Medical Physics Navigator for Clinical Trials

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Disclosures

- Timothy Ritter: Therapeutic medical physicist at Virginia Commonwealth University and the Department of Veterans Affairs. Perform work under AHRQ grant 1R01HS026486-01.
- Paige Taylor: Therapeutic medical physicist; NIH funding, grant CA180803.
- Shruti Jolly: Professor at the University of Michigan. On the advisory boards for Varian and AstraZeneca; salary support from Blue Cross Blue Shield of Michigan (MROQC).

Session Learning Objectives

- Distinguish the different types of clinical trials, identify their important elements, and identify key personnel involved in trial success.
- Understand the steps involved in clinical trial credentialing.
- Identify how medical physicists can contribute to clinical trials.

Outline

1. Trial Overview
2. Medical Physics Roles
3. Trial Organizations
4. Trial Credentialing
5. Physician Perspective

A Little History

- One of the first clinical trials looked at scurvy, a vitamin C deficiency that devastated sailors.
- James Lind, a Scottish Physician, studied citrus fruits as a cure.
- 12 sailors were divided into six groups of two men each.
- The “two oranges and one lemon” arm showed significant improvement after a 6 day trial (then the fruit ran out!).
- “A Treatise of the Scurvy” (1753) was published and then ignored.

For more information: https://www.medpagetoday.com/blogs/revolutionandrevelation/74568

Purpose of Clinical Trials

"Clinical trials are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people. Often a clinical trial is used to learn if a new treatment is more effective and/or has less harmful side effects than the standard treatment."

From ***https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies***

Major Elements of Clinical Trials

- A primary clinical endpoint (e.g. “five year disease free survival”)
- Sufficiently powered sample size determined by statistical analysis
- Randomization of the intervention when applicable (esp. Phase III)
- Institutional Review Board approval and oversight
- Informed consent from all participants
- Meticulous data collection and monitoring
- Monitoring for adverse events
- A detailed written protocol

Clinical trials look at safety and effectiveness.

How do we do this ethically?

A Little More History

- 10 principles of human research were outlined in the **Nuremberg Code** of 1947, a response to Nazi medical atrocities.
- The **Nuremberg Code** led to the **Declaration of Helsinki** in 1964.
- The **Belmont Report** was authored by a special U.S. commission for the protection of human subjects in 1979.
- The **Belmont Report** establishes three fundamental principles for ethical research: ***Respect for Persons, Beneficence, and Justice***.

For more information: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

A Little More History

The **Belmont Report**'s principles are implemented via:

1. **Informed consent**
2. **Detailed assessment of risks vs benefits**
3. **Equity in the selection of research subjects**

- For more information: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

A Little More History

- In the United States, the “Common Rule” for protection of human research subjects was passed as law (45 CFR Part 46).

- The “Common Rule” applies to all federally supported or conducted research.

  - For more information: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Clinical Trial Development

A great deal happens before you even see the trial!

- Identify the hypothesis / question
- Identify who will sponsor and conduct your clinical trial
- Grant application or letter of intent with study design
- Detailed protocol development
- Approvals, approvals, approvals
- Infrastructure development

Reference: A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI (version 1.2, 2014)

Randomized Clinical Trials

Comparison of Population-Based Observational Studies With Randomized Trials in Oncology

