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QUALITY ASSURANCE FOR CLINICAL TRIALS: A PRIMER FOR PHYSICISTS

A Report of the Subcomittee on Quality Assurance Physics for Cooperative Trials of the Radiation Therapy Committee

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1. INTRODUCTION

Today, nearly 70% of all radiation therapy centers participate to some degree in cooperative group [organized, multi-institutional, National Cancer Institute (NCI)-funded] clinical trials. About 25% of these centers participate actively in that they treat more than 12 patients per year under protocol. In all cases, specific quality assurance (QA) procedures need to be performed by the physicist to either be eligible for membership in the cooperative group or to maintain eligibility. In protocols involving radiation therapy, there are radiotherapy quality assurance and data submission requirements for each patient entered into the trial. In addition, participation in advanced technology protocols, three-dimensional (3D) conformal, intensity-modulated radiation therapy (IMRT), stereotactic radiotherapy, or brachytherapy require a significant physics effort to qualify the institution to enter patients and to provide the required data submission for each patient treated under protocol.

In the near future, both the number of centers participating in clinical trials as well as the number of patients enrolled in studies may rise substantially because of the emergence of the NCI-sponsored Cancer Trials Support Unit (CTSU). The CTSU permits patients to be treated under selected protocols by any radiation therapy center meeting the CTSU requirements regardless of whether that center is a member of the cooperative group conducting the study. Thus physicists who are either rarely or never asked to provide protocol support may soon be routinely involved with the quality assurance and data submission tasks for protocol patients.

In addition to the increased volume of protocol cases with which physicists may be faced, the complexity of radiation therapy protocols and their quality assurance is increasing as 3D conformal and IMRT-based studies are being opened. Here, the challenge to the physicist is to perform the benchmark tests for institutional certification successfully and then to ensure protocol compliance and provide the various patient-specific data items required by the quality assurance centers. Most physicists today are generally unaware of the demands of these new protocols.

Radiation therapy (RT) physics training rarely includes education in clinical trials in general, radiation therapy sections of clinical trials in particular, nor any specific instruction on quality assurance physics procedures necessary for clinical trial participation. This information and the required skills are largely learned on the job. At many institutions where relatively few patients are entered on clinical trials, non-physics personnel may fill out and submit quality assurance data forms, so that the physicist never sees the protocol and its requirements. Where the physicist is asked to prepare and submit data for patients on or completing protocol treatments or to perform measurements and benchmarks for new protocols, the extra work required in this unfamiliar area may be seen as burdensome.

Due to the mission of organizations like the Quality Assurance Review Center (QARC) and the Radiological Physics Center (RPC), institutions participating in clinical trials must demonstrate their ability to meet quality standards on an ongoing basis. It is the responsibility of the physicist at each participating institution to perform the measurements competently and to supply the data that these organizations require.

The consistency and accuracy with which each institution delivers radiation treatments are critical in establishing the statistical significance of the findings of the clinical trial. The various quality assurance centers and clinical trial groups have systematized the quality assurance process to help institutions follow the protocol guidelines so that the treatment dose and volume are per protocol. It is the duty of the knowledgeable institutional physicist to ensure quality treatments and adherence to protocol guidelines that ultimately enhance the ability of the trials to answer the questions posed.

The Subcommittee on Quality Assurance for Clinical Trials of the AAPM Radiation Therapy Committee has undertaken the writing of this primer in order to provide the information and references required for any physicist to be an informed, competent participant and a key resource to each institution involved in cooperative group clinical trials employing radiation therapy. This primer explains:

a. what constitutes a clinical trial;
b. the role of the physicist in preparing and maintaining the institution's credentials for participating in clinical trials requiring radiation therapy;
c. the special or additional physics tasks required, both to become credentialed and to meet specific protocol quality assurance and data submission requirements;
d. the quality assurance review process and how is the submitted data evaluated.

And in the appendices, which are an important adjunct to this document,

a. the three phases of clinical trials;
b. how QA affects the statistical analysis of clinical trials;
c. how to find the various groups involved in conducting and monitoring clinical trials;
d. the data review and resource centers that receive data submissions and what they do.

The result should be that the physics community, by having a better understanding of the clinical trial quality assurance process, will feel less frustration and more motivation with their important role in determining the most effective treatment strategy for a particular disease.

2. CLINICAL TRIAL BACKGROUND

a. What is a clinical trial?

Frequently, before new treatment regimens are made available to the public, they are tested in a clinical trial. Clinical trials are research studies designed to answer specific questions about the effects of a new therapy or technique designed to improve human health, including developing better methods of treating diseases like cancer. Cancer treatment trials are performed to find out whether promising approaches to cancer treatment (like a new cancer drug, new approaches to surgery or radiation therapy, new combinations of treatments, or new methods such as gene therapy) are safe and either superior or at least as effective as existing therapies. Many of today's standard treatments for cancer began in clinical trials. Although clinical trials are undertaken for advancement in diagnosis and prevention of disease as well, we will restrict our comments to those trials that in some way involve radiation therapy.

It is crucial that these trials are well designed and well run in order to determine the true effectiveness of a promising treatment. Each cooperative group has a study development office and a process that studies go through from concept to activated protocol. Since most studies involve several treatment modalities and disciplines, several investigators will work together with group staff to complete a well-written protocol document. Most groups identify one investigator to be the Principal Investigator or Study Chair. Investigators representing all of the involved modalities are usually assigned as co-chairs to field study questions pertaining to their expertise. The protocol explains what the study will do, how it will be carried out, and why each part of the study is necessary. For example, the protocol includes:

- The reason for doing the study.
- What are the endpoints?
- How many patients will be in the study?
- Who is eligible to participate in the study?
- What study drugs or therapies the participants will be given?
- What medical tests they will have and how often?
- What data will be gathered?
- What adverse events are anticipated and how will they be handled?
- The requirements for patient consent and authorization.

Every doctor or research center that takes part in the trial uses the same protocol. This helps to ensure that patients are treated comparably no matter where they are receiving treatment, and that information from all the participating centers can be combined and compared. The efforts of medical physicists to ensure that the delivered dose distribution is accurate and meets protocol requirements are crucial to the validity of this pooling of data.

Entirely novel radiation treatments must successfully complete three phases of trials before the federal Food and Drug Administration (FDA) approves them for general use. This allows researchers to ask and answer questions in a scientific and safe manner. The attention to radiation therapy quality assurance is tailored to its role in each situation. Briefly stated, the purpose of each of the three phases of clinical trials is to determine:

Phase I: Is the new treatment safe?
Phase II: Is the new treatment effective?
Phase III: Is the new treatment better?

For a more thorough discussion of the phases of clinical trials, see appendix A.

Individual physicians at cancer centers and other medical institutions can sponsor clinical trials themselves. The NCI sponsors a large number of clinical trials, and has four major programs designed to make clinical trials widely available in the United States. These include (1) institutions that have been designated as an NCI Comprehensive or Clinical Cancer Center and perform clinical trials independently, (2) members of the Cooperative Clinical Trials Program, (3) sites involved with the Community Clinical Oncology Program (CCOP), and (4) facilities enrolling patients through the Cancer Trials Support Unit (CTSU).

b. NCI's Clinical Trials Cooperative Group Program

Because the majority of patients in clinical trials who are treated with radiation therapy are enrolled in a cooperative group trial, we will discuss this program in greater detail. The Clinical Trials Cooperative Group Program, sponsored by the NCI, is designed to promote and support clinical trials (research studies) of new cancer treatments, to explore methods of cancer prevention and early detection, and to study quality of life issues and rehabilitation during and after treatment. NCI-sponsored cooperative groups are composed of academic institutions and cancer treatment centers throughout the United States, Canada, and Europe. They work with the NCI to identify important questions in cancer research and to design carefully controlled clinical trials to answer these questions. The program involves more than 1500 institutions that contribute patients to group-conducted clinical trials. Thousands of individual investigators also participate in NCI-supported cooperative group studies. Cooperative groups annually place approximately 20,000 new patients into cancer treatment clinical trials that would otherwise accrue too few patients if conducted at any one facility. The groups differ in structure and research focus. Some groups, such as the Cancer and Leukemia Group B (CALGB), concentrate on a few major types of cancer; some, such as the Radiation Therapy Oncology Group (RTOG), study a specific type of cancer therapy; and others, such as the Gynecologic Oncology Group (GOG), focus on a group of related

cancers. The groups share a common purpose—to develop and conduct large-scale trials in multi-institutional settings.

The Cooperative Group Program was established in 1955 following congressional approval to increase support for studies of chemotherapy for cancer. Congress initially appropriated $5 million for NCI to establish the Chemotherapy National Service Center. By 1958, 17 cooperative groups were part of the center. At that time, the main thrust of the program was to test new anticancer agents from NCI's drug development program. The emphasis on chemotherapy gradually shifted to studies of combined therapy approaches in cancer treatment.

The CCOP makes clinical trials available in a large number of local communities in the United States by linking community physicians with researchers in cancer centers. CCOPs allow potential investigators to participate in a majority of cooperative group trials, including phase I, II, and III trials. However, this program is not for people new to the research process. Potential CCOPs must have a proven track record of accrual to NCI-sponsored treatment and prevention and control clinical trials.

Conversely, the relatively new CTSU, established by the NCI in 1996, offers and facilitates individual participation in a selection of NCI-sponsored cooperative group phase III trials to qualifying oncologists who are not members of a cooperative group. It does this in part by permitting institutions that are members of one study group to enroll patients in trials run by other study groups. In 2003, this program was expanded to include institutions that are not members of any study group. CTSU members are not required to demonstrate prior experience in clinical trial participation, have no accrual requirements, and do receive reimbursement for research costs. As of this writing, CTSU has opened a number of protocols, including many that involve radiation therapy.

To participate in a trial opened through CTSU, an institution must submit an application to CTSU providing details about the treatment facilities and staff. The application allows an institution to indicate the study group of which it is a member (if any) so that it can get accrual credit through that group. For protocols involving radiation therapy, the institution must also submit a "radiotherapy facility" questionnaire, and agree to be monitored by the Radiological Physics Center (RPC) if they are not already. They will also be required to pass any credentialing tests required for participating in the protocol. CTSU utilizes the RPC web site to confirm that institutions claiming to be monitored in fact are. In the event that they are not currently monitored, CTSU contacts the RPC, which begins procedures to initiate monitoring. Once the institution is participating in the RPC monitoring programs, CTSU is notified. In 2003, CTSU began to take responsibility for registering all patients on specific clinical trials, even those from institutions that are members of the cooperative group sponsoring the trial. It appears likely that this practice will continue.

All together, there are more than 1000 NCI-sponsored treatment trials conducted each year with more than 23,000 cancer patients. As the new NCI pro-

grams for encouraging enrollment in clinical trials become more effective, more radiation therapy facilities and their physics staff who have never treated patients on clinical trials will be asked to participate in this challenging new experience. We expect a growing number of medical physicists will encounter protocol patients in the near future.

c. The Cancer Therapy Evaluation Program (CTEP)

CTEP, a program within the NCI, attempts to forge broad collaborations within the research community and works extensively with the pharmaceutical/biotechnology industry to develop new cancer treatments effectively. CTEP also seeks to involve outside experts and patients or their advocates in the formulation of research priorities. In the selection of clinical research for NCI sponsorship, CTEP attempts to fill critical gaps in the national cancer research effort and to avoid duplication of ongoing private sector efforts. In further efforts to control cancer, active new anticancer agents are made available as rapidly and widely as possible for patients.

The CTEP protocol review committee (PRC) reviews all proposed protocols. This committee is composed of the professional staff of CTEP and consultants from other NCI divisions; is chaired by the CTEP Associate Director; meets weekly; and usually reviews 10 to 20 protocols, letters of intent, and concepts at each session. Each protocol is assigned a minimum of five reviewers; as many as six to seven may be required for complex multi-modality protocols. For example, protocols involving the use of radiation therapy are reviewed by the Radiation Research Program staff, which includes radiation oncologists and medical physicists. An oncologist(s), biostatistician, pharmacist, and regulatory affairs professional(s) with expertise in informed consent issues review the protocol and informed consent form. The PRC discusses the protocol after hearing the reviews of each assigned reviewer and makes a decision as to whether the science and safety of the study are acceptable. The PRC disapproves relatively few submitted studies and only does so when it feels that a proposal is unnecessarily duplicative or irretrievably flawed in concept, design, safety, or feasibility.

d. What has been learned from radiation therapy clinical trials?

Information established from cancer cooperative group clinical trials has gained significant prominence in the past several years, as demonstrated by the fact that 70% of papers presented at plenary sessions at American Society of Clinical Oncology (ASCO) during the period between 1998 through 2002 have been from data generated from cooperative group trials. Results of these studies have had significant influence on daily clinical practice patterns of many diseases in multiple organ sites. In fact, clinical trials have served to define the standard of care for many diseases. Examples are the benefit of chemo-radio-

therapy in both cervix cancer and rectal cancer. Cooperative group trials confirmed the equivalent local control and survival benefits of mastectomy and lumpectomy with radiation therapy. In the United States today, more than 70% of children with cancer live at least 5 years after diagnosis, as opposed to only 55% in the mid-1970s because of the improved treatments validated in cooperative group trials.

Analysis of clinical trials data over the last 30 years demonstrates that the accuracy of the dose and target coverage obtained by participating institutions has improved. Quality assurance review of the first generation of cooperative clinical trials that contained radiation therapy revealed differences in computational methods between institutions, which resulted in inconsistent radiation dose delivery to target volumes. As commercial planning systems matured, computational deviations decreased. However, imaging and image interpretation have become a source of deviation in target volume definition. An example was seen in the cooperative group clinical trials for Ewing's sarcoma. Analysis of the data from the Pediatric Oncology Group (POG) Ewing's protocol 8346 revealed a statistically significant local control advantage for patients whose treatment volume was designed according to the guidelines of the study. Only 16% of patients had local control of their primary disease when their treatment volumes were inconsistent with study guidelines compared to 80% for those treated consistent with the guidelines (Donaldson et al. 1998). From two Ewing's sarcoma studies performed by the German Society of Pediatric Oncology, CESS 81 and CESS 86, a comparison was made between the rate of local control and radiation treatment quality. It was found that in CESS 81, 90% of local relapses occurred in patients with radiotherapy protocol deviations. When central treatment planning was implemented in CESS 86, the local control rates improved and none of the local relapses were associated with poor radiotherapy technique (Dunst et al. 1995). Deviations in delivered treatment resulting in increased treatment failures was also seen in a Hodgkin's lymphoma trial, the German Hodgkin's Study Group trial HD4. Here, freedom from treatment failure was 70% vs. 82% with or without protocol violations, respectively (Duhmke et al. 1996). POG [now Children's Oncology Group (COG)] elected to move towards pre-treatment review of diagnostic imaging and radiation therapy treatment data to ensure uniformity of treatment for the patient study population, particularly Hodgkin's disease. Centralized pre-treatment review has decreased the deviation rate from 30% to 6% as demonstrated in recent studies the QARC monitored for POG. The COG has now adopted pre-treatment review for several similar studies and the North Central Cancer Treatment Group (NCCTG) requires pre-treatment review by the RPC for an adult lung study. Other current efforts to improve protocol compliance include more clearly written protocol guidelines as well as the introduction of web-based tutorials that give examples of target volumes and treatment fields. For more information on the statistical issues involved in clinical trial data analysis and the relationship to treatment quality, see appendix B.

