inc. is governed by Bylaws that have been approved and adopted by the Foundation Board of Directors.

The Foundation is administered by the Board of Directors with input from members of the Advisory Committee.

RTOG Foundation has standardized site selection and performance criteria, which are applied to all sites participating in Foundation research. Publication, scientific misconduct, and conflict of interest policies and guidelines have also been adopted.

TRIAL-RELATED RESPONSIBILITIES

The RTOG Foundation engages with industry collaborators in a variety of ways to provide support for its research mission. In most instances the Foundation secures support from a collaborator to allow RTOG Foundation to serve as sponsor of a clinical trial furthering the Foundation's research objectives. When RTOG Foundation is the sponsor of a clinical trial it is responsible for all trial-related activities including design of the study; obtaining FDA and IRB approval; contracting with the participating sites; ensuring that all regulatory requirements are met; enrolling patients; collecting and reviewing the study data; and analyzing and reporting the results. At other times RTOG Foundation works with a sponsor collaborator and in those instances the Foundation is responsible for a subset of the trial-related activates (i.e., radiation therapy site credentialing, treatment plan reviews, results analysis for publication, etc.) and the collaborator is responsible for the overall conduct of the study.

This Operations Manual is written from the perspective that RTOG Foundation is the trial sponsor and responsible for all trial-related activities. If the Foundation is responsible for a subset of the trial-related for a study it will work with the collaborator to define its study-specific tasks, responsibilities, and procedures.

MEMBERS OF THE BOARD

1. Chair

The Chair of the RTOG Foundation Board of Directors provides scientific and administrative leadership for the Foundation. This includes chairing the Board of Directors meetings and co-chairing the RTOG Foundation Advisory Committee meetings. The Chair works closely with Headquarters staff to develop and achieve the Foundation's goals.

2. Board of Directors

The RTOG Foundation Board consists of at least nine members who are representative of the Foundation's research interests. The Board is responsible for setting RTOG Foundation's mission and goals and allocating the resources to accomplish these goals.

3. Board President

The Board President assists the Chair, Headquarters staff and participating investigators in the development and monitoring of protocols, data collection and publications. At the request of Headquarters, the Board President resolves questions concerning patient eligibility, morbidity scoring, and quality control procedures. The Board President represents the Chair at various meetings in their absence.

ADVISORY COMMITTEE

The Advisory Committee meets at least annually to discuss the Foundation's ongoing and future research projects and provide input to the Board about the state of the science and new research opportunities.

HEADQUARTERS

The RTOG Foundation Headquarters is based in the Philadelphia Office of the American College of Radiology (ACR) under the scientific direction of the RTOG Foundation Board of Directors through the Chair of the Board. RTOG Foundation staff may also provide support for NRG Oncology projects. Day-to-day Foundation operations are administered by the Senior Directors of Clinical Trials, Radiation Oncology Services, and Statistics and Data Management. They are assisted by the Directors of Protocol Development and Regulatory Compliance, Clinical Research Administration, Statistics, Data Management, and Radiation Therapy Quality Assurance. The RTOG Foundation Headquarters is organized in three functional areas: 1) Clinical Trials Operations; 2) Statistics and Data Management, and 3) Radiation Oncology Services. Within the three functional areas are five departments.

1. Clinical Trials Administration

The Clinical Trials Administration Department is responsible for assisting in the fiscal management of the Foundation and coordination of the site participation, project management, publication, communications, and data and specimen request processes. This includes: developing budgets and contracts for support of the Foundation's work by government and non-governmental entities; coordination of communications with industry partners; evaluation of new and active participating member sites; maintaining the Foundation site roster and per case reimbursement systems; coordination of the RTOG.org website; coordination of the submission process of Foundation research for presentation or publication and maintenance of the Foundation publication database; and management of the operational requirements for developing, implementing and managing RTOG Foundation programs and projects.

2. Protocol Development and Regulatory Compliance

The Protocol Development & Regulatory Compliance (PDRC) Department is responsible for the oversight of protocol development, and regulatory management of clinical trials. This includes management of the monitoring/ auditing program for trials conducted by RTOG Foundation.

Responsibilities also include registration of patients to studies, working with Canadian and Rest of World (ROW) member sites to facilitate their participation in protocol activities, working with collaborating partners to facilitate procurement and distribution of investigational agents, submission of applications to regulatory authorities, working with member sites to ensure compliance with all mandated regulatory requirements, coordination of adverse event reporting for investigational agents, and management of the audit/monitoring program.

3. Radiation Therapy Quality Assurance (RT QA)

RTOG Foundation has quality assurance monitoring procedures for each radiation therapy treatment modality. The department is responsible for:

- protocol review in conjunction with the study team,
- credentialing for advanced technologies,
- using web-based software tools to analyze and prepare cases for RT quality assurance reviews by the study chairs/investigators.

The RT QA team establishes RT QA standards, provides data management and analysis for RT treatment data and reports on technical and clinical aspects of Foundation trials. The RT QA team also provides education and research in clinical trial support. The RT QA group consists of experienced professionals including medical physicists, dosimetrists and technical support staff.

4. Statistics

The Statistics Department is involved in all research activities of the RTOG Foundation. RTOG Foundation statisticians are directly responsible for providing the assigned statistical aspects of a given RTOG Foundation trial, such as statistical support and oversight from trial design through study publication for RTOG Foundation research. Depending upon the study-specific contractual requirements the statisticians collaborate with the study chairs in the design of protocols, developing stratification schemes, setting randomization allocation, monitoring accrual and toxicity, and creating formal interim analysis plans and detailed final analysis plans for all study objectives.

