

Quality Assurance in Clinical Trials: A Primer for Physicists

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Quality Assurance in Clinical Trials: A Primer for Physicists

A report of the Subcommittee on Quality Assurance Physics for
Cooperative Trials of the Radiation Therapy Committee

Topics

- a) What constitutes a clinical trial?
- b) The role of the physicist in preparing and maintaining the institution's credentials for participating in RT clinical trials.
- c) The special or additional physics tasks are 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,
- f) The data review and resource centers that receive data submissions and what do they do
- g) Physics resource requirements

What Is 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.
- Tests new combinations or methods of treatments, are they safe and either superior or at least as effective as existing therapies?
- Many of today's standard treatments for cancer began in clinical trials.

Why Should You Care About Clinical Trial QA?

1. The Medical Physicist's efforts to ensure that treatments are delivered per protocol guidelines is critical in establishing the statistical significance of the findings of the clinical trial.
2. RT trials are using more complex treatments than in the past: IMRT, stereotactic RT, and brachytherapy
3. The NCI has created a new program which permits and encourages much wider participation in clinical trials throughout the country.

The QA Problem

- Hundreds of RT departments treating patients on a given protocol
- Each with different:
 - treatment planning systems,
 - treatment machines,
 - calibration protocols,
 - dose prescription practices
 - methods of treating the same disease

Your Role Is To Ensure
That The Protocol RT
Guidelines Are Applied
Correctly

The Protocol

Explains:

- 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 they will be handled?
- The requirements for patient consent and authorization.

Anatomy of a Protocol

RT section

- 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
- 9) other information that is relevant for a specific study.

**You job is to read and
understand these sections !!**

Novel Radiation Treatments Must Successfully Complete Three Phases of Trials Before the Federal Food and Drug Administration (FDA) Approves Them for General Use.

Phase I: Is the new treatment safe?

Phase II: Is the new treatment effective?

Phase III: Is the new treatment better?

NCI's Clinical Trials Cooperative Group Program

- Program established in 1955 by Congress

Currently:

- 1500 Institutions
- 20,000 new patients annually
- Over 1000 treatment trials
- Thousands of investigators
- Purpose—to develop and conduct large-scale multi-institutional trials.

The NCI has four major programs designed to make clinical trials widely available in the United States.

- 1) NCI Comprehensive or Clinical Cancer Centers perform clinical trials independently,
- 2) Cooperative Clinical Trials Program,
- 3) Community Clinical Oncology Program (CCOP),
- 4) Cancer Trials Support Unit (CTSU).

Cancer Trials Support Unit (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.
- Permits institutions that are members of one study group to enroll patients in trials run by other study groups.
- Permits institutions that are not members of any study group to enroll patients in clinical trials.

- It is the activity of the CTSU program which may increase your number of protocol patients.
- At least, that is the hope of the NCI....

What Has Been Learned From Radiation Therapy Clinical Trials?

- Clinical trials have served to define the standard of care for many diseases, i.e.
 - Benefit of chemo-radiotherapy in both cervix cancer and rectal cancer.
 - confirmed the equivalent local control and survival benefits of mastectomy and lumpectomy with radiation therapy.
- In the United States today, more than 70 percent of children with cancer live at least 5 years after diagnosis, as opposed to only 55 percent in the mid-1970s due to the improved treatments validated in cooperative group trials.
- Much of the data presented in our medical journals are the results from clinical trials.

Clinical Physicist's Role in Clinical Trials

Your Role

- The Medical Physicist is expected to be a knowledgeable resource to the Radiation Oncologist and staff in correctly delivering treatments to protocol patients.
- The Medical Physicist is responsible for all aspects of the Quality Assurance of clinical trials in which the Radiation Oncology Department participates.
 - Credentialing to be a clinical trial center
 - Performing various benchmark tests
 - Reading and understanding each protocol
 - Performing protocol specific QA
 - Creating and submitting required data to QA centers

And

Any Trial Using Radiation Therapy Will Involve the Radiation Physicist

- The rigorousness of QA and data submission is related to whether or not the protocol is testing radiation therapy.
- There may be special calculations to perform.
- There may be the requirement to treat or prescribe dose in an unfamiliar way.
- ICRU nomenclature, GTV, CTV, PTV may be used and there may be the requirement to contour OARs and limit their doses to given values.

Cooperative Group Membership

The physicist is responsible for providing documentation on:

- the types of accelerators used for treatment;
- diagnostic equipment used for definition of tumor volume and simulation;
- treatment planning system used for generating treatment plans for both external beam radiation therapy and brachytherapy;
- equipment used for any special procedures such as stereotactic radiotherapy, intra-operative radiotherapy, high dose-rate brachytherapy, and total body irradiation;
- physics and dosimetry equipment used for calibration, and quality assurance.
- Institutional QA procedures on all accelerators and other equipments used for patient treatment and/or treatment simulation.
- An independent confirmation of the calibration of their megavoltage beams

Understanding Image-based Protocol Prescription and Target Volume Specifications

- 3-D conformal and IMRT protocols require ICRU 50/62 nomenclature: GTV,CTV,PTV
- Dose *prescription* criteria (dose to be delivered) can be different from the dose *specification* criteria (dose to be reported)

Special Measurements

External Beam

Treatment delivery system specific dosimetric parameters, for example,

- TBI protocols : off-axis radiation beam characteristics including off-axis ratios and beam hardening and softening.