The quality assurance process has evolved through the years to better provide methods that assure study uniformity without hindering study accrual. It is clear that these efforts have had a major role in assuring the validity of information gained in cooperative group clinical trials. Concomitantly, cooperative group protocols have gained national and international recognition as the vehicle to establish clinical practice paradigms in cancer treatment.

3. THE CLINICAL PHYSICIST'S ROLE IN CLINICAL TRIALS

a. Protocols that involve the radiation physicist

To some extent, any trial incorporating radiation therapy will involve the radiation physicist. Clinical trials demand that patients be treated in a consistent fashion, not only within a single center, but also among the centers participating in multi-institutional studies. This is not to suggest that patients on protocols deserve more or better quality assurance; but it is more critical that all aspects of treatment be kept consistent, even those that might appear to have no influence on the trial.

Trials that employ, but do not evaluate, radiation therapy require only that the physicist be sufficiently familiar with the protocol to know that the treatment is administered in accordance with the protocol requirements. In many cases, the radiation therapy requirements may be minimal or vague, and require for example, only that patients receive "standard radiation therapy." In other cases, however, the protocol may impose requirements that are inconsistent with the way patients are normally treated at the institution. These requirements might include performing calculations with or without heterogeneity corrections, or normalizing to a point, or specific isodose line. In other cases, the protocol may prohibit brachytherapy, or require that brachytherapy be administered in a specific way, even though the radiation treatment is not being evaluated. It is important in such trials to ensure that differences in the radiation therapy do not mask changes in outcome due to the therapy (drugs or surgery) being evaluated. The physicist may need to review the calculations for patients on these trials to assure that even fairly vague or limited requirements are met.

Protocols that involve a "radiation question," in other words, ones that are testing the safety or efficacy of a new radiation treatment, are more demanding of the physicist. For such trials, it is critical that patients are treated in exactly the same manner. The physicist must not only be familiar with the trial, but also must ensure that planning and delivery are performed in strict agreement with the protocol. This requires that the physicist be proactive in determining which patients are on protocol and then **reviewing the protocol prior to the start of treatment planning.** Unfortunately, it is not uncommon for the physics staff to find out that a patient is on a protocol during or even after the treatment. Often, protocols require that clinical target volume (CTV) and organs-at-risk (OAR)

doses meet strict requirements and must be documented to the QA center as instructed in the protocol. In other cases, brachytherapy must be administered using a particular technique where more than one choice is available (for example, intracavitary vs. interstitial or low dose-rate vs. high dose-rate).

It is tempting to assume that the physicist need only be involved in phase III trials because these trials may determine the next new standard of care, but this is far from the case. A trial that is evaluating the safety and efficacy of a new form of treatment may be a phase I or phase II trial, but would demand the participation of the physicist to ensure that the treatment conformed to the requirements of the protocol. To do otherwise might endanger patients, and would compromise the outcome of the trial.

The relationship between the role of radiation therapy in a clinical trial, either as the study question or as a service, and the comprehensiveness of quality assurance, will be further discussed in section 4.

b. Cooperative group membership

Cooperative groups generally require institutions to become a member before they are allowed to participate in clinical trials sponsored by that group. The goal of the cooperative group is to ensure that an institution has all the resources necessary for successfully participating in such trials. The membership application process is unique to each cooperative group. Information on the various steps of this process can be obtained from the website of the appropriate cooperative group or by contacting their headquarters (see appendix C).

For example, the following gives a concise description of the various steps necessary to become a member of the Radiation Therapy Oncology Group (RTOG). This will give the physicist an appreciation of her/his role in the application process. RTOG offers three types of memberships. These are (1) Full membership, (2) Affiliate membership and (3) CCOP membership. The requirements for each type of membership are different although there are many similarities in the application process. Membership application consists of two steps; in the first step an applicant institution needs to fill out a Preliminary Application form. The RTOG Headquarters administration and the membership evaluation committee review this form. Information sought on this application pertains to all locations where treatment is received outside of the applicant institution. This also seeks information about the Institutional Review Board (IRB) acceptance that covers this site. In the second step of the application process, the applicant institution needs to fill out a Full Application form and provide documentation supporting the information sought in the application. This part of the application has been designed to obtain as complete information as possible about the applicant institution. These include, but are not limited to, information on the personnel in the department, the equipment in clinical use, clinical material (i.e., patient database), physics support, treatment records, and IRB acceptance of the institution's participation in the clinical trial.

The physicist is responsible for providing documentation and information on (1) the types of accelerators used for treatment; (2) diagnostic equipment used for definition of tumor volume and simulation; (3) treatment planning system used for generating treatment plans for both external beam radiation therapy and brachytherapy; (4) equipment used for any special procedures such as stereotactic radiotherapy, intra-operative radiotherapy, high dose-rate brachytherapy, and total body irradiation; and (5) physics and dosimetry equipment used for calibration, and quality assurance. Documentation is also needed on the institutional QA procedures on all accelerators and other equipment used for patient treatment and/or treatment simulation. Each institution is required by RTOG policy to have an independent confirmation of the calibration of their megavoltage beams. This can be obtained through the RPC mailed TLD (thermoluminescent dosimeter) service. The physicist thus plays a vital role in assembling and providing all physics, dosimetry, and equipment-related information. A physicist and a radiation oncologist at the RTOG headquarters then review the submitted application and documentation. If the documentation is complete then the institution is approved as a member of RTOG.

c. Assuring protocol compliance

Three-dimensional conformal radiation therapy (3DCRT), IMRT, and some brachytherapy protocols have special requirements, for which an institution must become credentialed before participation in these studies. It is the physicist's responsibility to ensure that his or her institution is credentialed for participation in such studies. Elements required for credentialing may include treatment planning of a benchmark case that represents a typical treatment for the disease in the protocol, the development of mechanisms for submission of patient treatment data (images and dose distribution) electronically to the Advanced Technology Consortium (ATC), verification that a patient treatment plan has been generated according to the guidelines given in the protocol, and verification that personnel involved in the planning and treatment of the protocol patient are knowledgeable about the specifics of that study. This last item is often accomplished by means of a practice case (dry run).

When a patient is enrolled in a given study, it is expected that the treatment will be delivered in accordance with the criteria set forth in the protocol. Compliance with protocol requirements is very important and failure to comply will weaken the study and may result in an unfavorable data quality score for the institution. Therefore, **the importance of reading and understanding the details of a protocol cannot be overstated.** A typical RTOG protocol contains the following sections: schema, eligibility, introduction, objectives, patient selection, pretreatment evaluations, registration procedures, radiation therapy, drug therapy, surgery, other therapy, pathology, patient assessments, data collection, statistical considerations, references, and appendices. Of all these sections, the section that requires a physicist's closest attention is the radiation

therapy section. This is the section that describes in detail how radiation therapy should be delivered and the data that need to be submitted to the QA center. This includes, but is not limited to, description of (1) treatment machines and modalities allowed for treatment; (2) target volume, treatment volume, and critical normal tissue definitions; (3) treatment planning, imaging, and localization requirements; (4) patient immobilization; (5) dose prescription and specification; (6) treatment verification; (7) radiation therapy toxicity adjustments and toxicity reporting guidelines; (8) compliance criteria, and other information that is relevant for a specific study. Other cooperative group protocols have similar language that describes the radiation therapy requirements. It is critical that the physicist and/or the dosimetrist understand every aspect of the radiation therapy section before starting the planning of any protocol patient.

d. Understanding image-based protocol prescription and target volume specifications

All current and proposed 3DCRT protocols use International Commission on Radiation Units and Measurements (ICRU) Reports 50/62 nomenclature and methods for defining the region to be treated (ICRU 1993, 1999; Purdy 1999, 2002). There are three components to the tumor/target volume: the gross tumor volume (GTV); clinical target volume (CTV); and planning target volume (PTV). The protocol defines how the GTV and CTV are to be drawn, and frequently includes an upper limit to the margin for the PTV. The QA office may request documentation of the adequacy of smaller margins used for the PTV. The definition of GTV, CTV, and PTV is a function of each particular protocol and disease site and is refined as necessary in the development of new studies.

The method for specifying the dose prescription for 3DCRT and IMRT protocols is still evolving as experience is gained with ongoing studies. Typically, protocols will define the dose *prescription* criteria (dose to be delivered) that can be different from the dose *specification* criteria (dose to be reported). Either can refer to a point, for example, the isocenter, or to an isodose surface. The original RTOG lung (93-11) and prostate (94-06) protocols used different dose prescription criteria. The prostate protocol's prescription dose was the minimum dose to be delivered to the PTV (1.8 Gy per fraction) with a maximum point dose no greater than 7% higher than the prescription dose (1.9 Gy per fraction). The lung protocol's prescription dose was specified as the dose at isocenter (ICRU Reference Point) with an additional requirement that a minimum of 93% of this reference point dose cover the PTV. A possible advantage of the lung prescription specification over that of the prostate is that it unequivocally defined a point where the dose per fraction was specified, which in turn defined the monitor units required to deliver the prescription. Subsequent RTOG 3DCRT protocols have used the ICRU reference point prescription criteria but other cooperative group 3D conformal and IMRT protocols have specified a

percentage of the PTV requiring a percentage of the prescribed dose. For RTOG IMRT protocols thus far the prescription is specified more as an "intended" or "goal" dose with the emphasis placed on dose-volume constraints given for the specified OAR. In addition, the maximum dose specification is moving away from relying on a single point (voxel). Instead, the maximum dose to a stated small percentage of the volume of either the PTV or of all tissue within the body is specified.

Image-based radiation therapy protocols are becoming standard and are likely to be the most frequent format in the future. Currently, dose prescription and dose specification rules are evolving. The physicist is responsible for understanding the accepted prescription and volume definitions of the protocol and for assuring that they are applied properly.

e. Protocol data submission to QA centers

There are three major national quality assurance review centers; QARC, RPC, and RTOG Headquarters QA office. There are also two resource centers: the Image-Guided Therapy QA Center (ITC) and the Resource Center for Emerging Technologies (RCET). Each center is funded in part by the NCI and has agreements with various cooperative groups to provide a range of quality assurance services, including chart, film, procedure, and dosimetry review or, in the case of the ITC and RCET, to develop and provide electronic data archival and retrieval services (figure 1). In 2002, the five centers joined to become the Advanced Technology Consortium (ATC) to coordinate efforts, reduce duplication, and unify the quality assurance practices across the country. In addition, the ATC is charged with providing the necessary database and web infrastructure to handle the transfer, archival, and retrieval of vast amounts of image and dose data from the newer clinical trials using advanced treatment technologies such as 3DCRT, IMRT, brachytherapy, and stereotactic radiosurgery (SRS) as well as a host of imaging technologies used for cancer diagnosis. More information about the efforts of these centers can be found in appendix D.

Associated with each protocol are various data and compliance evaluation forms. These protocol-specific data need to be submitted to the study group for evaluation at designated time intervals. Usually these data are obtained and prepared by either the clinical research associates (CRAs) or the physics staff. Typical data to be submitted include (physics staff responsibilities are in **bold** type):

1. Demographic data [Health Insurance Portability and Accountability Act (HIPPA) compliant]
2. Initial evaluation, history, and physical data
3. Diagnostic pathology report
4. Pathology slides
5. Diagnostic imaging studies [computed tomography, magnetic resonance imaging, positron emission tomograpy (CT, MRI, PET), gallium, etc.]

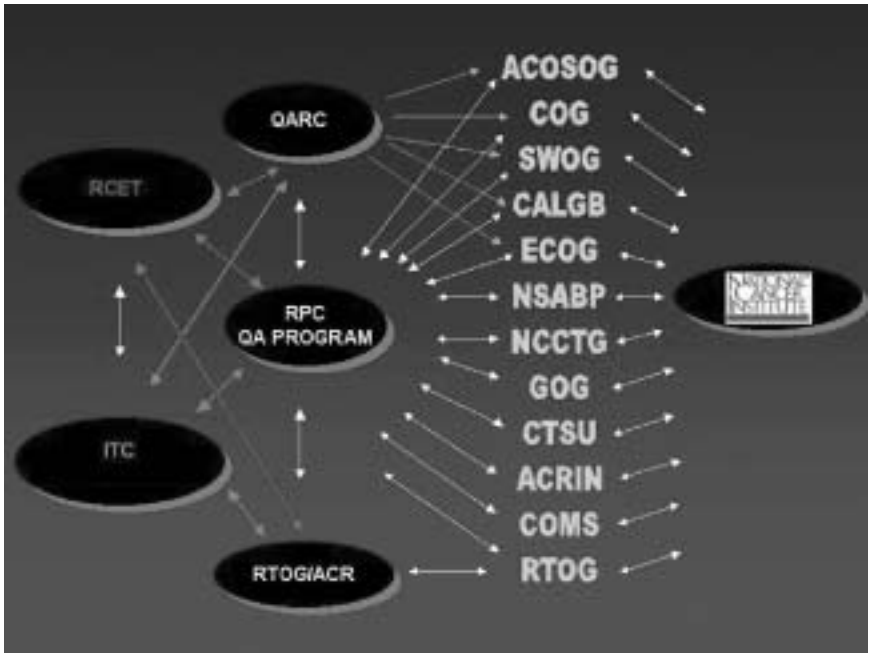


Figure 1. Organizational diagram of the various cooperative groups and their relationship to NCI and the QA and resource centers. The ATC includes RCET, ITC, QARC, RPC, and RTOG QA.

6. **Preliminary dosimetry information:**
   a. **Radiation therapy prescription**
   b. **Patient setup data [simulation, digitally reconstructed radiographs (DRRs), portal images, etc.]**
   c. **Dose distributions and monitor unit calculations—point doses, isodoses, dose-volume histograms (DVHs)**
7. **Final dosimetry information:**
   a. **Daily treatment record**
   b. **Dosimetry data if any changes from preliminary submission**
   c. **Dose distributions, calculations, and measurements—point doses, isodoses, DVHs for composite treatment (including any boosts), TLD or diode readings**
   d. **Patient setup data (simulation, DRRs, portal images, etc.) for any fields not initially submitted**
8. Hormone summary
9. Initial and long term follow-up form
10. Autopsy report

Timely submission of the protocol data to the quality assurance center of the cooperative group requires coordination between the institutional CRA and the physics staff. This task deserves the attention and expertise of the medical physicist. The accuracy and completeness of these forms are essential to the success of the cooperative group process. Some protocols require pre-treatment review. Imaging studies and the treatment plan must be reviewed before the patient receives the first fraction. Some cooperative groups require rapid review of submitted data for some protocols. Typically, the rapid review requires the submission of data within 24 to 72 hours of the start of the radiotherapy. These pre-treatment and rapid reviews require even more diligence on the part of the participating institution's staff. Most clinical cooperative groups are already set up to receive at least the textual data electronically. Some advanced technology protocols require radiation therapy planning, dosimetry, and verification data to be transmitted electronically to the QA center. The ATC supported by the NCI is developing electronic data archive, retrieval, and review infrastructures that are facilitating the conduct of certain clinical trials. These systems are designed with advanced medical informatic technology, which will allow clinical investigators to receive, share, and analyze voluminous multi-modality clinical data anytime and anywhere (see appendix D).

f. Special measurements

Protocol dose prescription and reporting are often straightforward and intuitive; for example, protocols that require dose prescription to a point within the target volume with a minimum and/or maximum dose constraint. There are some protocols that require reports of special measurements for protocol patients. These special measurements can be classified into three general categories. A few examples of each are supplied.