For RTOG Foundation studies that are monitored by the Statistics Department, the statisticians prepare the required statistical study reports of accrual and adverse events for trials open to new patient entry or in follow-up prior to publication of the primary endpoint on a semiannual basis. Protocol-specified endpoint interim analysis reports are prepared as required.

After a study has accrued the required number of patients and met the requirements for primary endpoint analysis, a detailed statistical analysis report is prepared for use in presentations at scientific meetings and in publications in peer-reviewed journals regarding treatment results. Statisticians also provide the analysis report for protocol-specified secondary endpoints beyond efficacy, for example quality of life, translational science, etc.

5. Data Management

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

RTOG Foundation data managers are assigned to study teams and a data manager is assigned as the study coordinator for each new concept approved by the RTOG Foundation Board. After study activation, eligibility, treatment compliance, disease response, toxicity, quality of data and data submission are a few of the areas monitored for each case. This monitoring requires frequent interaction with study chairs, statisticians, dosimetrists, and administrative staff. Periodic reviews by the appropriate study chairs are conducted in which data are examined and institutional compliance with respect to treatment delivery is assessed. The modality reviews of

medical oncology, surgery and other systemic agents are initiated and prepared by the RTOG Foundation data manager

The RTOG Foundation data manager is the primary contact at the SDMC with regard to data collection and the clinical aspects of protocols. Management of questions concerning eligibility, treatment, data reporting, adverse events, protocol interpretation, and forms completion are examples of departmental responsibilities.

III. PARTICIPATION FOR RTOG FOUNDATION SPONSORED STUDIES

A. INSTITUTION QUALIFICATION PROCESS

RTOG Foundation invites sites to participate in its research on a study-by-study basis. Institutions wishing to participate in an RTOG Foundation protocol should send an email to RTOGINFO@acr.org and include the name of the trial of interest in the email. If participation slots are available, the study project manager will send the site a feasibility questionnaire. Completed questionnaires are reviewed by the study project manager according to Foundation and study-specific criteria and sites re informed of the review outcome. Past performance of the institution including accrual to similar studies, data quality, submission timeliness, and audit and/or monitoring results are considered during the review.

Sites must sign a master service purchase agreement (MSPA) with RTOG Foundation that serves as the master contract for all Foundation study participation activities. Study-specific statements of work (SOWs) are executed for each study that the site is approved to participate in. Sites that do not have an MPSA executed with RTOG Foundation or have not received an MPSA and are interested in Foundation study participation should contact the RTOG Foundation Membership Associate (RTOG-Membership@acr.org) and one will be sent.

Each institution must designate an institutional principal investigator (PI) who has overall responsibility for the institution's conduct in Foundation protocols. The institution must also name a study-specific PI (SPI) who will direct the site's efforts for an individual protocol. The PI and SPI may be the same individual. The site must also name a lead research associate (LRA), and if appropriate a study-specific LRA, as the primary contact for all data management concerns for the institution's participation in a specific protocol.

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

Canadian and ROW sites are also eligible for participation in select Foundation trials and follow the same procedures for site qualification and review as US sites. Please contact RTOGINFO@acr.org as indicated on the website for additional information.

B. CONTINUING PARTICIPATION CRITERIA AND EVALUATION

Site participation in each study will be continually reviewed by the study-team. In addition, sites may also be reviewed for their participation across studies. The evaluation is based upon the prior calendar year for patient accrual, forms submission, data quality, monitoring reports, and the audit results.

Physics Requirements for Group Participation

To participate in RTOG Foundation trials involving radiation therapy, the participating institution must agree to be monitored by the MD Anderson Dosimetry Lab (MDADL), which serves as a resource to the Foundation for evaluating the accuracy of the delivered dose from any treatment equipment that is used by each participating institution for the treatment of all protocol patients by irradiating an antimorphic phantom All RTOG Foundation participating sites are required to participate in the MDADL ongoing optically stimulated luminescent dosimeter (OSLD) program which functions as an interim check mechanism for the accuracy of the institutional machine calibration.

Data Submission and Timeliness

All institutions are required to submit complete, accurate, and timely data for all study patients according to the calendar created for each patient registered/randomized to an RTOG Foundation study. Site compliance with the protocol data submission requirements will be continually reviewed on a study-by-study basis by the study team and appropriate actions will be taken if these requirements are not met. In order to be approved for participation in new RTOG Foundation studies the institution must maintain adequate data submission compliance.

C. CASE REIMBURSEMENT

The RTOG Foundation reimburses participating sites according to the payment schedule found in the study-specific statement of work (SOW) executed for each institution participating in a Foundation study.

IV. STUDY PARTICIPATION REQUIREMENTS

A. SITE & INVESTIGATOR RESPONSIBILITIES

Participating institutions are required to comply with the terms of the MPSA and study specific SOW. Sites must also comply with the qualification process outlined in Section III and must provide a list of the key personnel assigned to the study, especially the name of the person responsible for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet Health Insurance Portability and Accountability Act (HIPAA) standards. The general responsibilities for each participating institution will be outlined within each study-specific guide but key elements are summarized below.