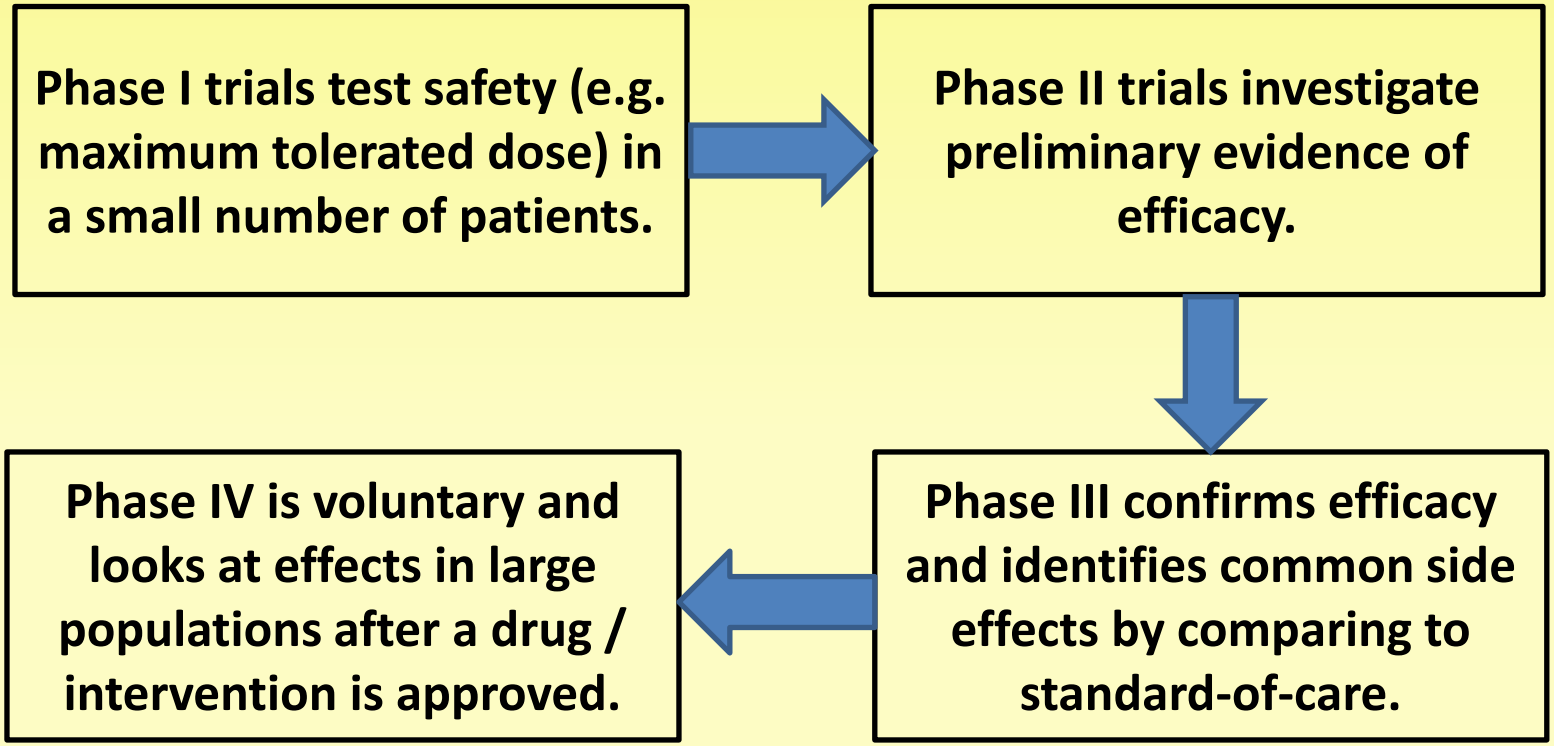
Payal D. Soni, MD[1]; Holly E. Hartman, MS[2]; Robert T. Dess, MD[2]; Ahmed Abugharib, MD[3]; Steven G. Allen, PhD[2]; Felix Y. Feng, MD[4]; Anthony L. Zietman, MD[5]; Reshma Jagsi, MD, DPhil[2]; Matthew J. Schipper, PhD[2]; and Daniel E. Spratt, MD[2]

Journal of Clinical Oncology 2019 37:14, 1209-1216

- "Randomized controlled trials (RCTs) are the gold standard for comparing treatment efficacy."

- Regarding observational studies and RCTs: ***"There was no agreement beyond what is expected by chance."***

Phases of Clinical Trials



CHEST®
Volume 124, Issue 5, November 2003, Pages 1946-1955

Preliminary Report

Extracranial Stereotactic Radioablation *: Results of a Phase I Study in Medically Inoperable Stage I Non-small Cell Lung Cancer

Timmerman, Robert MD [a], Papiez, Lech PhD [a], McGarry, Ronald MD [c], Likes, Laura RT [a], DesRosiers, Colleen MS [a], Frost, Stephanie MS [c], Williams, Mark MD [b]

Show more

Phase I Example in Radiation Oncology

Phase II Example in Radiation Oncology

Clinical Trial > JAMA. 2010 Mar 17;303(11):1070-6. doi: 10.1001/jama.2010.261.