1. External Beam
   a. Treatment delivery system specific dosimetric parameters
      - mechanical and radiation beam alignment of the radiation delivery system (radiosurgery protocols)
      - off-axis radiation beam characteristics including off-axis ratios and beam hardening and softening [total body irradiation (TBI) protocols]
      - skin or surface dose (TBI protocols)
      - validation of inverse-square-law of extended distances used in special treatments (TBI protocols)
   b. Patient-specific measurements
      - Measured and estimated doses to critical structures such as eye lens, gonads, spinal cord, etc.
      - average internal organ motion (lung tumor protocol)
      - transmitted dose through partial transmission blocks (TBI and Hodgkin's lymphoma protocols)

- delivered dose rate (TBI protocols)

2. Brachytherapy (for example, permanent prostate implant protocol)
   a. Treatment delivery
      - Assay of at least 10% of the sources in a manner that maintains direct traceability to either the National Institute of Standards and Technology (NIST) or an Accredited Dosimetry Calibration Lab (ADCL)
   b. Patient specific
      - A CT scan is to be performed 3 to 5 weeks following the prostate seed implant which is used to create the delivered treatment plan. A postero-anterior (PA) and lateral chest x-ray will be obtained to document any pulmonary source migration

g. Special calculations

Radiation therapy protocols that utilize large and extended field treatments typically require reporting dose for several points within the field. For example, all Hodgkin's and TBI protocols require dose calculations at multiple points within the irradiated volume. Therefore, it is critically important that the physicist review protocol requirements for dose reporting and calculates or measures the dose at each specified point. It is essential to identify the dose calculation points explicitly on the simulator film and/or CT images. When thickness measurements are necessary, the physicist must be aware of these and ensure that the measurements are made.

The 3DCRT protocols often require the reporting of DVHs for both the target volumes and OAR. It is the responsibility of the physicist to ensure that all required structures are correctly segmented and that the dose is calculated with appropriate dose matrix resolution to give accurate representation of dose-volume information.

Some examples of special dose calculations are:

External beam:

- Re-normalization of dose distribution to comply with the protocol prescription
- Specific point dose calculations
- Dose calculation with and/or without inhomogeneity corrections
- Dose to OAR
- DVHs for target volumes, OAR, and other specified normal tissues

Brachytherapy

- DVH-based analysis to calculate the volume of prostate receiving various percentages of the prescribed dose
- the maximum dose to the rectum and the volume of the rectum that receives specified percentages of the prescription dose

h. Physicist contributions to the clinical trial QA process

Today, physicists are involved in the development and review of protocols as well as the case review of data submissions to quality assurance review centers. The RTOG and COG have physics subcommittees which advise the group regarding the radiation therapy portion of clinical trial protocols as well as other physics issues and questions which may arise during the course of protocol development, accrual, and data analysis. Other cooperative groups utilize physicists at the QA centers and at their member institutions. The National Cancer Institute of Canada handles quality assurance internally; medical physicists and radiation oncologists chosen for their expertise in this area may perform individual protocol case reviews.

Within the quality assurance review and resource centers, medical physicists play a key role providing advice on and reviewing protocol language, case review of submitted dosimetry, design of special quality assurance tools, and radiotherapy department quality inspections.

4. QUALITY ASSURANCE IN CLINICAL TRIALS

a. Overview of quality assurance review

In many cases, new standards of care are based on the best treatment arm from clinical trials. The role of quality assurance is to ensure that all patients in each trial arm are treated comparably so the outcomes of these trials are valid. For each protocol there are specific requirements for the patient treatment and for data that need to be submitted. For protocols with radiation therapy, these requirements (may) include (1) eligibility criteria to be on the protocol, (2) studies to be performed for the diagnosis and staging of disease, (3) specifications for the definition of target volumes and critical normal tissues, (4) dose, and hence treatment planning specifications of radiation therapy, and (5) studies and timing for following the progress of the patient. Since protocols vary, the physicist needs to read the specific protocol for each patient in order to comply with the treatment and with the data submission requirements. The CRA and the physicist compile the data for review by the QA center. Please see appendix D for details on each of the resource and review centers.

The timing and extent of QA review depends on the cooperative group and the protocol. In general, there are different levels of detail of the QA review. For some protocols, the radiation therapy is standard and not likely to influence the analysis of the study question. For example, many acute lymphocytic leukemia protocols test different chemotherapy regimes and include whole brain irradiation for some patients. The parallel-opposed fields irradiation is straightforward. Quality assurance review will include only a chart review to assure that the irradiation was performed and that the fraction dose and total dose were as prescribed by the protocol.

Another level of QA review may occur for protocols that, as in the simple review, include standard radiation therapy without a radiation question but with concern for efficacy and toxicity caused by the radiation. An example is a protocol for lung cancer that is examining the efficacy of one drug versus another with all patients receiving the same radiation therapy. The QA review will occur after the patient has completed treatment and will include a thorough review of the target volumes (using diagnostic imaging studies, surgery reports, etc.), a review of the treatment plan, a review of the dosimetry including dose to specified critical organs (such as the spinal cord), a review of the treatment delivery from portal films or portal images, and a chart review to verify the dose was delivered as specified.

A comprehensive level of quality assurance is usually applied for protocols that ask a radiation question and/or include advanced technology radiation therapy. For example, a COG medulloblastoma protocol that tests 18 Gy versus 23.4 Gy to the posterior fossa and mandates 3D conformal treatment would have comprehensive QA at QARC. For this the treatment plan and treatment fields will be required to be reviewed before, or at least within a few days of beginning treatment. The diagnostic imaging acquired for staging will be reviewed concurrent with the planning CT scan. The accuracy of the delineation of the posterior fossa as the target volume will be reviewed, as will the treatment plan. The prescribed fractional and total dose will be verified. Simulator films will be compared to DRRs. If there are any questions from this initial review, interactions will occur between the QA center and the treating institution. The process will be iterated until there is agreement among the physician, the radiation therapy principal investigator (PI) for the protocol, and the QA center's physician that the treatment is in compliance with the protocol and that treatment shall be delivered. At the completion of treatment, a final review will be performed. The chart will be checked to verify that the treatment was delivered as planned, portal images will be verified, and the treatment plan again verified.

b. Benchmarking and credentialing

Prior to participation in some clinical trials, the cooperative groups require a demonstration of certain technological and treatment planning capabilities. The prerequisites vary significantly. For some, completing a simple questionnaire about the facilities and technology that are available suffices. Others require performing representative treatment planning exercises, referred to as *benchmarks,* which are reviewed by the QA center and verified as being appropriate. The benchmarks may test relatively simple aspects related to quality assurance, e.g., dose and monitor unit calculations for standardized plans. Figure 2 illustrates a representative standard benchmark.

In addition, benchmarks may be required for specific protocols or for classes of treatments (e.g., total body irradiation) to verify the institution's ability to comply with these more complex protocols. The benchmark may include nam-

Irregular Field Benchmark

QARC Benchmark: Irregular Field

The following case is used to evaluate your calculation methods for irregular fields. It represents a single AP mantle field.

1) The field diagram is provided on page 5. The dimensions are appropriate at isocenter.
2) Beam energy: 4 – 10 MV photons.
3) Single field: Collimator setting = 30 cm x 35 cm (W x L)
4) 5 HVL thickness blocks.
5) Central axis (CAX) separation (patient thickness): 20 cm.
6) Pt. B: The distance from the source to Pt. B is 4 cm greater than the distance to CAX. (For example, if the SSD at CAX is 100 cm, the SSD at Pt. B is 104 cm.)
   10 cm superior and 5 cm lateral to the CAX.
   Separation (patient thickness): 16 cm.
7) Pt. C: The distance from the source to Pt. C is 4 cm less than the distance to CAX. (For example, if the SSD at CAX is 100 cm, the SSD at Pt. B is 96 cm.)
   At midline and 3 cm superior to inferior field edge.
   Separation (patient thickness): 24 cm.

Using the methods and forms routinely employed in your institution calculate:

1) The equivalent square of the treatment field.
2) The monitor units to deliver 90 cGy at midplane at the central axis (CAX).
3) The dose delivered at midplane at the off-axis Pt. B.
4) The dose delivered at midplane at Pt. C.

Submit: All computer printouts and your department forms used to calculate the monitor units and dose. Clearly indicate all factors used.
Complete the Irregular Field Benchmark section of Appendix I (page 14).

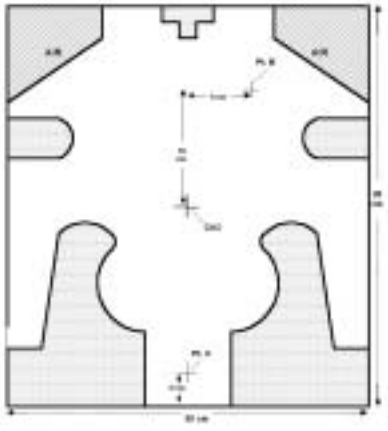


Figure 2. Example of a benchmark.

ing and certifying the experience of individual personnel who will be involved in the protocol treatment, such as the physician and the physicist for prostate seed implants. Examples of benchmarks which are being used by various cooperative groups with support from the Quality Assurance Review Center (QARC), the RPC, and the RTOG, include the following:

- Standard Benchmark Package
  —Wedged fields
  —Irregularly shaped field
  —Central axis blocked field
  —Cranio-spinal irradiation technique
- 3D Treatment Planning Benchmark
- 3DCRT Facility Questionnaire
- IMRT Questionnaire and Benchmark (may also include phantom irradiation)
- Total Body Irradiation Benchmark
- Stereotactic Radiosurgery (SRS) Benchmark, including anthropomorphic phantom irradiation
  —SRS with Gamma Knife
  —SRS with Linear Accelerator
- Prostate Brachytherapy Credentialing

Some credentialing processes involve mailed anthropomorphic dosimetry phantoms and electronic data submission. For example, the RTOG currently requires that institutions treating protocol patients with IMRT successfully complete a phantom test. The institution receives an anthropomorphic phantom, developed by the RPC, that contains dosimeters. The institution must perform imaging, transfer the images to a treatment planning system, develop an IMRT treatment plan, and deliver that plan to the phantom. The phantom and hard copies of the plan are to be submitted to the RPC, which evaluates the dosimeters and compares the measured doses to those calculated. If possible, instead of sending hardcopy plan data, the institution can submit the data electronically to the Image-Guided Therapy QA Center for the RPC to retrieve.

Individual protocols for 3DCRT and IMRT have strict requirements with regard to treatment volume definition, treatment planning, dose prescription, and submission of planning information. For protocols which require electronic submission of the radiation therapy treatment plan, “dry run” tests are required by the ATC to demonstrate electronic data submission capability and an understanding of the protocol planning and data submission requirements.

As appropriate, re-credentialing is required when important elements of an institution’s process change. These may include a new treatment unit, a new treatment planning computer system, or personnel.

Although these exercises may seem extraneous and onerous to the physicist, they may reduce the number of major protocol violations and are therefore essential to the success of the clinical trial. They should be approached as a

major contribution by physicists to the potential outcome of the studies. The QA centers work hard to make the certification of institutions as painless as possible.

c. How are the data that are submitted to the QA center evaluated?

Each protocol patient's data are reviewed by the QA center for completeness and compliance with protocol (figure 3). Certified research associates (CRAs) are responsible for obtaining and organizing all the data on each patient. These data may include multiple diagnostic, pre-treatment imaging studies, the treatment planning data, the target volume definition data, the dose calculation and dose to critical structure data, the treatment field verification data, the treatment chart, and follow-up studies.

The final evaluation of the patient's treatment is made by the responsible QA center in conjunction with radiation therapy PI for that protocol. Often experts in other specialties, such as diagnostic radiology, are included in the final review that occurs after the treatment is complete. The patients are evaluated for compliance with the specific requirements of the protocol on which they were entered (figure 4). The treatment is scored as *compliant, minor deviation, major deviation,* or *unevaluable.* These scores are based on a number of criteria, including patient eligibility, completeness of data submissions, and adherence to the protocol requirements. Enrolling a patient in a protocol carries with it an ethical responsibility for the participating individuals at an institution to complete all data submissions. CRAs will have actively pursued obtaining all the data before the final review. If you receive an inquiry from them, you need to respond promptly since a final review meeting may be imminent. It is most efficient to have supplied the required data initially.

At the final review the diagnostic information is reviewed to verify that the patient was eligible to be on the protocol. The pathology and surgical reports are reviewed and the diagnostic imaging studies thoroughly examined. The target volumes will be reviewed. This includes review of simulator films showing the blocking for two-dimensional (2D) treatments and an evaluation of the target volumes as delineated on the planning CT scan for 3D treatments. The volumes are scored as *compliant* if the reviewers agree they are as specified in the protocol, as a *minor deviation* if the treatment fields have too little margin or are too large, and as a *major deviation* if the treatment fields do not include all the GTV (as defined by the reviewers).

The treatment plan is assessed for compliance with the specifications of the protocol and the treatment chart reviewed to ascertain that the fractional dose and total dose were delivered as prescribed in the protocol. The physics and dosimetry staff at the QA centers evaluate the treatment plans, the beam calculations, the simulator films, and the chart. The plan is scored as compliant if the dose criteria are as required by the protocol. A *minor dose deviation* will be scored if the total dose or fractional dose exceeds the protocol specification by some stated range, e.g., –10% to –5% and +7% to +10%, or if the doses to

AHOD0031 DATA/FILMS CHECKLIST

Version Date 2/12/2004

QARC Contacts:

Email SKessel@QARC.org TBorchardt@qarc.org **Phone (401) 454-4301**

PRE-TREATMENT IS REVIEW REQUIRED FOR ALL INSTITUTIONS

INITIAL PRE-TREATMENT DATA:

_____ RT-1 Form
_____ RT simulation/ DRR films
_____ RT verification (portal) films or real time portal imaging
_____ Photograph(s) of patient with treatment fields marked and clearly visible
_____ Monitor Unit calculations
_____ Calculations required for gaps and critical organ doses (when applicable)
_____ Reference point dose(s) and attendant calculations
_____ Isodose plans (when applicable and should be in color)
_____ Photos of Electron fields (when applicable)
_____ All required diagnostic imaging**** (see list below)
_____ Copy of treatment prescription for entire treatment

FINAL DATA:

_____ RT-2 Form
_____ Daily RT Treatment Chart (including cumulative doses to all required areas, critical organs, reference points)
_____ Additional calculations or data required to assess the RT volume(s)
_____ RT-1 Form for subsequent field modifications
_____ Calculations or data for subsequent field modifications
_____ RT simulation films for subsequent field modifications
_____ RT verification (portal) films for subsequent field modifications
_____ Copy of treatment prescription for entire treatment

DIAGNOSTIC IMAGING:

****must be submitted for pre-treatment review if not previously submitted for a response review*

The following studies and radiology reports are required at the time points identified below:

_____ CXR (PA & Lateral)
_____ Gallium Scan (Planar & Spect– if done)
_____ PET Scan (if applicable)
_____ Bone Scan (if applicable)
CT
_____ Neck
_____ Chest
_____ Abdomen
_____ Pelvis

Please identify the time point(s) for the study or studies included in this film submission:

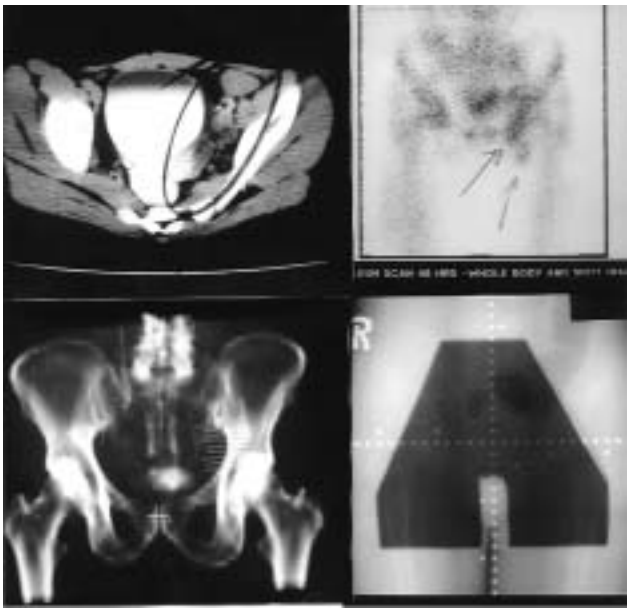
_____ Baseline (Pre-study)
_____ After 2 cycles of chemotherapy
_____ After 3 cycles of chemotherapy
_____ After completion of chemotherapy
_____ Relapse/ Progression

- MAIL ALL DATA & FILMS TO: **(If you need verification of receipt of this data, please write your name & address):**

QARC
272 West Exchange Street, Suite 101
Providence, RI 02903

Figure 3. Checklist for CRAs for one protocol, indicating the data that must be sumitted for QA review.