The site investigator must adhere to the procedures of their clinical site and the RTOG Foundation procedures for the conduct of clinical research by:

- Meeting the record keeping policies of the clinical site
- Making certain that each protocol has the full approval of an authorized Institutional Review Board (IRB) prior to involvement of human subjects
- Making certain that each patient signs and is given a copy of the IRB-approved consent form. The consent forms should be maintained on file by the investigator.
- Complying with Foundation and FDA policies concerning essential document collection. For example,
    - Filing a signed FDA Form 1572, a signed Financial Disclosure Form, and CV with RTOG Foundation
    - Observing institutional policy and procedures for the proper and secure storage of study agents, including maintaining Agent Accountability Records.
- Informing the Foundation of any change in study personnel as detailed in Section III.A.
- Agreeing that primary medical records of patients may be monitored and/or audited in accordance with the policies of the clinical site, RTOG Foundation, and FDA.

B. SITE IRB APPROVALS

Initial Approval

Before an institution may participate in an RTOG Foundation study, the institution's IRB, Ethics Board or an approved study-specific central IRB must review and approve the protocol. All sites must submit certification of that approval to the RTOG Foundation. International non-English speaking institutions must send their Ethics Committees' regulatory documents in English.

In a multi-center arrangement, the primary institution identified with an RTOG Foundation participation number is responsible for maintaining a record of IRB approvals for each center associated with it for Foundation participation. 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.

Amendment Approval

All protocol amendments must obtain IRB approval within 90 days of the broadcast and posting of the amendment to the website before being implemented at the site, unless, otherwise specified. All amendment approvals must be submitted to the RTOG Foundation.

Renewal / Continuing Review

Federal regulations stipulate that all clinical research protocols must be IRB reviewed / approved at least once per year during the data collection phase. Individual investigators are responsible for tracking their protocol IRB expiration dates and submitting for annual IRB review. All annual renewals must be submitted to the RTOG Foundation.

If a protocol is not IRB reviewed and approved prior to the IRB approval expiration date, it will be considered a deviation with federal regulations and will result in temporary closure of the trial at the site until the annual approval is obtained.

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

C. FOREIGN LANGUAGE / TRANSLATION REQUIREMENTS

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

Case Report Forms (CRFs) may be translated into a local language for completion by site investigators and staff. The institution is responsible for all translation costs. Certification of the translation is optimal but due to the prohibitive costs involved, RTOG Foundation will accept, at a minimum, a verified translation. A **verified CRF translation** consists of the actual data form in English and in the native language, along with a cover letter on organizational or letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third-party translator must be specified as well. ***Note that Patient Reported Outcome (PRO) measures, neurocognitive functioning (NCF) testing, and other validated and/or trademarked tools may not be translated. PROs may or may not be available in other languages and if so will be study specific.***

V. SPONSOR RESPONSIBILITIES FOR RTOG FOUNDATION

OVERVIEW

The various types of studies undertaken by RTOG Foundation to evaluate new treatments are best defined in terms of the objectives. All clinical trial designs should be based on sound statistical principles. Issues such as sample size, stopping rules, endpoints, and the feasibility of relating endpoints to objectives are pivotal to a successful trial. The RTOG Foundation can design and conduct Phase I, II and III clinical trials.

A. PROTOCOL DEVELOPMENT & ADMINISTRATION

All protocols are reviewed and approved by the Foundation Board of Directors and the collaborating partner including any regulatory agency prior to activation. A procedure has been designed by Headquarters to assist the Foundation investigators in the development, review, and activation of an approved protocol. This procedure consists of 1) concept development review and approval; 2) protocol development, review and

approval; 3) protocol activation; 4) processing protocol amendments; and lastly 5) management of the protocol website.

1. Concept Development, Review and Approval

Prior to writing a full draft of a protocol, an investigator must present the idea to the members of the Board. The proposed study will be examined in relation to the overall goals of the Foundation's current research strategy.

To assess if the Foundation has sufficient patient resources and interest to complete the proposed study in a timely fashion, the study chair, with support from the disease site chair, presents the concept to the Board. If the Board decides to proceed, the study chair in conjunction with the protocol associate and corporate liaison are charged with developing the concept for submission to collaborating partner.

2. Protocol Development, Review and Approval

Upon collaborating partner approval of the concept, the study chair writes a draft of the protocol, according to the directions embedded in the Foundation Protocol Template with input from the study team and submits it to Headquarters. Study co-chairs are assigned according to guidelines found below in Section B.1. The protocol associate initiates circulation of the protocol based on the timeline required for the respective protocol submission, edits the study chair's draft protocol, and begins the review process. The protocol associate refers discrepancies, ambiguities, or unclear instructions to the relevant modality study chair for resolution. Failure to resolve problem issues in a timely fashion may delay protocol activation. The study team is comprised of:

a. Protocol Development

The protocol associate (PA) ensures that the protocol and consent are in the proper format and contains all necessary information and documentation. The PA also works with the internal study team to verify that the administrative procedures are consistent with established RTOG Foundation policy and that text reflects current federal- and collaborator-provided language. The consent form is reviewed to make sure that the document contains all required elements, as mandated by federal policy. The PA maintains version control of the master protocol and consent documents across all reviewer circulations.

b. Statistics

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

c. Data Management

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

d. Radiation Therapy Quality Assurance (RTQA)

RTOG Foundation RTQA staff and medical physics team members review the radiation oncology component of each developing protocol to ensure the clarity, consistency, and accuracy of the protocol's treatment specifications. The MD Anderson Dosimetry Lab (MDADL) reviews each protocol to ensure inclusion of the appropriate credentialing processes. 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 Foundation 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.

e. Clinical Trial Management

The study project manager (PM) reviews the final draft of the protocol documents and is responsible for the overall coordination and management of the study from development, through implementation to closeout and analysis and final reporting. The PM works closely with the other study team members to develop study documents for site initiation and maintains the study documents throughout the life cycle of the study. The PM tracks site documentation and is the primary point of contact for the study between sites, Headquarters, and the study chairs. The PM organizes the team operational meetings to determine timelines and logistics. This includes developing agendas and ensuring minutes are taken and distributed.