- Patient-specific measurements

- Measured and estimated doses to critical structures such as eye lens, gonads, spinal cord, etc
- IMRT QA

Special Calculations

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 Organ at Risk (OAR)
- Dose-volume histograms for target volumes, OAR, and other specified normal tissues

Benchmarking and Credentialing

- **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 require “dry run” electronic data submission

Assuring Protocol Compliance

- Completing Credentialing Benchmarks
- Ensuring that the treatment plan is consistent with the RT guidelines for target dose, dose uniformity, OAR dose
- Providing the required special measurements or calculations required
- Providing the data output for submission

Impact of Protocol Violations

- Pediatric Oncology Group (POG) Ewing's protocol 8346
 - 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 1998)
- Ewing's Sarcoma studies (German)
 - CESS 81, 90% of local relapses occurred in patients with radiotherapy protocol deviations
- German Hodgkins Study Group trial HD4
 - Treatment success was 12 percentage points higher without protocol violations

Centralized pre-treatment review has decreased the deviation rate from 30% to 6% (QARC).

Protocol Data Submission

- Timely and accurate data submission is essential to the success of the cooperative group process.
- Pre-treatment review or
- Rapid review – submit data 24-72 hours after start of RT.
- Some advanced tech trial require electronic data submission

Protocol Data Submission Items

- **Radiation therapy prescription**
- **Patient setup data (simulation, DRRs, portal images, etc.)**
- **Daily treatment record**
- **Dose distributions, calculations, and measurements – point doses, isodoses, DVHs for composite treatment (including any boosts), TLD or diode readings.**

Overview of Quality Assurance Review

Levels of Quality Assurance Review

- Standard radiation therapy (not study question)
 - A.L.L.- whole brain irradiation given to all patients, study is testing chemo agents.
- Radiation therapy not study question but toxicity and efficacy of RT is of interest
 - Lung cancer protocol- same RT to all patients, tests different chemo agents.
- Comprehensive Review (RT is study question)
 - COG medulloblastoma protocol testing reduced dose and volume, 3-D required, IMRT allowed.

3 Major National Quality Assurance Review Centers (NCI Funded)

- QARC, Quality Assurance Review Center
- RPC, Radiological Physics Center
- RTOG (Radiation Therapy and Oncology Group)
Headquarters QA office

Each has agreements with various cooperative groups to provide a range of quality assurance services, including chart, film, procedure, and dosimetry review

Two National Resource Centers (NCI Funded)

- The Image-Guided Therapy QA Center (ITC) and
- The Resource Center for Emerging Technologies (RCET)
 - develop and provide electronic data archival and retrieval services

Image-Guided Therapy Center (ITC)