(a)



(b)

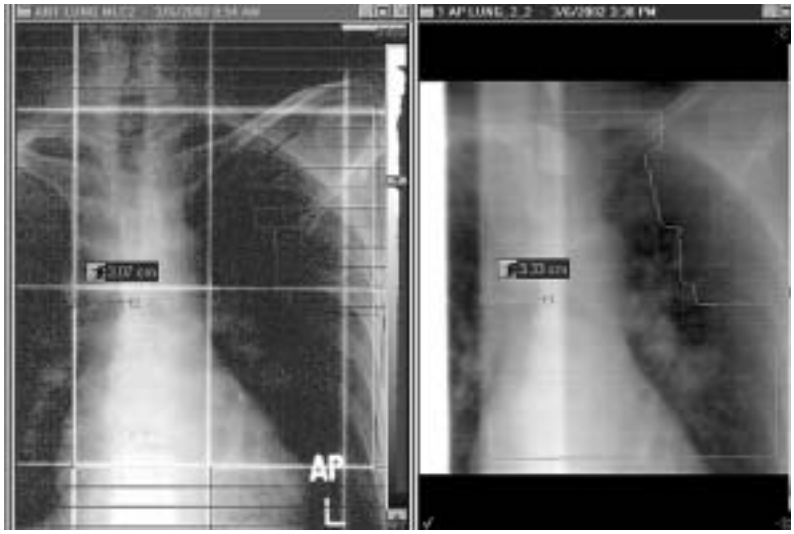


Figure 4. (a) Sample variety of imaging reviewed for one protocol patient. (b) DRRs (left), or simulation films, are compared to portal images (right) or portal films.

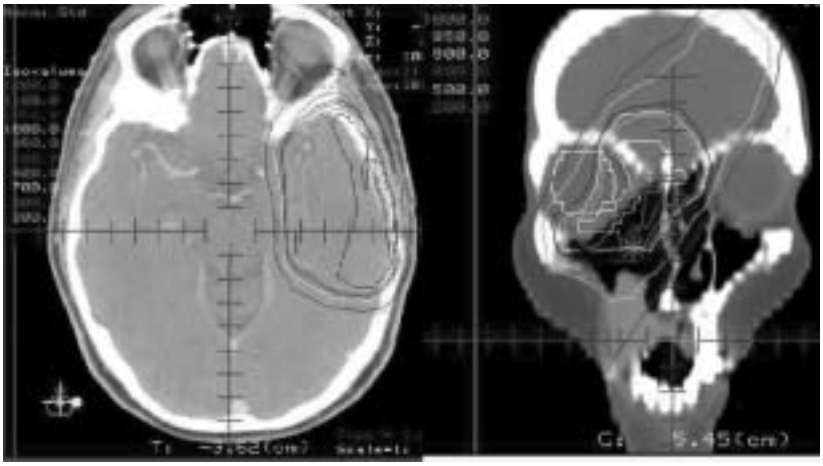
(c) 

Figure 4 (continued). (c) Target volumes, normal tissues, and dose distributions are reviewed for compliance to protocol and dose.

requested normal tissues are not reported or are not within the specifications. A *major dose deviation* will be scored if either the total dose or the fractional dose is not within the limit specified in the protocol, which is usually greater than ±10%. A major deviation will also be assigned if the planned dose distribution does not include all the GTV or the dose to certain specified normal tissues exceeds the protocol limits. For 3DCRT and IMRT protocols, compliant and minor and major deviation statements are defined in terms of dose-volume relationships for target and normal tissues.

Another criterion to be reviewed is that the treatment fields were appropriately positioned to deliver the planned treatment. Simulation films, DRRs, and verification portals are compared. Treatment delivery is scored as *compliant,* or as a *minor* or *major deviation* depending on the degree of compliance with the radiation treatment guidelines in the protocol.

These planning and delivery aspects will be reviewed for each patient by some QA centers for certain cooperative groups. In other cases, QA centers use proven sampling methods to select patients for review. The radiation therapy principal investigator (RT PI) for the study makes the final determination as to whether or not each patient is scored as compliant or as having a major or minor deviation. The final score is recorded and sent to the operations and statistical offices of the cooperative groups and to the PI and the RT PI of the institution that treated the patient. Most of the cooperative groups are organized with committees by disease sites and by discipline. Radiation Therapy Quality Assurance is usually a subcommittee of the Radiation Therapy Discipline Committee. Some groups, such as RTOG, have quality assurance performed by internal staff; others, such as COG and ECOG (Eastern Cooperative Oncology

Group), have an outside organization, such as QARC and RPC, perform the reviews. The compliance scores for each institution are sent to the RT QA committee of the group. The composite scores of all patients is a major and often sole component of that institution's radiation therapy performance, and are factored into the institution's overall performance score. The continuation of an institution's participation in the cooperative group is contingent on maintaining a satisfactory performance score.

5. PHYSICS RESOURCE REQUIREMENTS

In general, the physicist's role can be categorized in three areas: program start-up, routine QA, and protocol-specific support. In the sections below, a variety of physics tasks for each area are discussed. Collectively, these efforts can require a significant amount of physics staff time. The radiation oncology department administration should understand and support this time commitment when the department decides to participate in clinical trials. This document can provide support to the physicist and administrator in anticipating this extra physics time commitment.

a. Start-up, cooperative group participation, and credentialing

Time for filling out forms for institutional application, including data regarding radiation oncology can easily take 3 hours. The various benchmarks required by the group and/or a specific protocol must be satisfactorily completed. The standard set and the 3D benchmark may take about 4 hours each. The IMRT questionnaire and benchmark may require more time than this, depending on the QA measurement and analysis techniques of the institution. For those protocols that require the scanning, planning, and irradiation of anthropomorphic phantoms, at least a day's work will need to be allocated. Some protocols require digital submission of the treatment planning data. The effort required to accomplish this varies depending on one's planning system and hospital network infrastructure. Validation of the data exchange feature of one's planning system, an effort that is beyond standard commissioning, is required, and significant interfacing with the hospital information systems group may also be needed.

b. Routine QA physics support

Every institution that desires to participate in NCI-sponsored clinical trials involving radiation therapy must participate in the RPC TLD dosimetry program. Annually, on an anniversary schedule, a subset of the beams in the radiation oncology department must be used to irradiate TLD-containing blocks (appendix D, section 3). Setup and irradiation time and forms completion and preparation for return to the RPC take about 1 hour for a dual-energy linear

accelerator (linac), assuming that the TLD irradiation immediately follows the routine output check. Additional time should be allotted if additional output measurements must be made to determine the dose on the day of the TLD irradiation.

c. Protocol-specific physics support

The physics involvement for specific protocols varies significantly. The most important time-saver is to be aware that a patient is on a protocol and to read the protocol for physics-related requirements. Going back to fulfill the requirements after the patient has completed treatment planning and maybe even after treatment can be frustrating, time-consuming, and, most significantly, perhaps impossible.

Some protocols will only require completion of one or two forms that document the details of the treatment, taking 30 minutes or so. Protocols which require submission of planning scans with target volumes and normal tissue contours with isodoses overlaid, DVHs, and DRRs may require an additional hour to create the hardcopy or to transmit the data electronically. For the image-based protocols, the physics staff rather than the CRA will prepare and send full digital data sets including CT images with RT structures, plan data, 3D dose matrices, DVHs, and DRRs. The physics staff may also be charged with submitting diagnostic image data electronically, which can take 1/2 to 1 hour depending on the situation. Thus, filling out the necessary forms, producing the hard copy or electronic data submission, and sending these data to the cooperative group's QA center can take more than 2 hours of physics staff time per patient.

6. SUMMARY

The clinical radiation therapy physicist has a large and important role in the success of clinical trials involving radiation therapy by ensuring that the patients at his/her facility are treated per the protocol specifications, that the treatment equipment is quality assured, and that the treatment plan data and other required dosimetric data are submitted accurately and on time to the quality assurance review center.

This role is often not included in the job description or in the calculation of FTEs (full-time equivalents) but can indeed take a significant amount of physics staff time. This document can help the physicist to both understand the duties required for assuring protocol compliance and also to serve as a resource to educate administrators and radiation oncologists regarding the physics commitment needed for a successful clinical trials program.

As technology advances, the use of radiation therapy in clinical trials becomes more sophisticated. Currently, there are clinical trials that require 3D treatment planning and delivery and electronic data submission to the QA

center. More and more protocols will allow and even encourage or require the use of IMRT. This is indeed a new era and the physicist must be aware and able to provide the services necessary to comply with these more complex protocols.

In the near future, facilities and their physicists which have not had a significant exposure to clinical trials involving radiation therapy will encounter an increasing number of patients on national clinical trials due to the NCI program to encourage the participation by patients seen at any institution that is credentialed by the RPC. In anticipation of these changes, this document attempts to educate and prepare the physicist to be a competent member of the clinical trial team and for a much more involved role in the treatment of patients on clinical trials in the future.

APPENDIX A

Phases of Clinical Trials

Phase I trials: These studies evaluate how a new radiation treatment should be given, for example, what dose is safe or tolerated and how often and by what delivery mechanism should the radiation be given. Typically, phase I trials involve patients with a cancer that does not respond well to standard treatment. An example of a pure radiation therapy phase I trial to assess feasibility and toxicity was the Children's Oncology Group (COG) study 9951, where children with recurrent brain tumors were treated with stereotactic radiosurgery by delivering a single fraction of 14 to18 Gy (depending on target volume). In such cases, the quality assurance for the radiation treatment needs to be stringent because the question being asked in the study is about radiation toxicity. A phase I trial usually enrolls only a small number of patients, sometimes as few as a dozen. These studies frequently focus on a variety of cancers, such as all solid tumors. If the results are promising, then a phase II trial may be designed to study a narrower population based on what is learned in the phase I trial.

Phase II trials: A phase II trial continues to test the safety of the radiation treatment or of the drugs used in combination with radiation and begins to evaluate effectiveness. Phase II studies involving radiation therapy typically focus on a particular type of cancer. They usually are based on other phase II trials or on phase I trials. For example, the maximum tolerable dose (MTD) for a chemotherapy agent determined in the phase I trial will then be used in a phase II trial to determine its effect more completely. In most phase II trials, all participants receive the same dose of the tested drug or radiation. The new treatment is assessed for effectiveness, and additional safety information is noted. Even if the new treatment seems effective, it usually requires further testing before entering widespread use. Because the treatment has not been compared to any other therapy or technique, its relative value is unclear, and it is impossible to rule out other factors that may have influenced its effectiveness. Frequently, phase I and phase II trials are combined, testing toxicity and efficacy in the same study. For example, in the Children's Cancer Group (CCG) 9942 trial, children aged 3 to 21 years with newly diagnosed intracranial ependymoma were given vincristine, cisplatin, cyclophosphamide, and etoposide chemotherapy prior to radiation therapy to assess the response rate and toxicity of this therapy. Here, the radiation therapy is given as an adjuvant (additional therapy given equally to both arms of the study) to the chemotherapy. Typically, the quality assurance of the radiation therapy in the adjuvant setting is less stringent than when the radiation therapy itself is the study question. In RTOG H-0022, a phase I/II study of conformal and intensity-modulated irradiation for oropharyngeal cancer, the feasibility of adequate target coverage and major salivary gland sparing in these patients is assessed. If the therapy regimen being studied appears to improve local control with reasonable toxicity,

a phase III clinical trial may be designed that tests this new therapy against the best current standard therapy.

Phase III trials: These studies test a new drug, a new combination of drugs, a new radiation therapy regimen, or a new surgical procedure to determine if it is superior to the current standard for a specific cancer. 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. In phase III trials, patients are randomly assigned to either a control group or an investigational group. The control group receives the most widely accepted treatment (standard treatment) for their cancer. The investigational group receives the new agent or therapy being tested. When the protocol question concerns the effectiveness of a particular radiation therapy regimen, then the experimental group gets the new radiation treatment while the control group gets standard treatment which may or may not include radiation therapy. As for phase II studies, protocols with a radiation therapy question require more intense quality assurance. Phase III trials often enroll large numbers of people and may be conducted at many doctor's offices, clinics, and cancer centers nationwide. For example, in the RTOG H-0129 phase III trial of concurrent radiation and chemotherapy for advanced head and neck carcinomas, the control arm was standard fractionation of 70 Gy in 35 fractions in 7 weeks plus cisplatin while the experimental arm was accelerated fractionation by concomitant boost giving 72 Gy in 42 fractions in 6 weeks plus cisplatin. Because the question being asked in the trial was about how well a certain radiation therapy regimen works, a comprehensive quality assurance review was demanded. At the end of the study, if one group has a statistically better outcome than the other, the investigators will be able to conclude with confidence that one treatment is better than the other. The results of these studies are reported in peer-reviewed scientific journals. Once an intervention is proven safe and effective in a clinical trial, it may become the new standard of practice.

APPENDIX B

Statistical Analysis in Clinical Trials

a. The role of statistics in clinical research

Clinical trials are experiments on human subjects. Comparative treatment efficacy studies (also called phase III trials) compare the effectiveness of alternative medical interventions for a particular disease, with patients often assigned to a specific treatment through some random process. As Richard Simon has said, "A good intervention trial asks an important question, gets a reliable answer, and is honestly reported (Simon 1999)." Statisticians contribute to assuring that intervention trials are "good" in a variety of ways.