3. Protocol Activation

Once RTOG Foundation receives all regulatory approvals (IRB and/or FDA) of the trial, the Board Chair and collaborating partner provide protocol sign-off. The study

project manager ensures that all administrative procedures and tools are in place for protocol activation. The study is made available to the selected sites on the RTOG.org website for IRB review. Sites must submit all required documentation to Headquarters in order to begin patient enrollment.

4. Processing Protocol Amendments

The PA coordinates all changes to active studies. The study chair/team submits all amendments to the PA in writing. The PA circulates these amendments to the study team members and, via the PM to the collaborating partner for review and approval. Following approval by the contracted IRB, amendments are released to participating sites and posted on the RTOG.org website. Participating sites are notified of protocol amendments and status changes (e.g., temporary closures for routine toxicity evaluation) by broadcast.

An institution may not make institution-specific changes to an RTOG Foundation-approved protocol or consent without prior approval of Headquarters.

5. RTOG Foundation Website

All RTOG Foundation-coordinated protocols are posted to the website www.rtog.org. This information is password protected and available only to sites participating in each specific protocol. Additional protocol information includes site-relevant information such as updates (activations, closure, meetings, etc.), study summary reports, safety reports, adverse event reporting guidelines, investigator brochures, and CRFs. A history of prior protocol versions and amendment summaries is also available.

B. STUDY CHAIRS

1. Assignment of Study Chairs

- Each protocol will have one principal investigator or study chair who is responsible for the development, conduct, and initial analysis of the protocol.
- A co-chair will be appointed for each protocol-specific treatment modality that is not represented by the chair. All modality chairs will be required to review and sign a modality-specific Roles and Responsibilities Form in the protocol development phase.
- If a central review is planned for the study, the appropriate co-chair(s) will be named (e.g., radiation oncologist, medical physicist, medical oncologist, surgical oncologist, pathologist and/or proton investigator.) If the study allows the use of protons, then a proton co-chair must be named.
- If translational research is planned, a translational science co-chair will be identified.
- If quality of life and neurocognitive function are part of the protocol, co-chairs for those sections will be named.
- Other study chairs may be appointed to assist with modality reviews as well as additional correlative studies not mentioned above.

2. Study Principal Investigator Responsibilities

The study principal investigator (PI) of an RTOG Foundation clinical trial assumes certain responsibilities in addition to those of the site participating investigator. Specifically, these include:

- Writing the protocol document
- Assuring that necessary approvals are obtained, including those of the IRB and other regulatory agency, the collaborating partner, and any others for the protocol and subsequent amendments
- Restrict patient entries to those fitting the eligibility criteria in each protocol. Requests for exceptions to these requirements are not permitted. Changes to eligibility must be done through a protocol amendment.
- Collaborate with statistics, protocol development, project management, data management, and RTQA staff, including close collaboration with the study statisticians during the development of the study and during the preparation of interim and final study reports. Ongoing collaboration with the project management, data management and RTQA staff is needed during the accrual and follow-up phase of the study to identify any problems with treatment delivery, toxicity, data collection, or monitoring.
- Prepare an abstract and/or a manuscript reporting the final results of the study.

C. OTHER SPONSOR RESPONSIBILITIES

In addition to the oversight of contractual obligations with sites/collaborating partners, and the scientific and protocol development involved in planning and conducting clinical research, the RTOG Foundation has additional responsibilities as a sponsor which may include but are not limited to:

- Sponsorship of Investigational New Drug Applications (INDs) including centralized agent procurement, accountability and storage, when applicable
- Project management
- Provide centralized IRB for a study, when applicable
- Provide central registration/randomization
- Provide central data management including
    - Modality reviews
- Unblinding procedure for placebo-controlled (blinded) studies
- Biospecimen banking
- Adverse event reporting
- Quality Assurance/Quality Control Program
- Statistics

These are explained further in the following sections.

VI. SPONSORSHIP OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS)

The IND is the official record at the Food and Drug Administration (FDA) of the sponsor's clinical research with the agent. Under FDA regulation, RTOG Foundation, as sponsor, submits and maintains all information concerning the agent’s clinical use, including all protocol amendments, adverse events, and an annual report on all clinical trials and any new relevant preclinical (particularly toxicological) or manufacturing data. This means that no one is permitted to use an investigational agent without the IND sponsor’s

knowledge and prior approval.

After a sponsor submits an IND, FDA has 30 days to complete its review. Please note all correspondence is between the industry collaborator, RTOG Foundation and the FDA.

Agent Procurement
The Foundation works with pharmaceutical companies and third party distributors to obtain investigational drug for distribution to sites, unless the product is commercially available.

Each protocol provides detailed information about supply and distribution of the study agent.