Stereotactic body radiation therapy for inoperable early stage lung cancer

Robert Timmerman [1], Rebecca Paulus, James Galvin, Jeffrey Michalski, William Straube, Jeffrey Bradley, Achilles Fakiris, Andrea Bezjak, Gregory Videtic, David Johnstone, Jack Fowler, Elizabeth Gore, Hak Choy

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0236

A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I/II Non-Small Cell Lung Cancer

Phase III Example in Radiation Oncology

NIH U.S. National Library of Medicine

ClinicalTrials.gov

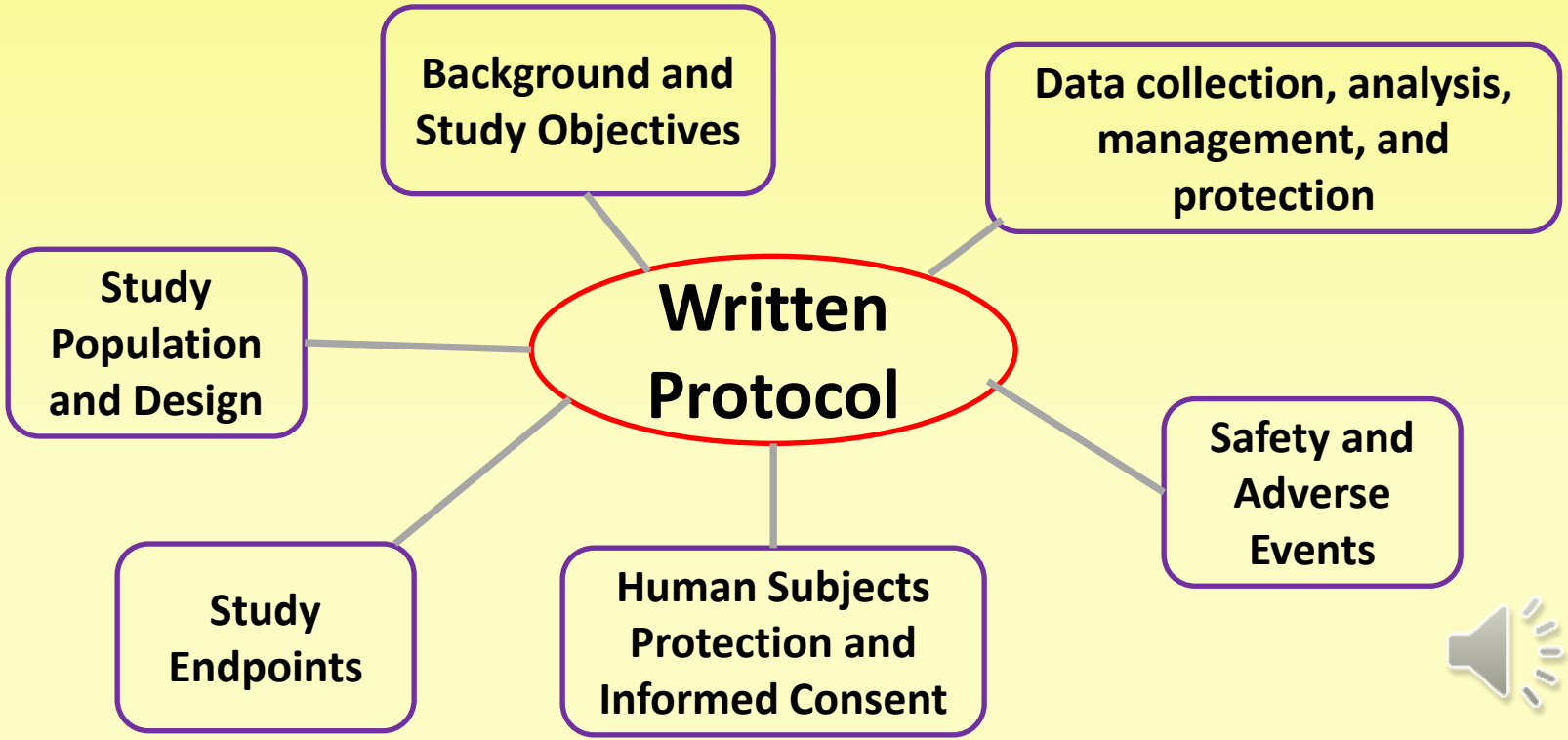
Find Studies ▾ About Studies ▾ Submit Studies ▾