Design: Statisticians collaborate on study design, in part by developing study "statistical considerations." These considerations establish the outcome parameter(s) that will be used to decide if the treatments produce medically important differences in outcome. They define the size of the difference thought to be medically meaningful, and they calculate the sample size required to provide some fixed assurance that, if a specific difference in outcome exists, the analysis of the study data will lead to a statistically significant result. For example, the Intergroup Rhabdomyosarcoma Study (IRS) Group conducted a study (IRS-IV) of conventional radiotherapy (C-RT; 50.4 Gy) versus hyperfractionated radiotherapy (HF-RT, twice daily; total dose 59.4 Gy) for patients with rhabdomyosarcoma and gross residual disease at study entry (Donaldson et al. 2001). The study was designed with failure-free survival (FFS: time to the first occurrence of progression, relapse after response or death from any cause) as the primary study endpoint. The total sample size was set to be at least 438 eligible patients. This sample size was chosen because it provides 80% confidence that the comparison of FFS between the two treatments would be statistically significant (testing at the 5% level of statistical significance, two-sided) if the true 5-year FFS was 65% for C-RT (from prior experience) and 77% for HF-RT (postulated).

Conduct: Researchers conducting comparative trials have an obligation to study subjects to see that toxicity and efficacy are monitored during the conduct of the trial and that the study is changed or suspended if there is convincing evidence that important differences between treatments exist. A Data Monitoring Committee, independent of the study researchers, often performs this function (Smith et al. 1997, Ellenberg 2001). Statisticians have developed special statistical methods that allow for multiple interim "looks" at the outcome data as the study is ongoing that allow the study to be stopped when there is sufficient evidence that treatment differences exist, while minimizing the chance that the outcome by regimen will be declared different when, in fact, they are the same.

Analysis and Reporting: Because comparative efficacy trials are most often designed to assess whether one treatment is to be preferred when used in standard clinical practice, statistical analysis and reporting should focus on all eligible patients entered on protocol. This "intent to treat" principle means that all eligible patients are to be analyzed, irrespective of their adherence to protocol treatment. For instance, the comparison of C-RT to HF-RT in IRS-IV involved the analysis of all eligible randomized patients, even though it turned out that only 57% of the patients less than 5 years of age randomized to HF-RT actually received it (Donaldson et al. 2001). Statisticians also understand the difficulties that can exist when attempts are made to compare the outcome of patient subsets which are themselves defined by "outcomes" (like compliance to therapy). The following section describes the role of quality assurance reviews in the interpretation of the outcome of clinical research trials, and also the appropriateness of their use in the analysis of outcome data.

b. The role of quality control review in the analysis of clinical research trials

Investigators are often interested in assessing to what extent patients treated on a clinical trial received the protocol-specified therapy. For instance, a process of radiation therapy quality assurance might assess whether the volume, dose, and timing of the radiation therapy delivered is consistent with protocol requirements. Surgical quality control might assess the completeness of surgical resection, and evidence for negative margins.

Quality assurance processes are important, because they provide important information on how therapy is delivered in practice. Quality control feedback to treating physicians may increase the likelihood that future patients receive protocol-specified therapy. **Efforts to reduce the variability in the treatment delivered are likely to increase the power to detect important differences in outcome by treatment.** Feedback to the protocol research team may lead to changes in the protocol-specified therapy, and a greater likelihood that therapy will be delivered according to protocol. For instance, the QARC has demonstrated that the longer institutions participate in its process of radiotherapy quality review, the lower the protocol non-compliance rate (Reinstein et al. 1985). It also showed that the process of "on treatment" review of radiotherapy planning reduced the rate of major deviations by 50%.

Data from the radiation therapy quality assurance process performed by QARC for IRS-IV showed that some radiation oncologists or parents were unwilling to deliver hyperfractionated radiotherapy to children less than 5 years of age, compromising the randomized comparison of conventional versus hyperfractionated radiation for these patients (Donaldson et al. 2001). QARC has also reviewed the quality of prophylactic cranial radiotherapy in 353 patients with childhood acute leukemia treated on Pediatric Oncology Group trial 9404 (Halperin, Laurie, and Fitzgerald 2002). It was found that major deviations

were more likely to be seen in institutions treating a small number of patients (1 to 4 study entries, 11%; 5+ entries, 5.5%). They also showed that compliance with radiotherapy guidelines increased over the period the study was open (percent major deviations: 1996–1997, 15.5%; 1998–2001, 4.7%).

Investigators are often interested in comparing outcomes between patients who comply with protocol-specified treatment and those who do not. For instance, investigators from the French Society of Pediatric Oncology (SFOP) studied the impact of radiotherapy targeting deviations on outcome for 169 patients with medulloblastoma (Carrie et al. 1999). They found that the number of *major* deviations in targeting was correlated with the risk of tumor relapse. The estimated 3-year relapse rates by number of major and minor deviations were: 0 major or minor deviations, 23% (N = 49); 0 major but with at least 1 minor deviation, 38% (N = 67); 1 major, 17% (N = 37); 2 major, 67% (N = 11); 3 major, 78% (N = 6). In addition, the role of quality of radiation on local control was examined by Donaldson et al., during analysis of POG 8346 for Ewing's sarcoma. It was found that patients with a major deviation in either definition of target volume or of dose distribution had a 5-year local control rate of only 16%; those with a minor deviation had a 48% local control rate; while those whose treatment was appropriate in both volume and dose had a 5-year local control rate of 80%, $p = .005$. This trend also pertained to event free survival, $p = .074$ (Donaldson et al. 1998).

While the analysis of outcome by compliance may be useful in identifying treatment planning problems that may have an impact on outcome, such analyses have the potential for bias and may be misleading (Shuster and Geiser 1998). Compliance may be related to patient or disease characteristics. The dose of protocol-specified radiation may be decreased appropriately because of toxicity; the protocol-specified field size may be modified in an attempt to reduce toxicity to vital organs. Hard-to-treat tumors may also be inherently more difficult to cure, and it may be impossible to adequately adjust these compliance comparisons for differences in important prognostic factors.

APPENDIX C

Cooperative Groups

ACOSOG: American College of Surgeons Oncology Group
DUMC BOX 3627
Durham, NC 27710
http://www.acosog.org

ACRIN: American College of Radiology Imaging Network
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103
http://www.acrin.org

CALGB: Cancer and Leukemia Group B
CALGB Central Office
Suite 2000
208 South LaSalle Street
Chicago, IL 60604-1104
http://www.calgb.org

COG: Children's Oncology Group (includes National Wilms' Tumor Study)
COG Operations Center
P.O. BOX 60012
Arcadia, CA 91066-6012
http://www.childrensoncologygroup.org/

ECOG: Eastern Cooperative Oncology Group
ECOG Coordinating Center
Frontier Science
900 Commonwealth Avenue
Boston, MA 02215
www.ecog.org

EORTC: European Organization for Research and Treatment of Cancer
EORTC Central Office
Avenue E. Mounier 83, BTE 11
1200 Brussels
Belgium
http://www.eortc.be/default.htm

GOG: Gynecologic Oncology Group
GOG Administrative Office
Four Penn Center
1600 JFK Boulevard
Suite 1020
Philadelphia, PA 19103
http://www.gog.org

JROSG: Japanese Radiation Oncology Study Group
Email JDM05126@nifty.com
http://www.jrosg.jp (in Japanese)

NABTT: New Approaches to Brain Tumor Therapy
Johns Hopkins Hospital
Bunting Blaustein Bldg, G87
1650 Orleans Street
Baltimore, MD 21231-1000
http://www.nabtt.org

NCCTG: North Central Cancer Treatment Group
NCCTG Operations Office
200 First Street, SW
Rochester, MN 55905
http://ncctg.mayo.edu

NCIC: National Cancer Institute of Canada Clinical Trials Group
Queen's University
10 Stuart Street
Kingston, ON K7L 3N6
Canada
http://www.ctg.queensu.ca/

NSABP: National Surgical Adjuvant Breast and Bowel Project
Division of Surgical Oncology
Allegheny General Hospital
320 East North Avenue
Pittsburgh, PA 15212-9986
http://www.nsabp.pitt.edu

PBTC: Pediatric Brain Tumor Consortium
Operations and Biostatistics Center
St. Jude Children's Research Hospital
Department of Biostatistics
332 North Lauderdale Street
Memphis, TN 38105
http://www.pbtc.org

RTOG: Radiation Therapy Oncology Group
Radiation Therapy Oncology Group
Fourteenth Floor
1818 Market Street, Suite 1600
Philadelphia, PA 19103
http://www.rtog.org

SWOG: Southwest Oncology Group
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
http://www.swog.org

TROG: The Trans-Tasman Radiation Oncology Group
TROG Central Operations Office
Department of Radiation Oncology
Newcastle Mater Hospital
Locked Bag 7
Hunter Region Mail Centre NSW 2310
Australia
http://www.newcastle.edu.al/centre/trog

APPENDIX D

The Quality Assurance Resource and Review Centers

a. Quality Assurance Review Center (QARC)

QARC was created in the late 1970s to develop radiotherapy guidelines and a system to accumulate radiotherapy data in a systematic fashion for the Cancer and Leukemia Group B (CALGB). In 1980, QARC was formally established and has been funded since then by the NCI to provide quality assurance review for various cooperative groups. Currently QARC provides quality assurance review for the Children's Oncology Group (COG), the Pediatric Brain Tumor Consortium (PBTC), the Cancer and Leukemia Group B (CALGB), the Eastern Cooperative Oncology Group (ECOG), the American College of Surgeons Oncology Group (ACOSOG), and the Southwest Oncology Group (SWOG). Over the years, QARC has reviewed and has files on more than 30,000 patients treated on protocols. All data, including imaging, films, and charts, are stored at QARC and are available for retrospective studies.

Currently, QARC receives data from approximately 800 institutions on patients entered into more than 90 protocols. The foundations of QARC's work are the five components of a comprehensive quality assurance program: (1) facilities inventory; (2) protocol development; (3) data management; (4) credentialing; and (5) patient data review (interventional and final) and feedback. Active interactions with the RPC are maintained in order to assure that participating institutions are currently being monitored by RPC and their calibrations and treatment planning data are acceptable.

The physicians, physicists, and CRAs at QARC work with the radiation study PI on new protocols to develop consistent guidelines for diagnostic studies, target volume definition, target and organ-at-risk dose goals, dosimetry verification, quality assurance documentation, and protocol compliance. QARC staff is involved in multiple iterations of the protocol as it is developed.

As radiation therapy becomes more technological and complex, the cooperative groups increasingly want to assure that institutions have the treatment planning and treatment delivery expertise to participate in the study. Benchmark cases have been developed by QARC that represent various treatment planning situations. These benchmarks were discussed in section 4b.

Once a study is activated, QARC receives notification of each patient when registered into the protocol. QARC's CRAs communicate with the institutions to ensure that the correct data are submitted at the desired times. Most current protocols reviewed by QARC require a pre-treatment or on-treatment (within 3 days of beginning radiation therapy) review. These interventional reviews are performed within 24 hours of data arriving at QARC. A CRA checks that all required data are available, including diagnostic imaging studies, treatment plans, and patient setup data (DRRs, simulation images, etc.). If not complete,

the institution is notified. The physics staff reviews the dose prescription and treatment plan. The QARC radiation oncologist reviews the staging and diagnostic imaging studies and the target volumes and treatment fields. A telephone call to the treating physician is made when modification in either the target volumes or the treatment plan is needed. A fax summarizing the review is sent to the treating physician.

Radiation oncologist PIs periodically review patients on their studies who have completed treatment. A final review is performed at QARC on every protocol patient. Verification of dosimetry and delivered dose and evaluation of the target volumes and the treatment fields are completed. As studies have become more complex, reviews have extended the traditional boundaries of radiation therapy. Surgical, diagnostic, and medical oncology experts often are included to review protocol eligibility, diagnostic staging, extent of surgical resection, and patient's response to therapy. In general, there are three levels of detail of the QA review at QARC: (1) simple; (2) standard; and (3) comprehensive. These levels of QA were described in section 4a. Results of the final review are entered into the QARC database and transferred to the cooperative group's statistical and operations center. Annually, QARC provides scores on each institution's performance that reflect the completeness of data submission and the compliance with the treatment specifications of the protocols.

QARC accepts imaging, treatment planning, and patient position verification data in multiple formats. Electronically transferred DICOM (Digital Imaging and Communications in Medicine) images, jpeg files, and hardcopy are all acceptable for QARC's review process. Electronic transfer of imaging and treatment planning data is becoming more standardized and many institutions are now finding it easier and more efficient to submit these studies digitally. QARC can read DICOM data, received either across the Internet (securely) or on compact disks (CDs). These data are stored on a separate server but linked to the patient in the QARC database for rapid retrieval and review. QARC is an active participant in the ATC, which is developing the infrastructure to receive, archive, and retrieve for review all radiation therapy data from cooperative group trials.

b. Resource Center for Emerging Technology (RCET)

The RCET at the University of Florida was established in April 1999 in response to Request for Applications (RFA) from the Radiation Research Program, Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI) to develop and then disseminate resources that would facilitate the conduct of NCI-sponsored advanced technology clinical trials such as 3DCRT and stereotactically directed radiation therapy. RCET has developed an infrastructure for distributed database, visualization, and analysis systems for collecting, sharing, and distributing information generated by institutions participating in clinical trials. The technology developed at the RCET enables users

to submit multi-modality imaging data, radiation therapy planning, and delivery data, and conventional database objects using a secure upload method that is fully compliant with Health Insurance Portability and Accountability Act (HIPAA) regulations. The system consists of a centralized database, web server, 3D data visualization tools, ActiveX and Java browser components, and an object transaction server. The software modules enable users to share multidimensional treatment planning and Quality Assurance (QA) data objects, which include 3D visualization and imaging information, as well as conventional database objects. In 2002, RCET became an integral part of the ATC.

The RCET system provides a set of services for institutions that participate in clinical protocols. Using RCET client software, participants of a clinical trial can make anonymous and send required study data for each case. The submitted information becomes readily available for remote review using a Web browser. In addition, users can perform retrieval of original archived data for visualization, modification, and analysis similar to a DICOM-RT–based picture archiving and communication system (PACS). It also provides the opportunity for remote peer review. This infrastructure and the developing software tools are the basis for the future ATC web-based system described in section f below.

c. The Radiological Physics Center (RPC)

The RPC was established in 1968 upon the recommendation of the Committee on Radiation Therapy Studies (CRTS), under the sponsorship of the American Association of Physicists in Medicine (AAPM) to ensure the correctness and consistency of radiation dosimetry among institutions participating in inter-institutional cooperative clinical trials. Today, the RPC monitors some aspects of dosimetry for all of the active NCI-funded cooperative groups and several intergroup activities. Review of radiation dosimetry is accomplished principally by on-site visits to institutions by a physicist, evaluation of various mailed dosimeters, and by evaluation of the radiotherapy treatment of patients (both benchmark and actual protocol patients). When errors are discovered, the RPC works with the institution to help them rectify the errors. The RPC is unique in that it is the only QA program related to cooperative groups that performs comprehensive evaluation of radiation dosimetry through an on-site evaluation.