Agent Accountability
Unless the study agent is commercially available, the investigator is to follow all steps outlined in the protocol for ensuring the agent is appropriately triggered or ordered and ensure the specific agent is available on site prior to the time it will be needed. Agent reporting procedures will be outlined in the protocol and/or study guide and must be followed by the investigator. As sponsors of investigational drug trials, RTOG Foundation is required to follow and enforce regulations of the FDA which require investigators to establish a record of receipt, use and disposition of all investigational agents. To assure compliance with these FDA requirements, investigators must use an investigational agent accountability form for each agent supplied to RTOG Foundation. It is highly recommended the NCI/PMB Drug Accountability Record (DARF) be used. Studies with patient specific drug require an accountability record be available for each patient, who receives the study drug or placebo as applicable. A separate record must be kept for each study and for each specific drug. Each drug dose dispensed must be accounted for on the form. A complete drug inventory including shelf count should be done routinely.

All drug accountability records must be available to RTOG Foundation upon request and will be reviewed as part of the Foundation's institutional audit/monitoring program. ***Investigational agents may not be mailed to patients' homes.***

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

Transfer of Investigational Agents
Study agent provided through RTOG Foundation by a pharmaceutical company or third-party distributor may be transferred from the site that received the shipment to another affiliated RTOG Foundation recognized site for agent administration by courier only.

Return of Unused Agents and Drug Destruction
Unless otherwise stated in the protocol, investigators are highly recommended to return any remaining study agent within 90 days of the study closure broadcast or last study patient dose. Damaged or expired drug should be destroyed at the site according to institutional policy. Unused, unopened, non-expired drug must be destroyed at the site according to institutional policy. If the site does not have a written drug destruction policy,

drug should be returned to the distributor for destruction. Please review the protocol and/or study guide for specific end of study drug return or destruction information. A return receipt should be requested for all returns and the applicable Drug Accountability Form must be updated to reflect returned drugs. In a case where drug expires and requires replacing during the study, the drug can be destroyed on site. Please contact the specific distributor and the Foundation to replace expired or damaged drug.

VII. PROJECT MANAGEMENT

RTOG Foundation provides project management support to all Foundation studies. This includes site feasibility/site selection, preparation of study materials, managing the trial master file, and overseeing the trial life cycle activities from study initiation through conduct and close out.

VIII. CENTRALIZED IRB

Depending on the study and the collaborating partner, the Foundation may contract with commercial IRB vendors to provide a centralized IRB for multicenter studies. This is designed to help reduce the administrative burden on local IRBs and investigators while continuing a high level of protection for human subjects.

IX. RTOG DATA MONITORING COMMITTEE

The RTOG Foundation Data Monitoring Committee (DMC) reviews ongoing trials, for which they are the responsible DMC, for accrual and adverse events at least twice a year. The RTOG Foundation DMC also reviews the results of the protocol-specified interim analyses. Based on their review, the DMC recommends to the Foundation Board and/or study-specific steering committee a possible future course for each study.

The DMC can make one of six possible recommendations: 1) continue the study as it is; 2) revise the study because of adverse events or accrual issue problems; 3) close the study before it has realized its accrual objectives because of insufficient patient accrual or adverse event issues; 4) close the study and report early because a high significant advantage is observed on one of the arms; 5) close the study and report early because the interim analysis has found statistically significant evidence of futility; or, 6) another specified recommendation, as applicable for a given study.

The DMC also reviews specific trials outside of regularly scheduled meetings as needed for any major study issue.

For more information, refer to the RTOG Foundation DMC Charter posted on the RTOG website.

X. PATIENT ENTRY PROCEDURES

In addition to site submission of regulatory documentation, there may be protocol-specific requirements (PSRs) for institutions to fulfill prior to being granted accrual access. These may include special certification in neurocognitive training, submission of study agent shipment forms or special radiological advanced technology certification.

These requirements and how to fulfill them are described in detail in the protocol or in the study-specific guide. It is the responsibility of the institution to review the protocol and study guide to see if these apply.

All patients entered on study must meet the eligibility requirements as defined in the protocol. The study chair cannot approve cases for entry that do not meet the eligibility requirements. All questions related to eligibility must be addressed prior to case enrollment by contacting the RTOG Foundation data manager assigned to the study. In addition to eligibility information, other baseline and prognostic information may be collected at the time of registration/randomization. The applicable stratification variables for randomized trials can be found in the schema and in the statistical section of the protocol.

On-Line Registration

RTOG uses single sign on (SSO) technology called ACR Login which employs technology from SSO market leader Okta. This allows site users to easily access their RTOG account, while keeping their login credentials safe. Online registration is mandatory for all studies. Institutional staff must have an ACR Login to register patients on the RTOG.org website. The login credentials are restricted for the sole use of the assigned individual. Confidentiality is to be maintained for the login credentials. To obtain login credentials institutional users must complete the Password Authorization Form available on the RTOG.org website. Site staff are to use their institutional email and are not permitted to use personal email addresses, e.g., gmail, yahoo, etc. Site staff including the Investigator must have completed human subjects training and been issued a certificate before login credentials will be activated.

Transfer of Patient to Another Facility

Patients on RTOG Foundation studies can only be transferred to another site already approved for participation in that trial. To transfer the care of a protocol patient enrolled on an RTOG Foundation trial by a participating site to another site participating in the trial, the investigator who originally enrolled the patient must contact the study project manager and complete/submit a patient transfer form for approval. The transfer form must include signatures of the principal investigators at both the transferring and recipient sites. Documentation of IRB study approval for the recipient investigator must be on file at RTOG HQ before the transfer can be reviewed.