Home > Search Results > Study Record Detail

Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy (VALOR)

The standard of care for stage I non-small cell lung cancer has historically been surgical resection in patients who are medically fit to tolerate an operation. Recent data now suggests that stereotactic radiotherapy may be a suitable alternative. This includes the results from a pooled analysis of two incomplete phase III studies that reported a 15% overall survival advantage with stereotactic radiotherapy at 3 years. While these data are promising, the median follow-up period was short, the results underpowered, and the findings were in contradiction to multiple retrospective studies that demonstrate the outcomes with surgery are likely equal or superior. Therefore, the herein trial aims to evaluate these two treatments in a prospective randomized fashion with a goal to compare the overall survival beyond 5 years. It has been designed to enroll patients who have a long life-expectancy, and are fit enough to tolerate an anatomic pulmonary resection with

The Protocol



N Engl J Med. 1987 Jul 16;317(3):141-5. doi: 10.1056/NEJM198707163170304.

Equipoise and the ethics of clinical research

B Freedman

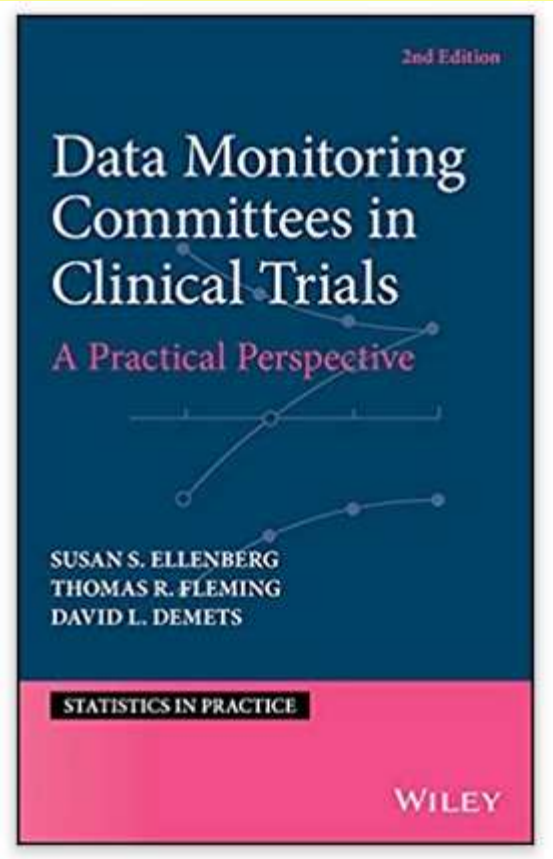
PMID: 3600702 DOI: 10.1056/NEJM198707163170304

Abstract

The ethics of clinical research requires equipoise--a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment. The current understanding of this requirement, which entails that the investigator have no "treatment preference" throughout the course of the trial, presents nearly insuperable obstacles to the ethical commencement or completion of a controlled trial and may also contribute to the termination of trials because of the failure to enroll enough patients. I suggest an alternative concept of equipoise, which would be based on present or imminent controversy in the clinical community over the preferred treatment. According to this concept of "clinical equipoise," the requirement is satisfied if there is genuine uncertainty within the expert medical community--not necessarily on the part of the individual investigator--about the preferred treatment.