The RPC communicates and interacts with all of the active NCI funded cooperative clinical trial groups through attendance at their semi-annual meetings, membership on various committees, and interaction with the group's quality assurance offices. The RPC serves as a resource to the cooperative groups during the development and execution of protocols. Services include advice on the feasibility of the study from a dosimetry standpoint, assistance in drafting the dosimetry and reporting sections to assure that the treatment can be delivered by multiple institutions using multiple energies and techniques, credentialing institutions to participate, and evaluating patients treated on the protocol.

The RPC, which is funded by the NCI, serves as a national resource in radiation dosimetry and physics for cooperative clinical trial groups and all radiotherapy facilities that deliver radiation treatments to patients entered onto cooperative group protocols. To accomplish this, the RPC has implemented a quality assurance program that monitors the basic machine output and brachytherapy source strengths, the dosimetry data utilized by the institution, the calculation algorithms used during treatment planning, and the institution's quality assurance procedures. The methods of monitoring include (1) on-site dosimetry reviews by an RPC physicist, (2) various remote audit tools, and (3) patient chart reviews. During the on-site evaluation, the institution's physicist and radiation oncologist are interviewed, physical measurements are made on the therapy machines, dosimetry and quality assurance data are reviewed, and patient dose calculations are evaluated. The remote audit tools include: (1) mailed dosimeters (TLD) evaluated on a periodic basis to verify output calibration and simple questionnaires to document changes in personnel, equipment, or dosimetry practices; (2) comparison of dosimetry data with RPC "standard" data; (3) evaluation of reference and/or actual patient calculations to verify the validity of the treatment planning algorithms; (4) review of the institution's written quality assurance procedures and records; and (5) mailed anthropomorphic phantoms to verify tumor dose delivery for special treatment techniques. Criteria for compliance between the RPC and the participating institutions are found in Table D–1. Any discrepancies identified by the RPC are pursued to help the institution find the origin of the discrepancy and to identify and implement methods to resolve them. Thus the RPC overall QA review program impacts not only on the quality of an institution's clinical trial patient treatments, but on the quality of all patient treatments at the institution.

The RPC routinely monitors all conventional therapies including external beam megavoltage photon and electron therapy as well as low and high dose-rate brachytherapy. Monitoring procedures are modified to accommodate new techniques and special procedures used in cooperative group trials. Therefore, asymmetric jaws, multileaf collimators, dynamic wedges, and non-coplanar beam procedures are monitored as well as some special procedures including total body photon, intra-operative electron beam, stereotactic radiosurgery, image-guided radiotherapy, and conformal radiotherapy. Monitoring of proton beams is anticipated in the near future.

i. On-site dosimetry review visits

On-site dosimetry review visits by an RPC physicist are done on an as-needed basis according to the RPC's prioritization schema. An institution becomes a priority for an "immediate visit" if a dosimetry discrepancy exceeding 5% is identified. These problems can be identified from the mailed TLD program, mailed anatomic phantom, evaluation of dosimetry data, evaluation of a reference treatment case, or evaluation of a protocol patient either by the RPC

Table D–1. Criteria for Acceptable Compliance Between the RPC and Participating Institutions

1. Absorbed Dose: External beams (photon and electron)	
a. Tumor dose delivery	±5%
b. Beam calibration	±3%
c. Relative measurements (e.g., tray, wedge, depth dose factors, cone ratios, etc.)	±2%
d. Depth for a stated percentage depth dose for electrons	±3mm
2. Absorbed dose: Brachytherapy	
a. Dose delivery or	±15%
position of isodose line	±1 mm
b. Source calibration	±5%
3. Mechanical	
a. Congruence of light field and radiation field on an edge	±3 mm
b. Agreement between light field and field size indicators	±3 mm
c. Agreement between treatment distance indicators	±3 mm
4. Anatomic Phantoms	
a. Absorbed dose near the center of the target	±5%
b. Placement of the field (depends on phantom)	±1–4 mm

or one of the QA offices. The remainder of the prioritization scheme is based on participation in cooperative group trials, time since last visit, and whether the institution has a therapy unit for which the RPC has limited sets of measured data. These various features are assigned points, and institutions with the most points are the highest priority for an on-site visit.

During the on-site dosimetry review, the physicist is interviewed to determine his methods of machine calibration and calculation of tumor dose. After the normal treatment day is complete, the RPC physicist makes dosimetry measurements on the therapy units. The RPC follows the Task Group 51 (TG-51) calibration protocol (Almond et al. 1999) for megavoltage photons and electrons. The TG-25 protocol (Khan et al. 1991) is used for electron dosimetry and the TG-40 guidelines (Kutcher et al.1994) are used for the review of QA procedures at the institution. For photons mechanical measurements and ion chamber measurements are made in-air and in-water. For electrons only in-water measurements are made. The RPC physicist performs all calculations at the time of the measurements so any discrepancies with the institution are known and can be pursued and potentially resolved on the spot. The RPC physicist attempts to identify the origin of discrepancies at the 1% level if possible. Discrepancies that could lead to a discrepancy in the delivery of tumor dose to a patient exceeding 5% are pursued aggressively. However, discrepancies exceeding 3% are typically discussed with the physicist to attempt their resolution. An exit interview is held with the radiation oncologist and physicist

where all discrepancies are reviewed and suggested modifications of the institution's dosimetry system are discussed. The first draft of the detailed report is left with the institution at the time of the exit interview. The institution is advised to review the report, pursue modifications of their system, and submit to the RPC changes in their dosimetry system implemented as a result of the RPC visit while the RPC reviews the report internally. The detailed report of the visit is finalized and forwarded to the institution. This final report incorporates the results of any changes made by the institution. The institution is encouraged to review the document for completeness, within one month, so that the RPC can send a summary report of the on-site visit to the chairman of the cooperative group(s) and the chairman of the radiotherapy committee for the group(s).

ii. Remote Audit Tools

(1) Mailed TLD program

All institutions that are active on clinical trials are monitored by annual mailed TLD, sent to verify basic machine calibration. This system provides a mechanism for identifying potential problems at new institutions and provides remote surveillance of the participating institutions.

The mailed TLD program began in September 1976 with the monitoring of photon beam output and in March 1983 was expanded to include electron beams. The electron TLD also verifies electron beam energy. The number of TLD mailings has continued to increase over the years as more institutions participate in clinical trials and the old single-energy machines are replaced with dual-energy linacs as seen in figure D–1. The Outreach Physics Section of the University of Texas M.D. Anderson Cancer Center also sponsors a fee-for-service program called Radiation Dosimetry Services (RDS) which includes a mailed TLD program for photons and electrons similar to that of the RPC. The RPC estimates that the two TLD programs, RPC and RDS, presently monitor more than 80% of the approximately 1750 radiotherapy facilities in the United States. The RPC and RDS intercompare their TLD systems quarterly to assure their consistency.

The results of the RPC assessment are reported to the institution. If the RPC and institution disagree by more than 5% on absorbed dose, the discrepancy is discussed by phone with the participating physicist to identify the source of the discrepancy. A second set of TLD is then mailed immediately. If the discrepancy persists, the RPC schedules an on-site dosimetry review visit.

(2) Mailed anthropomorphic dosimetry phantoms

The advanced technology protocols being developed by the various cooperative study groups typically involve image-based conformal or intensity-modulated treatment techniques. In order to QA these particular treatments,

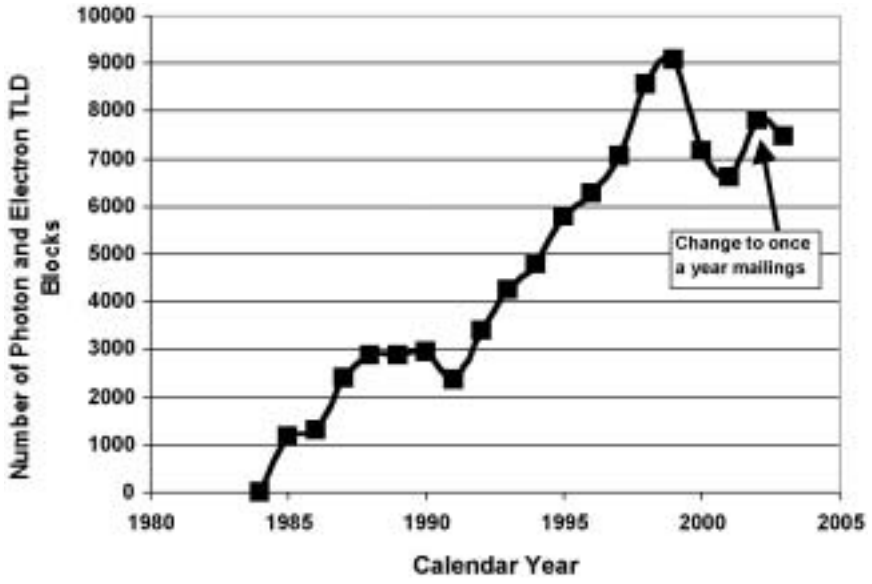


Figure D–1. Number of TLD blocks sent per year by the RPC for both photons and electrons.

anthropomorphic QA phantoms are being built or have been built that will verify radiation dose delivery and placement. All of these QA phantoms have the same basic design of a water-filled outer plastic shell with inserts from the base containing critical structures, imageable targets and dosimeters (TLD for absolute dose and Gafchromic® film to verify field placement).

The first of these phantoms to be used extensively is the stereotactic head phantom that has been sent to over 50 institutions participating in the RTOG stereotactic radiosurgery protocols. This phantom was designed to determine the dose with a precision of ±5% and to locate the edge of the field in three dimensions to within ±1mm.

Following the success of the head phantom, three other anthropomorphic phantoms were designed and built. One of the phantoms is a modification of the head phantom to test intensity-modulated radiation therapy (IMRT) treatments of the head and neck. It is currently required for the RTOG H-0022 and H-0225 protocols. Another is an anthropomorphic lung phantom for the RTOG 93-11 protocol and a new protocol for lung tumor ablation. The third is a pelvic phantom for IMRT treatments of the prostate, as prescribed by RTOG P-0126. These three phantoms are seen in figure D-2. The IMRT pelvic phantom was designed specifically to have the same cross-sectional profile as a real pelvis imaged with CT.

(a)

(b)

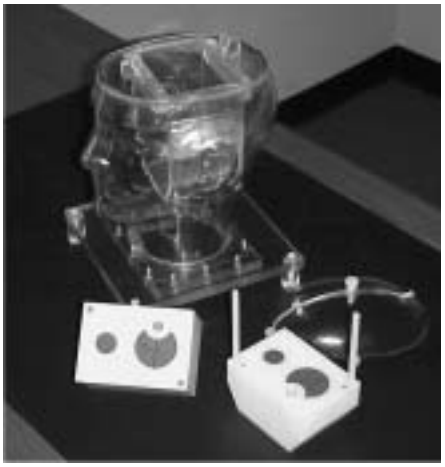


Figure D–2. The four RPC anthropomorphic phantoms: (a) stereotactic; (b) IMRT head and neck.

iii. Off-site dosimetry review using "Standard Data"

The RPC has measured data stored in its relational database consisting of depth dose, output factors, wedge factors, and other dosimetry parameters on several thousand radiation therapy machines for both photons and electron beams, including 5 or more consistent data sets for over 82 photon beams on 48 makes and models of accelerators. Review of these data suggests that machines of the same make and model have very similar characteristics (standard deviations of ±1%). The RPC has identified "standard data" (field size dependence,

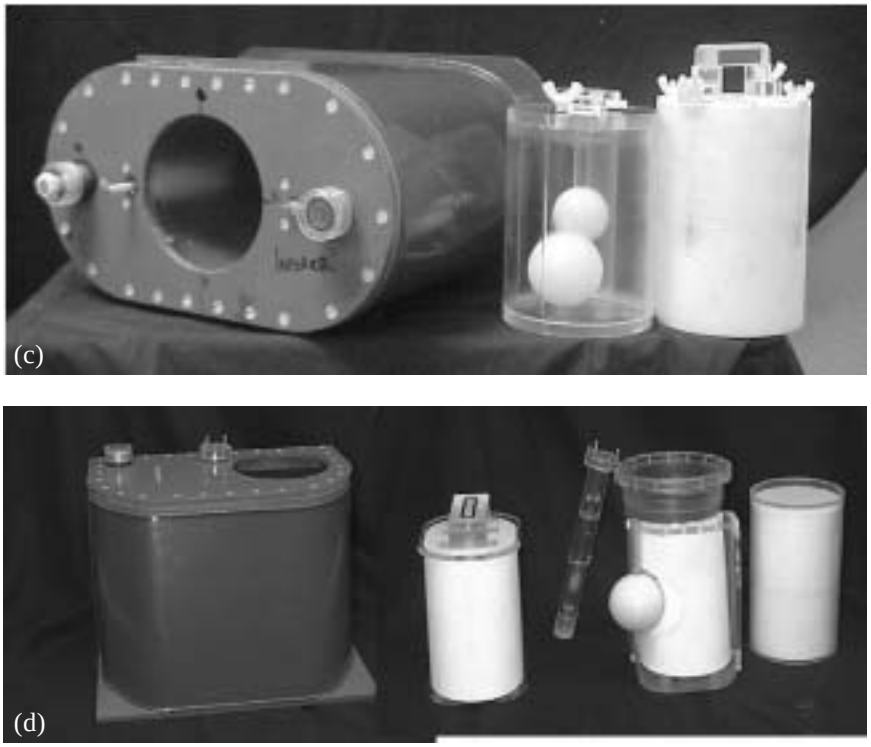


Figure D–2 (continued). (c) pelvic; and (d) thorax.

depth dose wedge factors, tray factors, electron cone ratios and off-axis factors) for most of these 48 makes and models of accelerators. The RPC standard data are constantly updated as additional measurements are made during on-site dosimetry review visits.

The off-site dosimetry review program provides a greater level of quality review for all participating institutions and in turn helps identify those institutions that may have a dosimetry problem. If an institution's dosimetry data do not match the "RPC standard data," either the therapy unit is not operating properly or the institution's data are potentially incorrect (Followill et al. 1997, Davis et al. 1992). Electron dosimetry data are not as reproducible as that for photons, but with the aid of the TLD results for the particular accelerator, beam output and electron depth dose data can be verified reliably. The off-site dosimetry review program utilizes the RPC TLD results, standard data, and specific benchmark cases to assess the three major components of the dosimetry chain: beam output, dosimetry data, and treatment planning algorithms or monitor set calculations, as well as quality assurance programs. Institutions are asked to complete several questionnaires, submit dosimetry data for all beams,

complete two benchmark treatment cases, and describe their quality assurance procedures. These data are evaluated by RPC physicists and dosimetrists at headquarters. Any dosimetric or procedural deviations are noted, the physicist is contacted to resolve any differences, and a comprehensive report written and sent to the institution.

iv. Review of protocol patient dosimetry

Historically, the RPC has been involved with many of the cooperative groups in the evaluation of protocol patients. The RPC performs the technical (dosimetry) review and assists the cooperative group in the clinical evaluation of the patients. A comprehensive (type I) review involves the recalculation of the delivered dose and comparison of that to the institution's reported dose. Because the type I review is time consuming, an alternate review (type II) was developed as a cost saving effort when no systematic dosimetry problems are expected, based on previous submissions from the institution. This review verifies that the dose reported is that required by the protocol, no data entry errors have occurred in the calculation, and that there are no transcription and/or reporting errors.

d. RTOG QA Center

The RTOG, through its RTOG QA Center (affiliated with the ACR), 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.