Transfer of a patient to another institution results in transfer of case reimbursement unless reimbursement has already been distributed. Case reimbursement will be made to only one institution. Issues related to medical insurance are the responsibility of the investigators involved in the patient 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 patient transfer, responsibility for all data requests and data submission is transferred to the recipient investigator including institutional requirements.

XI. ADVANCED TECHNOLOGY QUALITY ASSURANCE

The technology used for radiation oncology is changing rapidly. RTOG Foundation strives to devise QA processes that are generic so that they can accommodate a broad array of different imaging and dose delivery technologies. In order to meet this need, the MDADL and RT QA/Medical Physics group at RTOG Foundation Headquarters developed procedures and guidelines aimed at controlling the safe and effective use of new technologies. The technologies that the RTOG Foundation aims to evaluate in clinical trials include 3-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), stereotactic body radiation therapy (SBRT), particle therapy (protons), image-guided radiation therapy (IGRT), image-guided brachytherapy (IGBT), and biological imaging modalities such as positron tomography (PET). IGRT refers broadly to treatment delivery employing modern imaging methods such as CT, MRI, PET, and ultrasound. Each institution planning to participate in RTOG Foundation 3DCRT, IMRT and proton protocols must be credentialed.

An integrated approach has been developed and adopted with the following specific aims:

- Credentialing and monitoring by Headquarters RT QA/medical physics team and MD Anderson Dosimetry Lab.
- Assurance of the clarity, consistency, and accuracy of the treatment specification for each specific protocol (protocol review).
- Prevention or minimization of potential variations from the protocol treatment guidelines (pretreatment review).
- Categorization of any variations from the protocol treatment prescription that do occur, so that they can be considered in a statistical analysis (final/post treatment review).
- For advanced technology protocols remote reviews are performed using the web-based tools at the RTOG Foundation Core Lab to facilitate QA reviews, which allows visualization of DICOM images, structure sets, and dose distributions.
- Compilation and reporting of the review results for statistical analyses.
- Education of research associates through organized orientation programs.

Initial RT Pretreatment Review

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

Final/Post Treatment Review

The purpose of the post treatment RT review is to confirm the treatment was delivered based on the protocol criteria compliance for the statistical analysis. If the patient did not receive the total protocol dose as described in the protocol. The RTQA team works closely with each study chair/investigator to maintain the protocol-specific evaluation criteria. These compliance criteria are designed to ensure consistency in scoring each case and are derived from the protocol stipulations.

Image-Guided Radiotherapy Quality Assurance (IGRT QA)
IGRT refers broadly to treatment delivery employing modern imaging methods such as CT, MRI, PET, and ultrasound. Each institution planning to participate in Foundation protocols that requires IGRT credentialing for the use of reduced margins must submit specific information and data that is defined in the IGRT submission page under each trial located in the protocol. The submitted IGRT is reviewed using web-based software tools.

Credentialing
Sites must undergo a credentialing process to participate in protocols with some treatment modalities such as SBRT, , IMRT, proton, brachytherapy and IGRT for reduced margins. This is protocol-specific and details are included either in the protocol or in the study-specific guide.

XII. DATA MANAGEMENT PLAN

Data collection for RTOG Foundation studies is done exclusively through Medidata Rave with the exception of subject enrollment and treatment assignment. The processes involved with subject enrollment and treatment assignment are done through a web-based data collection system. Enrolled subject data and treatment assignment is pushed to iMedidata Rave via Rave web services.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the RTOG Foundation database. To access iMedidata/Rave, the site user must have an active RTOG Foundation account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator).

Upon initial site registration approval for the study, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. Invites are user specific and sent to the user's institutional email address (e.g., @gmail or @yahoo, etc. accounts are not acceptable) as indicated on the roster form. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their username and password and click on the "accept" link in the upper right corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until the invite is accepted, and all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and will be listed in the upper right pane of the iMedidata screen.

Each study will have a protocol-specific Data Management Plan. The DMP will be shared with the study collaborator, per contractual agreement.

Data Submission requirements are as follows:

- Baseline Data- Due within 7 days of calendar due date
- Treatment Data- Due within 15 days of calendar due date
- Follow-up Data- Due within 30 days of calendar due date

Patients can be deemed Lost to Follow-up only if the site has been unable to get ANY information related to the patient for 2 continuous years. Attempts to obtain additional

information are expected to continue during this 2-year period. The site will be required to document all efforts made during that two-year period to obtain information.

The "Consent Withdrawal Process" should be followed when study participants no longer wish to have ANY future data submitted. The Consent Withdrawal Form can be found in RAVE.

XIII. PATHOLOGY/BIOSPECIMEN MATERIALS

1. Introduction

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

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

2. Specimen Transmittal Form

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

3. Materials Preparation

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

4. Shipment of Specimens

The study-specific protocol and study guide provide instructions for the collection and shipment of specimens.

5. Return of Pathology Material

Specimens submitted for review are not routinely returned to the institutions, but will be preserved in the RTOG Biospecimen Bank, or other study-specified bank, for access during future studies. If the patient withdraws consent, he/she may request in writing, that her/his specimens be returned to the institution.

6. Unavailable Pathology Material

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

7. Translational Research Embedded in the Protocol

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

XIV. MODALITY REVIEWS

All RTOG Foundation protocols are subject to modality quality assurance and quality control reviews as part of the off-site centralized monitoring program as part of the Foundation's risk-based monitoring approach explained in Section XVII.