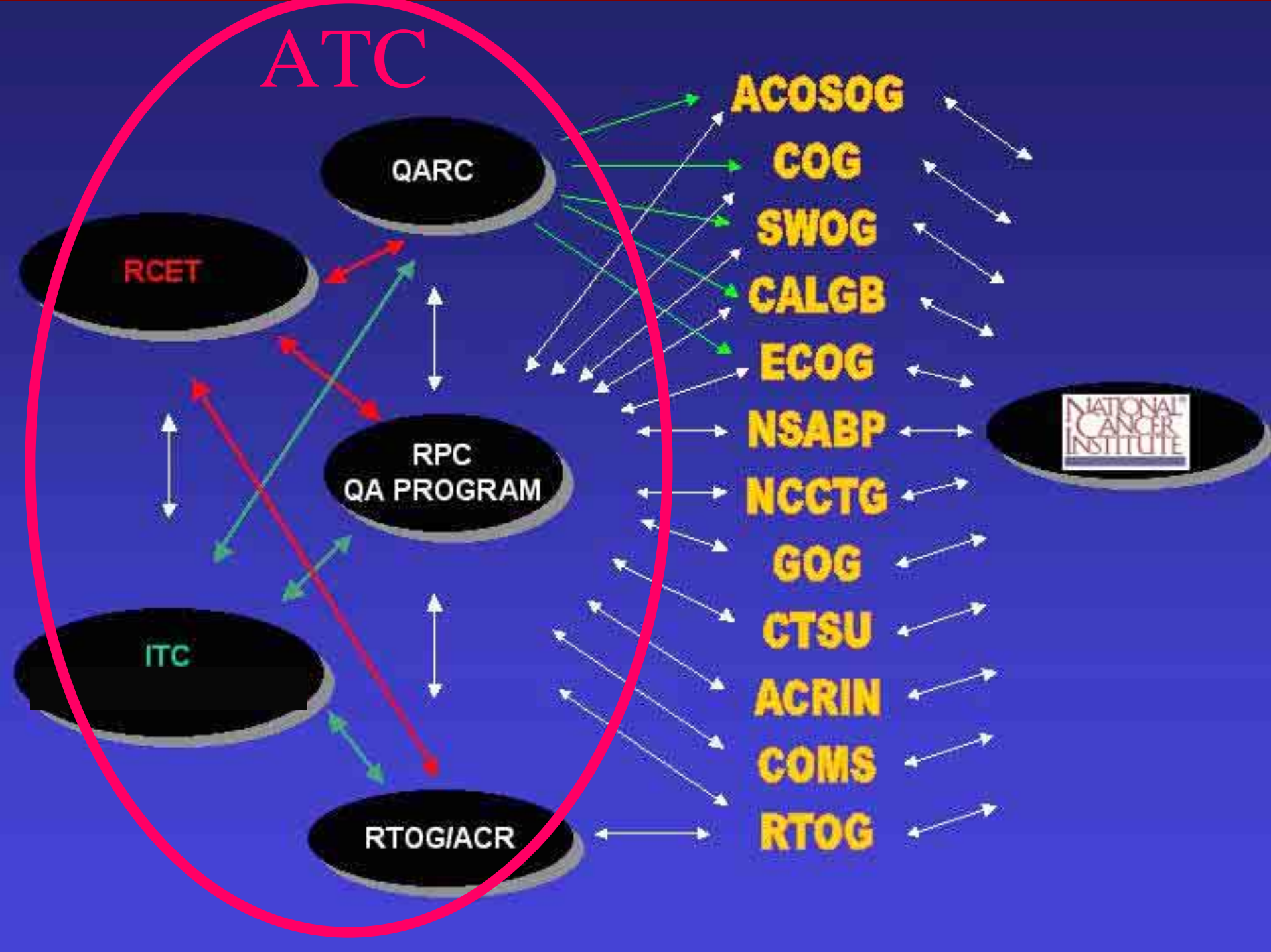
- In 1992, the Image-Guided Therapy Center (ITC) was created to provide quality assurance for multi-institutional 3DCRT trials sponsored by the RTOG.
 - Approves participants in the 3DCRT trials by ensuring that they meet the minimum technical requirements for participation in these protocols and correctly interpret the protocol requirements
 - Facilitates quality assurance reviews by the QA review center of 3DCRT treatment planning verification (TPV) data
 - Develops a database to accommodate all of the TPV and clinical data submitted to the ITC.

Resource Center for Emerging Technology (RCET)

- The RCET at the University of Florida was established in April 1999 to develop and disseminate resources that would facilitate the conduct of NCI sponsored advanced technology clinical trials
- Developed an infrastructure for a distributed database, visualization, and analysis systems for collecting, sharing and distributing information generated by institutions participating in clinical trials.
- Facilitates remote review of protocol data

In 2002 the NCI awarded a 5 year grant providing that the 5 centers join to become the Advanced Technology Consortium (ATC) to coordinate efforts, reduce duplication, and unify the quality assurance practices across the country

ATC



Electronic Data Submission

Currently: FTP or Media-based
Transfer of RT Data to the ITC

In Development: Web-based
RT Data Upload

How Are The Data That Are Submitted Evaluated?

- Treatment is scored by QA center and/or P.I. as:
 - Compliant or,
 - Minor violation or,
 - Major Violation or,
 - Unevaluable

Depends on adherence to protocol criteria and, completeness of data submission and patient eligibility

Volume and Dose are scored separately

The outcome of all patients who are eligible to be on study are included in the final statistics for outcome, no matter what their violation status is.

Even if they were on an RT arm and didn't get any radiation treatments !!

The principle of Intent to Treat

However, subset analysis is often done.

Physics Resource Requirements

Start-up, Cooperative Group Membership, and Credentialing

- Filling out forms for institutional application – 3 hrs.
- Standard or 3-D benchmark – 4 hrs each
- IMRT benchmark – up to one day
- Validation of your data exchange software- hours

Routine and Patient Specific QA Physics Support

- Annual RPC TLD dosimetry program: 1-2 hours
- Time to fill out data submission forms:
 - If protocol uses standard RT: 30 minutes
 - For 3-D protocol, need to generate DRRs, DVHs, specific isodoses, plus forms: 2 hours
 - Submitting data electronically (once created) – 1/2 hour

Summary

- 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 CTSU program
- 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.
- A significant amount of physics staff time may be required
- Physicist must be aware and able to provide the services necessary to comply with advanced technology protocols.

Community Clinical Oncology Program (CCOP)

- 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.
- Potential CCOPs must have a proven track record of accrual to NCI-sponsored treatment, prevention and control clinical trials.