The RTOG quality control process consists of five components. These are: (i) patient eligibility; (ii) treatment delivery; (iii) data monitoring and data management; (iv) pathology; and (v) institutional audits. Each of these components consists of multiple processes to assure delivery of treatment according to protocol specifications. Of these, the treatment delivery component consists of radiation oncology quality assurance, medical oncology quality control, and surgical oncology quality control. Since this primer is directed toward physicists, only the radiation oncology quality assurance component will be described in some detail.

The RTOG quality assurance monitoring procedures have been developed and adopted in an integrated approach with the following specific aims:

- Credentialing and monitoring (by Medical Physics Committee, Radiological Physics Center (RPC), Image-guided Therapy Center (ITC).
- Assure the clarity, consistency, and accuracy of the treatment specification for each specific protocol (protocol review).

- Prevent or minimize potential variations from the protocol treatment prescription (initial review).
- Categorize any variations from the protocol treatment prescription that do occur so that they can be considered in a statistical analysis (final review).
- Compile and report the review results for statistical analyses.
- Educate research associates through organized orientation programs.

i. Review of developing protocols

The RTOG QA staff reviews the radiation oncology component of every RTOG developing protocol. The focus of the review is to ensure the clarity, consistency, and accuracy of the treatment specification for each protocol. 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. This consistent attention to detail is intended to eliminate the potential for variation from the intent of the protocol.

Guidelines for dose specifications for all RTOG protocols follow the recommendations contained in ICRU Report 50, 1993, "Prescribing, Recording, and Reporting Photon Beam Therapy" and ICRU Report 62, 1999, "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.

ii. Initial radiation therapy (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.

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.

Case data submitted within the designed time frame and identified for sampling are then reviewed by the radiation oncologist for field placement, planned course of treatment, and dose specification. Results of this review as well as the timeliness of data submission are recorded. If protocol deviations are identified, a telephone call is made by the reviewer to the treating radiation oncologist to request changes or to clarify the dosimetry information on hand.

iii. Final radiation therapy (RT) review

The purpose of the final RT review is to confirm the treatment delivered and to define protocol compliance for the statistician. The final review is an overall

evaluation of protocol compliance and is performed by the RT study chair and staff dosimetrist.

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, isodose distributions at several levels through the tumor, and a copy of the daily radiation therapy treatment record.

Upon receipt of this information, the data is recorded in the ACR RT QA database, the dosimetrist compiles all treatment data and films, and prepares a summary of the radiation administered. The study chair uses this information 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. Machine calibration data are forwarded to the RTOG RT Quality Assurance Center from the Radiological Physics Center (RPC), thus allowing the dosimetrist to perform the dose recalculations. Agreement in dose delivery must be maintained at ±5%. The dosimetrist works closely with the reviewing physician to develop and maintain evaluation criteria. These criteria are designed to assure consistency in scoring cases and are derived from the protocol specification requirements. 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.

The compliance rate of the treatment delivery relative to the protocol prescription is derived and reported. The treatment-related questions that arise during this reporting time period are resolved. Any questions that may arise from the Statistics Department are also addressed.

iv. Reporting of results

Study Chair final reviews are based on overall scores relative to radiation oncology only and are protocol specific. Protocol compliance can be defined as the ability to complete protocol treatment within an acceptable variation range. Statistically, the overall scores are based on a relative value scale and used in a variety of ways. They are a combined score that includes the compliance of field borders, dose, fractionation, and elapsed days. The overall compliance score is reported in the statistical reports and sent to each member and the clinical trial group on a semiannual basis.

v. Educational research associates orientation programs in radiation oncology

The RT Quality Assurance staff has developed a Dosimetry Orientation Booklet that is given to the research associates at the semiannual meetings as well as to newly hired research associates at headquarters. This information has helped the research associates at the institution to better understand the RT

Quality Assurance aspect of the protocol and gathering and completing the appropriate RT information that is needed in headquarters to perform an RT Quality Assurance review on protocol patients.

vi. QA for new modalities

Special QA programs have been developed for new modalities. The Medical Physics Committee has been especially active in the quality assurance aspects for all protocols that use such new modalities such as stereotactic radiosurgery/radiotherapy, 3DCRT, prostate brachytherapy, and IMRT.

The QA guidelines and credentialing procedures for various treatment modalities such as IMRT, 3DCRT, or brachytherapy are unique and involve diverse requirements: for example, prior to enrolling patients on stereotactic radiosurgery/radiotherapy protocols institutions are required to fill out a stereotactic facility questionnaire and submit it to the RTOG Headquarters (HQ). The questionnaire was designed to document that each institution has committed facilities to participate in clinical trials of this modality and to obtain information about physics and quality assurance data to enable review and verification of protocol treatment. Many of the 3DCRT, brachytherapy, and IMRT protocols require an institution to undergo credentialing by the Radiological Physics Center and the Advanced Technology Consortium. The Medical Physics Committee and the RTOG HQ works with the Advanced Technology Consortium and the Radiological Physics Center to ensure that institutions are credentialed before any patient can be placed on the technology intensive protocols. The HQ dosimetry staff is also involved with the Advanced Technology Consortium in the quality assurance and analysis of electronically transferred images and treatment planning data.

vii. Collaboration with the Advanced Technology Consortium (ATC)

The American College of Radiology (ACR), through the Radiation Therapy Oncology Group (RTOG), collaborates with the Advanced Technology Consortium (ATC) for Quality Assurance, which consists of the Image-guided Therapy Center (ITC), the Resource Center for Emerging Technologies (RCET), the Radiological Physics Center (RPC), the Quality Assurance Review Center (QARC), and the RTOG Headquarters Dosimetry Group. This arrangement utilizes each group's strengths and avoids duplication of the existing programs and thus develops uniformity in QA for advanced technology trials throughout all participating cooperative groups.

Specifically, the RTOG QA Center provides:

1. A medical dosimetrist QA review of advanced technology clinical trials using the ATC web-based remote review tools (RRT), which utilizes a secure web server. The dose-volume analysis of case data is ongoing in RTOG protocols.

2. Evaluation of the RCET NetSys software system for use with RTOG protocols.
3. Patient registration and clinical outcome data management and statistical support for the ongoing RTOG clinical trials evaluating advanced technologies.
4. Expertise in the areas of design, monitoring, and analysis for any new clinical trial utilizing advanced technologies.
5. A review of all advanced technology protocols that are developed through the ATC to help ensure uniformity of guidelines.
6. Expertise in maintaining and improving the current electronic link between the RTOG's clinical trial database and the ITC's treatment planning and verification (TPV) database.

e. Image-Guided Therapy Center (ITC)

In 1992, the Image-Guided Therapy Center (ITC), (previously referred to as the RTOG 3DQA Center) was created to provide quality assurance for multi–institutional 3DCRT trials sponsored by the RTOG, but now provides data archival and retrieval services to any quality assurance review center or principal investigator. The ITC provides three different functions. The first is to approve participants in the 3DCRT trials by ensuring that they meet the minimum technical requirements for participation in these protocols and correctly interpret the protocol requirements with respect to the volumetric data sets and prescription implementation. Second, the ITC's role is to facilitate quality assurance reviews by the QA review center of 3DCRT treatment planning verification (TPV) data that are submitted by participating institutions for patients enrolled in 3DCRT cooperative trials. The TPV data that are submitted to the ITC for later QA review include volumetric CT scans, contours for all critical structures, tumor and target volumes, beam geometry data, prescription and verification images or films, volumetric dose distributions (including fractionation information), and dose-volume histograms (DVH). The third charge of the ITC is the development of a database to accommodate all of the TPV and clinical data submitted to the ITC (Bosch et al. 1997, 2000). The ITC is part of the Advanced Technology Consortium (ATC), and is one of two national resource centers supporting advanced technology clinical trials data archival, retrieval, and analysis.

i. ITC web site

The ITC has established a worldwide web site at http://itc.wustl.edu to disseminate advisory information and pertinent forms to current and potential participants in 3DCRT and IMRT trials. In addition to providing an overview of the ITC's role in the 3DCRT/IMRT trials with references to those trials, it contains documents such as data submission checklists for individual studies, the QA guidelines specific to each study and a Dry Run Guide specific to each

study. These documents provide simple access to a valuable resource for institutions participating in these studies as well as for institutions preparing for certification. The Facility Questionnaires for RTOG protocols are available *only* at this site. This questionnaire must be completed and submitted to the ITC with supporting documentation prior to an institution's being approved for study participation. In addition, the document containing the digital data exchange format required for participation, *Specification for Tape/Network Exchange of Treatment Planning Data* is also published at this web site (Harms et al. 1997), as well as the ITC DICOM Conformance statement. This web site and those of the other QA review and resource centers can be found in appendix F.

ii. 3D RTP system required capabilities

There is a set of minimum capabilities that a three-dimensional radiotherapy treatment planning (3DRTP) system must have to meet the requirements of participation in the 3DCRT trials. A significant number of commercial 3DRTP systems make this technology widely available to institutions that wish to participate in these studies. The required functions are documented in the QA guidelines for each study located on the ITC web site. While the QA guideline documents are generally protocol specific, the 3DRTP system requirements are currently standard across all studies and are listed in Table D–2.

iii. Digital data exchange

Currently, most data are submitted to the ITC using a digital patient data exchange format adapted from earlier NCI-supported collaborative working

Table D–2. 3DRTP System Required Capabilities

• Supports a minimum of 40 contiguous CT slices (more may be required for protocol compliant CT studies based on minimum allowed slice spacing and superior–inferior extent of CT study required for a particular protocol
• Beam's-eye-view (BEV) display with the capability of displaying tumor and target volumes, critical structures and the beam aperture is required for the design of treatment portals
• Set up and calculate doses for non-coplanar (non-axial) beams
• Compute and display DRRs
• 3D dose matrix calculation with a maximum axial dose point spacing of 3 mm or 10,000 points per axial plane (whichever contains fewer points) and, as a minimum, must compute axial dose matrices on each axial CT slice
• Display and generate hard copy isodose distributions superimposed on grayscale CT image
• Compute DVHs using a 3D sampling grid at least as finely spaced as the dose matrix and identifies both absolute volume (cubic centimeters) and dose (Gy or cGy)
• Supports RTOG Data Exchange or DICOM-RT (conforming to ITC standard)

groups (RTOG exchange format). These working groups began with a format specified in AAPM Report No. 10, which was expanded to suit their requirements (Baxter, Hitchner, and Maguire 1982). The treatment planning data that are submitted using this digital exchange format can be found on the ITC web site (http://itc.wustl.edu).

There are currently several commercial 3DRTP systems that have the capability to submit data correctly to the ITC. The commercial systems that have demonstrated compliance with this standard are listed on the ITC web site. The RTOG exchange format has also been extended to include brachytherapy seed implants and the ITC has implemented code to read seed plans from this exchange format (Matthews et al. 2000). The capability to exchange data with the ITC should be considered when selecting a new treatment planning system. Users of systems that lack this capability should ask the system vendor for the data exchange capability.

This digital data exchange for 3DCRT patient image and external beam treatment planning data is currently in use in support of all RTOG 3DCRT/IMRT protocols. The ITC has implemented appropriate processing and conversion software to allow the submitted data to be viewed and manipulated using an in-house 3DRTP QA review system and/or the ITC web-based Remote Case Review Tool (RCRT) that allows reviewers and authorized investigators to access these data remotely with minimal on-site infrastructure of their own. The ITC is actively working with 3DRTP manufacturers to encourage them to implement the DICOM-RT standard for all of the objects required by radiotherapy clinical trials and to ensure that the objects they export as identified in their conformance statement match the requirements of radiotherapy clinical trials.

The challenge facing the ITC is that while most 3DRTP systems have some DICOM-RT capability, it is quite narrowly focused and not presently adequate for radiotherapy clinical trials. Most 3DRTP systems have the ability to export a rather limited set of DICOM-RT data objects. Most frequently available are RT Plan export to record and verify systems and RT Image (digitally reconstructed radiographs) export to DICOM print servers. Five objects are necessary to support radiotherapy clinical trials: CT or MR images, Structure sets, RT Plans, RT Image, and RT Dose. Since several of these objects, notably RT Dose, are not currently exported by most 3DRTP systems, the use of DICOM for exchange of data in advanced technology trials must be regarded as a work in progress. However, for vendors of planning systems that have not yet achieved compliance with ITC data exchange, the DICOM format will much more likely be pursued than the original RTOG format.

iv. Dry run test

The dry run test is intended to ensure that an institution preparing for participation in a particular 3DCRT study has both the technical capability and an appropriate understanding of the requirements of the protocol (contours, tumor and target volumes, and prescription). Each 3DCRT study has its own dry run

test that must be successfully completed to qualify for participation in a particular study. The dry run test is designed to ensure that the patient data exchange software in use by a prospective participant in the 3DCRT studies correctly formats the patient data for submission to the ITC. The digital data required are: CT image set, contour set for all critical, tumor and target volumes, beam geometry, digital film images for all beams, the 3D dose, and DVHs in terms of total dose. While a misunderstanding of a particular protocol issue may only cause a warning to correct such misunderstanding on actual patients, a data exchange format error will always require a new test to correct the errors.