Medical Modality Review
All studies utilizing systemic agents will require a medical oncology PI or co-PI. It is the responsibility of these investigators to review their trials in a timely fashion with particular attention to toxicity evaluation and management so pro-active interventions can be enacted, if necessary. Delinquency will result in warnings and potential transfer of PI responsibilities to alternative investigators with loss of authorship. Reviews will be conducted directly in Rave.

Surgical Modality Review
All studies where surgery is part of protocol directed therapy will require a surgical oncology PI or co-PI. It is the responsibility of these investigators to review their trials in a timely fashion with particular attention to toxicity evaluation and management so pro-active interventions can be enacted, if necessary. Delinquency will result in warnings and potential transfer of PI responsibilities to alternative investigators with loss of authorship. Reviews will be conducted directly in Rave.

Pathology Modality Review
All studies with a central pathology review will require a pathology PI or co-PI. It is the responsibility of these investigators to review their trial in a timely fashion with particular attention to the sections related to pathology materials collection and analysis. The pathology PI will review all required cases. Delinquency will result in warnings and potential transfer of PI responsibilities to alternative investigators with loss of authorship. The final results of the reviews will be entered into the Rave database.

RT Case Review

Clinical trials require adherence to specific details relating to the application or delivery of each treatment modality. The RT component of trials can range from relatively simple descriptions of the required treatment technique to detailed information relating to both critical structure and target identification and required dose distributions. In addition, verification of the use of certain ancillary devices and techniques (e.g., IGRT or motion management) that aid in the precise delivery of radiation is sometimes necessary. All cases with advanced RT (3D CRT, IMRT, Protons) are reviewed for protocol compliance. The Digital Imaging and Communications in Medicine (DICOM) data is submitted and evaluated by RTQA staff and prepared for review by the radiation oncologist PI or designee(s). Feedback is provided as requested by reviewer. More complex trials may require pre-treatment reviews where the plan has to be reviewed and approved prior to the patient receiving any RT. The final results of the reviews will be entered into the Rave database.

XV. UNBLINDING PROCEDURE FOR PLACEBO-CONTROLLED (BLINDED) STUDIES

The decision to break the unblinding code is based on the assessment of an extraordinary clinical circumstance for which knowledge of treatment assignment is essential for the medical management of the subject, or a serious adverse event unexpected for and related to the study drug (i.e. IND safety report submission to FDA) that may provide critical safety information about a drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). For all blinded, placebo-controlled trials, unblinding procedures are included in the protocol. The protocol contains contact information to ensure unblinding is possible 24 hours per day, 7 days a week.

XVI. ADVERSE EVENT REPORTING

For detailed information regarding expedited and routine adverse event reporting, RTOG Foundation Adverse Event Reporting Guidelines are available for each study.

SAE Reporting to Collaborating Partners

Collaborating partners receive serious adverse event (SAE) reports generated on the study per the contract. If the partner requires further documentation or clarification, RTOG Foundation Regulatory Compliance acts as interlocutor between the partner and the clinical site to obtain the requested information.

XVII. QUALITY ASSURANCE/QUALITY CONTROL PROGRAM

The RTOG Foundation supports a risk-based monitoring approach that is intended to oversee all aspects of data monitoring, verify data validity and integrity, and ensure the safety of participants in clinical trials. All protocols approved by the RTOG Foundation Board must include a protocol-specific Data Quality Plan (DQP) and a Data Safety and Monitoring Plan (DSMP). Both documents will include monitoring and auditing criteria and frequency. The protocol-specific DQP and DSMP will be developed based on discussions with the RTOG Foundation Operations Center, the RTOG Foundation Statistics and Data Management Center (SDMC) and the industry partner. Once the documents have been accepted, the protocol-specific DQP will be part of the industry

partner agreement and the protocol-specific DSMP will be part of the site study start-up packet. If it is determined that the protocol will be for registration-intent the DQP will be shared with the FDA to assure acceptance of the plan.

The risk-based monitoring approach is outlined in the RTOG Foundation Plan for Data and Safety Monitoring of Clinical Trials.

XVIII. STATISTICS

Statistical analyses will follow the protocol-specified statistical analysis plan.

Routine Reporting

The Statistics Department prepares summary reports for each RTOG Foundation trial at least twice a year for all studies open to patient entry or in follow up until the initial publication (abstract or manuscript) of the primary endpoint. In each semiannual statistical study report, the following information is included:

- Projections for completion of patient accrual based on the rate observed over the entire study and the last 6 months (until study closes to accrual).
- Patient accrual by institutions.
- Case status for all the cases entered into the study.
- Distributions of important demographic/disease variables by treatment arm.
- A summary of reported adverse events by treatment arm for trials that are not blinded, and by combined arms for blinded trials.

Early Phase Trials

For specified early phase trials, study reports focusing on accrual and adverse event data will be prepared regularly and the PI/study team will have regular conference calls (biweekly or monthly) to review the accrual/safety data.

Final Analyses – Initial Treatment Results

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

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

Patients included in the analysis are defined by the protocol-specific analysis population.

XIX. STUDY STATUS DEFINITIONS

Not Yet Open to Accrual - RTOG has obtained IRB approval and has released the protocol documents to sites for initiation procedures, but the trial is not yet open to enrollment. On the Clinical Trials.gov website the status would be "Not yet recruiting".

Open for Accrual - The study becomes open for accrual once at least one participating site has met all the regulatory and protocol-specified criteria to enroll a patient. Thus, the trial is now open to enrollment. On ClinicalTrials.gov website the status would be "Recruiting".