There are several items of importance regarding the DVHs, which are computed and submitted to the ITC (in digital form only). A DVH for *Unspecified tissue* is required. *Unspecified tissue* is the tissue contained within the boundary of the skin that is not identified as any other structure through contouring. To ensure uniformity of DVH data across all patients enrolled in the 3DCRT studies, the ITC computes DVHs for all normal structures and target volumes for inclusion in the image database. Early testing by the ITC demonstrated a wide range of DVH results for identical contour sets and dose distributions between different institutions.

v. Radiation therapy data submission

The data that must be submitted to the ITC include digital patient data and hardcopy documentation. Each portion of the data is due at the ITC at times specified in the particular protocol. Data submission checklists are maintained on the ITC web site for the open 3DCRT/IMRT studies. Under the well-established transfer methodology, the digital data that are required can be submitted to the ITC by either the use of *ftp* (file transfer protocol) via the Internet or the use of magnetic tape or CD ROM, which is mailed together with the hardcopy documentation (figure D–3). A new web-based method of digital data submission is under development at the time of this writing and is described in the next section.

f. Advanced Technology Consortium

In 1994, the NCI funded nine institutions, to form the 3D Oncology Group (3DOG) whose charge was to develop a multi-institutional trial to determine whether 3DCRT could allow safe administration of escalated doses of radiation in men with prostate cancer. Because of the highly technical and sophisticated nature of this technology, it was critical to create a robust QA process to collect and review the image-based planning and verification data for patients registered to this trial. The RTOG was funded by the NCI to manage the 3DOG protocol registration, outcome data management, and statistical analysis. The Image-Guided Therapy Center (ITC) (previously referred to as the RTOG 3DQA Center) was funded to develop the mechanism for QA review and to assist in

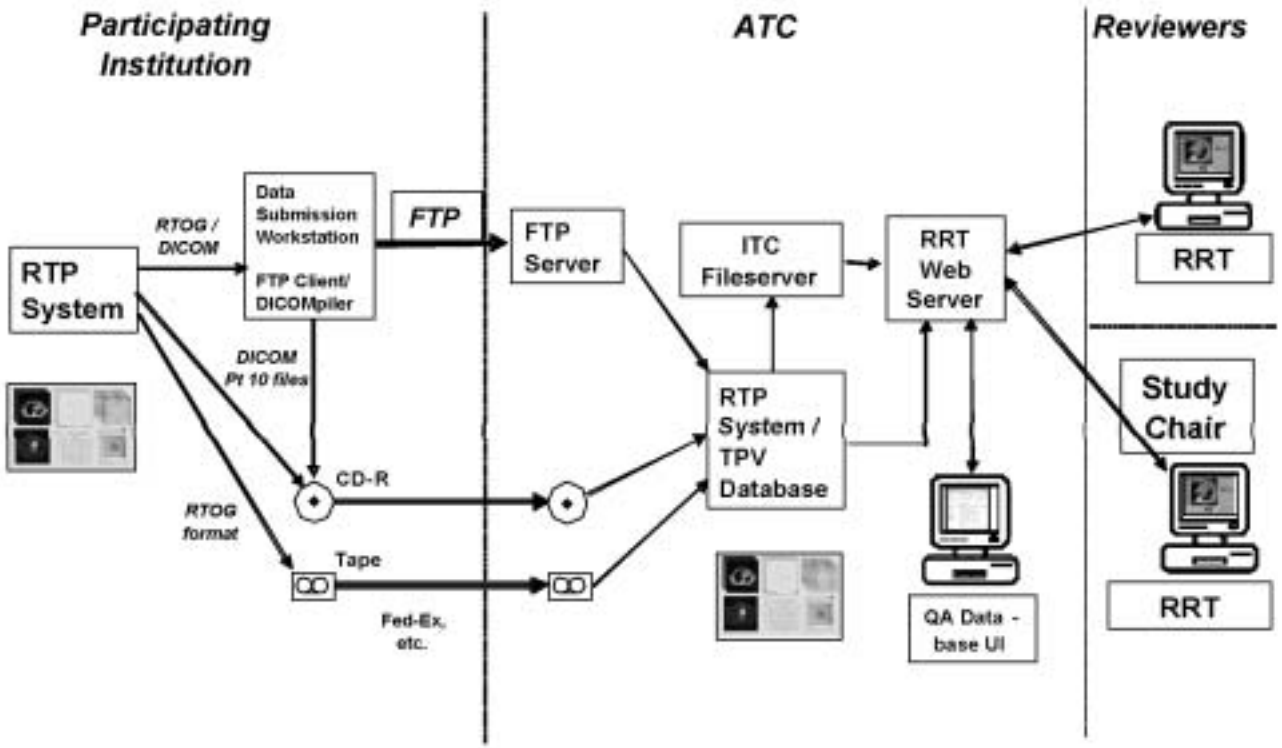


Figure D–3. Scheme for FTP or media-based transfer of RT data to the ITC.

establishing the minimal requirements for study participation (Purdy et al. 1996, 1998). After 1995, the 3DOG protocol participation was expanded and opened to other RTOG member institutions that could demonstrate that they met the protocol QA requirements (RTOG 9406 protocol). Most importantly, the ITC developed a data exchange specification for the electronic transfer of volumetric treatment planning digital data (Harms et al. 1997). Using this specification, essentially all of the 3DCRT planning data for each accrual could be transferred in an electronic format for QA review and later outcome analysis.

Based on the success of the 3DOG/RTOG 94-06 clinical trial, the NCI recognized the need to expand this form of QA support for all clinical trials utilizing advanced technology and requiring digital data submission. In 2002, the NCI awarded a 5 year grant to the Advanced Technology QA Consortium (ATC) (consisting of ITC, RCET, RPC, QARC, RTOG HQ Dosimetry) to support clinical trials QA. The ATC was charged to develop and provide credentialing of institutions to participate in advanced technology trials, to develop basic technical and QA criteria for each protocol assessed, and to provide a mechanism for both prospective and retrospective review of image-based treatment plans to assure that they are within protocol specifications. Their charge also included the development and maintenance of a comprehensive database of TPV digital data, including tumor and normal structure contours and 3D dose data, which can be *correlated with treatment outcomes*. This database is to serve as a national resource to researchers evaluating toxicity and control where volumetric dose fractionation data for target volumes and critical structures are necessary to evaluate these endpoints quantitatively.

Most recently the newly formed ATC has activated it's website (http://atc.wustl.edu) and focused its mission to facilitate the conduct of NCI-sponsored advanced technology radiation therapy clinical trials that require digital data submissions while maintaining patient confidentiality. This effort includes radiation therapy quality assurance, image and radiation therapy digital data management, and clinical research and developmental efforts.

Under the umbrella of the ATC, the ITC and RCET have collaborated in the development of a new method of advanced technology radiotherapy data archival, retrieval, and review shown in figure D–4, that provides a secure upload of data to the ATC Data Submission Server using web-based client software, WebSys. The underlying technology for data archive and distribution is based on the development done under the original RCET grant, which is described in a recent paper (Palta, Frouhar, and Dempsey 2003). This method, which uses tools, developed by both ITC and RCET support data that includes CT images, RT structures, beam geometry, 3D dose distributions, DVH, DRR, MR, screen capture images, and textual data. The system is fully DICOM and DICOM-RT compliant. The system is designed in such a way that the data archived at the site of the production server (ITC) is automatically replicated at RCET to preserve redundancy. Ultimately, the data will reside in a distributed data base environment with data servers located at all ATC member sites. This

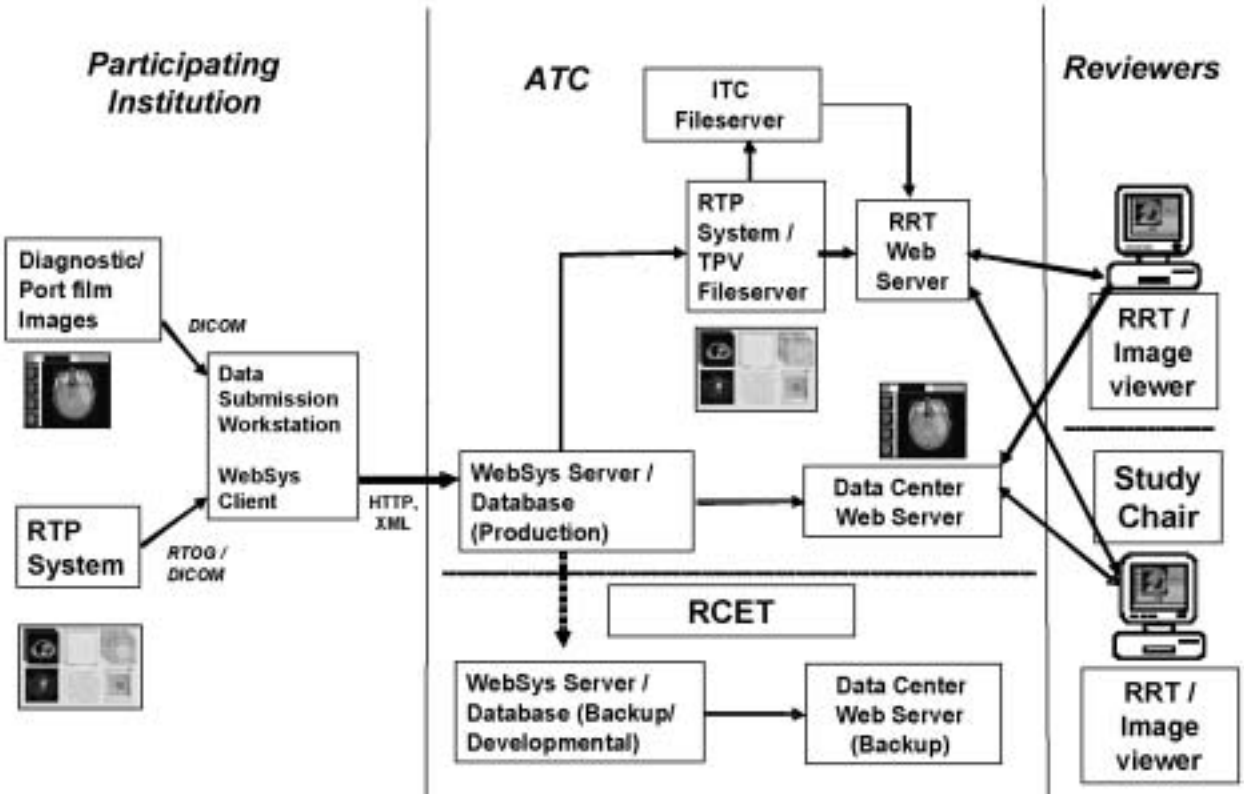


Figure D–4. Scheme for ATC web-based RT data upload.

will ensure easy access to the archived data at all times. Once the data arrives at the ITC, the staff imports the treatment planning data into the treatment plan review system for review using a web-based remote review tool. The DICOM images (CT, MR, DRR, Port films, etc.) are separately processed using the web-based NetSys client software. This method for data submission and review is, at the time of this writing, undergoing extensive testing at volunteer institutions. The goal is to have this method in widespread use by the end of 2004 while the established method of data submission and review, originally developed by ITC, continues to be used for data collection on advanced technology clinical trials.

The ATC believes strongly that advanced medical informatics can facilitate education, collaboration, and peer review, as well as provide an environment in which clinical investigators can receive, share, and analyze volumetric multi-modality treatment planning and verification digital data. The ATC's ultimate goal is to improve the standards of care in the management of cancer by improving the quality of clinical trials medicine. To accomplish this mission, the ATC is committed to the following:

1. Serve as an educational and developmental resource to the nation's clinical trial cooperative groups and participating institutions for support of advanced technology radiation therapy clinical trials.
2. Develop electronic data exchange mechanisms of treatment planning and verification (TPV) data between the ATC QA Centers and the protocol participating institutions, and between the ATC members and cooperative group Operations, Statistics, and Data Management Section(s).
3. Develop software tools to facilitate QA reviews by RTOG, QARC, and RPC of TPV data submitted by institutions participating in cooperative group clinical trials that utilize advanced technologies, including 3DCRT, IMRT, and brachytherapy. Emphasis is on the development and improvement of web-based remote-review tools that allow for the efficient review of centrally located image-based data.
4. Develop an archival TPV database for the advanced treatment modalities that can be linked with the cooperative group's clinical outcomes database.
5. Provide expertise for and facilitate protocol design, credentialing, monitoring, and both protocol and outcome data analysis for new clinical trials that utilize advanced technologies and require digital data submission, with the intent to ensure uniformity of guidelines.

APPENDIX E

Sources of National Cancer Institute Information

Cancer Information Service
Toll-free: 1-800-4-CANCER (1-800-422-6237)
TTY (for deaf and hard of hearing callers): 1-800-332-8615
NCI Online : http://cancer.gov

CancerMail Service
To obtain a contents list, send an e-mail to: cancermail@cips.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service
Dial 1-800-624-2511 or 301-402-5874 and follow the voice prompt instructions.

The clinical trials page of the NCI's web site, at
http://www.nci.nih.gov/clinicaltrials/
on the Internet, provides general information about clinical trials. It also offers detailed information about specific ongoing studies by linking to PDQ®, a cancer information database developed by NCI.

APPENDIX F

Quality Assurance Review Centers

(Please check web sites for current information)

Image-Guided Therapy Center (ITC)
4511 Forest Park Ave., Suite 200
St. Louis, MO 63108
Phone: 314-747-5414
FAX: 314-747-5423
http://itc.wustl.edu

Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, RI 02903-1025
Phone: 401-454-4301
Fax: 401-454-4683
http://www.qarc.org

Radiological Physics Center
Mailing address:
1515 Holcombe Blvd., Box 547
Houston, TX 77030

Courier address:
Radiological Physics Center
7515 South Main Street, Suite 300
Houston, TX 77030

Phone: (713) 745-8989
Fax: 713-794-1364
URL: http://rpc.mdanderson.org/rpc/
Email: rpc@mdanderson.org

Resource Center for Emerging Technologies
Department of Radiation Oncology
University of Florida
PO Box 100385
2000 Archer Road
Gainesville, FL 32610
Tel: 352-265-8217
Fax: 352-265-8417
Website: http://rcetsystem.org
Email: rcetmail@rcet.health.ufl.edu

RTOG QA Center
American College of Radiology (ACR)
Radiation Therapy Oncology Group (RTOG)
1818 Market Street, Suite 1600
Philadelphia, PA 19103
http://www.rtog.org

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LIST OF ACRONYMS

2D	Two-dimensional
3DCRT	Three-dimensional conformal radiation therapy
3DOG	3D Oncology Group
3DRTP	Three-dimensional radiotherapy treatment planning
AAPM	American Association of Physicists in Medicine
ACOSOG	American College of Surgeons Oncology Group
ACR	American College of Radiology
ACRIN	American College of Radiology Imaging Network
ADCL	Accredited Dosimetry Calibration Laboratory
ASCO	American Society of Clinical Oncology
ATC	Advanced Technology Consortium
BEV	Beam's-eye-view
CALGB	Cancer and Leukemia Group B
CCG	Children's Cancer Group
CCOP	Community Clinical Oncology Program
CD	Compact disk
COG	Children's Oncology Group
CRA	Clinical research associates
C-RT	Conventional radiotherapy
CT	Computed tomography
CTEP	Cancer Therapy Evaluation Program
CTSU	Cancer Trials Support Unit
CTV	Clinical target volume
DICOM	Digital Imaging and Communications in Medicine
DICOM-RT	Digital Imaging and Communications in Medicine-Radiation Therapy
DRR	Digitally reconstructed radiographs
DVH	Dose-volume histogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FDA	U. S. Food and Drug Administration
FFS	Failure-free survival
FTE	Full-time equivalent
ftp	File transfer protocol
GOG	Gynecologic Oncology Group

GTV	Gross target volume
HF-RT	Hyperfractionated radiotherapy
HIPAA	Health Insurance Portability and Accountability Act
IMRT	Intensity-modulated radiation therapy
IRB	Institutional Review Board
IRS	Intergroup Rhabdomyosarcoma Study (Group)
ITC	Image-Guide Therapy Center
jpeg	Joint Photographic Experts Group
JROSG	Japanese Radiation Oncology Study Group
MRI	Magnetic resonance imaging
MTD	Maximum tolerable dose
NABTT	New Approaches to Brain Tumor Therapy
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada (Clinical Trials Group)
NIST	National Institute of Science and Technology
NSABP	National Surgical Adjuvant Breast and Bowel project
OAR	Organs-at-risk
PA	Postero-anterior
PACS	Picture archiving and communication system
PBTC	Pediatric Brain Tumor Consortium
PET	Positron emission tomography
PI	Principal investigator
POG	Pediatric Oncology Group
PRC	Protocol review committee
PTV	Planning target volume
QA	Quality assurance
QARC	Quality Assurance Review Center
RCET	Resource Center for Emerging Technology
RCRT	Remote Case Review Tool
RDS	Radiation Dosimetry Services
RFA	Request for Applications
ROM	Read-Only Memory
RPC	Radiological Physics Center
RRT	Remote review tools
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group

SFOP	French Society of Pediatric Oncology
SRS	Stereotactic radiosurgery
SWOG	Southwest Oncology Group
TBI	Total body irradiation
TLD	Thermoluminescent dosimeter
TROG	Trans-Tadman Radiation Oncology Group

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