Temporarily Closed to Accrual - This designation can have a few meanings for RTOG which are outlined below. However, on ClinicalTrials.gov website the status would be "Suspended".

- Scheduled Closure (protocol-specified). Study closed because it met protocol-driven cohort level/ AE reviews. This type of closure may lead to re-opening.
- Unscheduled Closure. Study has not met accrual and needs to be temporarily closed for example, due to a safety concern, new data findings, or drug commitment. The study may or may not be reopened.

Closed to Accrual – The study is permanently closed to accrual; however, data collection will continue, and an analysis will occur. Patients may still be receiving treatment/intervention or may have completed treatment/intervention and be in follow up. On ClinicalTrials.gov website the status would be "Active, not recruiting".

If an analysis will **not** occur and no patients enrolled the study will be permanently closed and on clinical trials.gov the status would be "Withdrawn".

Completed/Terminated - No further data will be collected. This trial meets the FDAAA 801 rule and on ClinicalTrials.gov website the status would be "Completed".

Site Requests for Early Study Closure

If it is determined that the participating site is terminating its collaboration with RTOG for a specific study, it is the responsibility of the participating site PI or LRA to notify the study project manager prior to ceasing research activities at their site. There is a formal process to requesting an early study closure and this process can be found within the study specific manual.

XX. PUBLICATIONS

The study chair drafts the abstract/manuscript reporting the study results based on the study statistical analysis report. The section on statistical methods in the abstract/manuscript is prepared by the statistician. The study chair and statistician will work together on the first draft of the abstract/manuscript and once finalized, this will be circulated to abstract/manuscript co-authors.

All publications (abstracts, manuscripts, and presentations) reporting results of RTOG Foundation trials must sent to its Publication Department for circulation to RTOG leadership for review and approval prior to the publication's submission to a journal or conference or presentation.

Publication Department staff will ensure that the publication is reviewed by the RTOG Foundation leadership in accordance with the RTOG Foundation Publication Guidelines. Publication Department staff will also ensure that the publication is reviewed by the industry collaborator(s) if appropriate, that the author line is in accordance with the Guidelines, that co-author reviews are completed, and that all conflict of interest statements are collected. Department staff will provide approval to the first author to submit the abstract for presentation and will submit manuscripts to the journal on behalf of the first author.

XXI. DATA SHARING AND RELEASE OF STUDY DATA

A. DATA SHARING

Requests to use data from RTOG Foundation studies will be reviewed by the Foundation Board of Directors and, if appropriate, the study-specific steering committee and will be contingent upon pre-existing agreements with corporate sponsors/supporters, scientific merit, and available funding.

B. Release of Study Data

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

- The study chair is reviewing individual patient charts for the study.
- An individual other than the study chair has a project approved by the study-specific steering committee, the industry collaborator, and the RTOG Foundation as required by the contractual requirements of the study. Requests must be made in writing to the Headquarters stating the data which is needed and the purpose for which it will be used. In certain circumstances, it may be necessary to receive IRB approval as well.
- See Section XX for more information regarding publication procedures.

XXII. RECORD RETENTION

For RTOG Foundation held IND studies:
FDA regulations require investigator to keep all research records (including patient charts, case report forms, images, and scans that document response, IRB approvals, signed informed consent documents and all agent accountability records) for at least 2 years after an NDA or BLA has been approved for that indication, or the RTOG Foundation IND has been withdrawn from the FDA.

For Non-IND studies:
The point of reference used to determine the length of time required for record retention for non-IND studies would be the study's termination date, which is when the database

is locked, and no further information would be required. Institutions will be notified via broadcast of all study terminations. Sites should follow their institutional guidelines.

Record retention provisions set forth in the study specific SOWs may contain certain further details and are to be complied with.

XXIII. BUSINESS CONTINUITY

As the RTOG Foundation Operations and Statistics & Data Management Center, are located at the offices of the American College of Radiology in Philadelphia, PA. The Foundation will follow the Business Continuity Plan (BCP) of the American College of Radiology Center for Research and Innovation (ACR CRI) for communication disruptions in service, outages, breaches, and any other event that may affect and the conduct of RTOG Foundation Operations.

The BCP is written to cover a worst-case disaster situation. However, the BCP may also be activated in less than worst-case scenarios, with any potential interruption to or imminent threat. The BCP aims to ensure the continuation of services to sites, investigators, sponsors, etc.

XXIV. COMMUNICATIONS FRAMEWORK

A communication plan (CP) is developed for each study and provides a framework to manage and coordinate the wide variety of communications that take place during the study. The CP covers who will receive the communications, how the communications will be delivered, what information will be communicated, who communicates, and the frequency of the communications. It will also include status reporting and issue escalation process.

The purpose of the CP is to ensure relevant, accurate, and consistent information about the study is provided to all stakeholders ensuring their timely and efficient involvement, support and cooperation where required.

Issue Escalation and Resolution

The purpose of issue escalation is to raise emerging and/or unresolved issues to the industry collaborator's attention for timely resolution, as appropriate.

Quality, regulatory or safety issues are escalated in real-time within the appropriate channels through the study team, RTOG Foundation leadership, and industry collaborator to develop a plan of action and timeframe in which to resolve the issue.

Remediation for these issues can be found within RTOG Foundation SOPs, policies, guidance documents and may include the following: retraining of site staff on protocol requirements, a corrective action plan, and follow-up. Continued infringements may lead to suspension of accrual to the study until completion of mandatory audit visit or immediate removal from the trial.