Terms

Equipoise

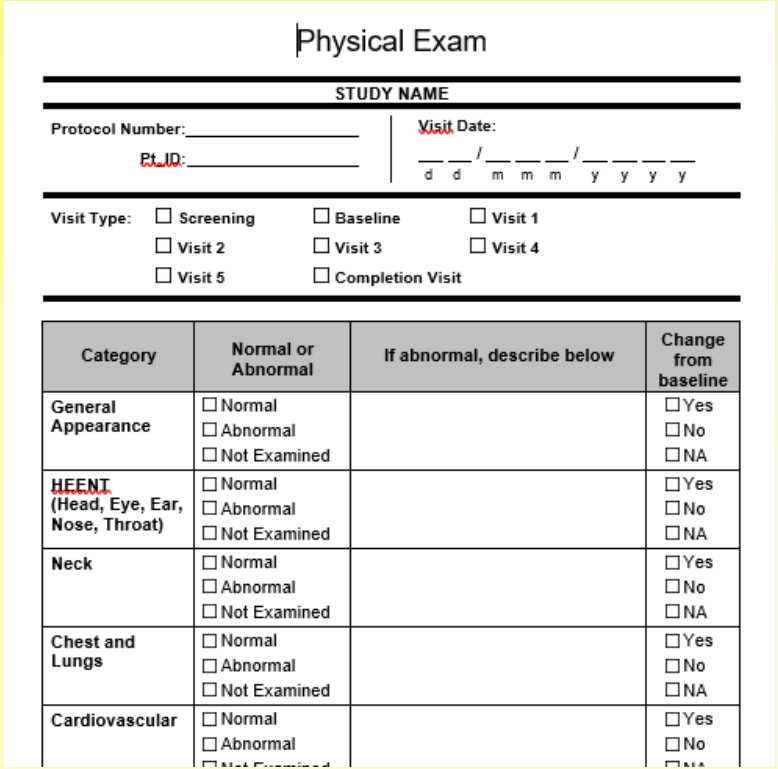


More Terms

Data Monitoring Committee

An independent panel that protects trial participants by monitoring and acting upon ongoing trial results.

From: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics



Physical Exam

STUDY NAME

Protocol Number:_____

Pt. ID:_____

Visit Date:

__ __ / __ __ __ / __ __ __ __

d d m m m y y y y

Visit Type: ☐ Screening ☐ Baseline ☐ Visit 1 ☐ Visit 2 ☐ Visit 3 ☐ Visit 4 ☐ Visit 5 ☐ Completion Visit

Category	Normal or Abnormal	If abnormal, describe below	Change from baseline
General Appearance	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
HEENT (Head, Eye, Ear, Nose, Throat)	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Neck	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Chest and Lungs	☐ Normal ☐ Abnormal ☐ Not Examined		☐ Yes ☐ No ☐ NA
Cardiovascular	☐ Normal ☐ Abnormal		☐ Yes ☐ No

More Terms

Case Report Forms

Case report forms are used to collect the data from clinical trials. They are carefully designed and each data element is tied to a ***source document***.

Study Principal Investigator

The study Principal Investigator is responsible for all aspects of the trial such as: screening, enrollment, treatment, compliance with federal regulations, ensuring proper IRB oversight, data collection, data monitoring, data reporting, financial aspects, patient welfare, the conduct of other co-investigators and staff….

AN ENORMOUS RESPONSIBILITY!

Medical Physics Co-Chair

Clinical trials that involve radiation therapy, advanced imaging, or novel uses of ionizing radiation may include a *Medical Physics Co-Chair*. She/he reports to the principal investigator and manages medical physics aspects of the trial.

Site (Principal) Investigator

Circulation

Volume 135, Issue 13, 28 March 2017, Pages 1185-1187

https://doi.org/10.1161/CIRCULATIONAHA.116.026650

FRAME OF REFERENCE - ON MY MINDON MY MIND

Site Principal Investigators in Multicenter Clinical Trials

Appropriately Recognizing Key Contributors

Robert J. Mentz, MD and Eric D. Peterson, MD, MPH

Key Words: clinical science

The success or failure of multicenter clinical trials will remain dependent in large part on the engagement of the site principal investigator (PI). Site PIs play an important role in trial selection, site activation, and study execution, including the development and implementation of a strategy to maximize enrollment, optimize data quality, and ensure patient retention. It is notable that the legal, regulatory, financial, and workload burden for site PIs has

Applies to a multi-center clinical trial: A site PI will oversee, and be responsible for, the conduct of the trial at each participating site.

Site Clinical Research Coordinator

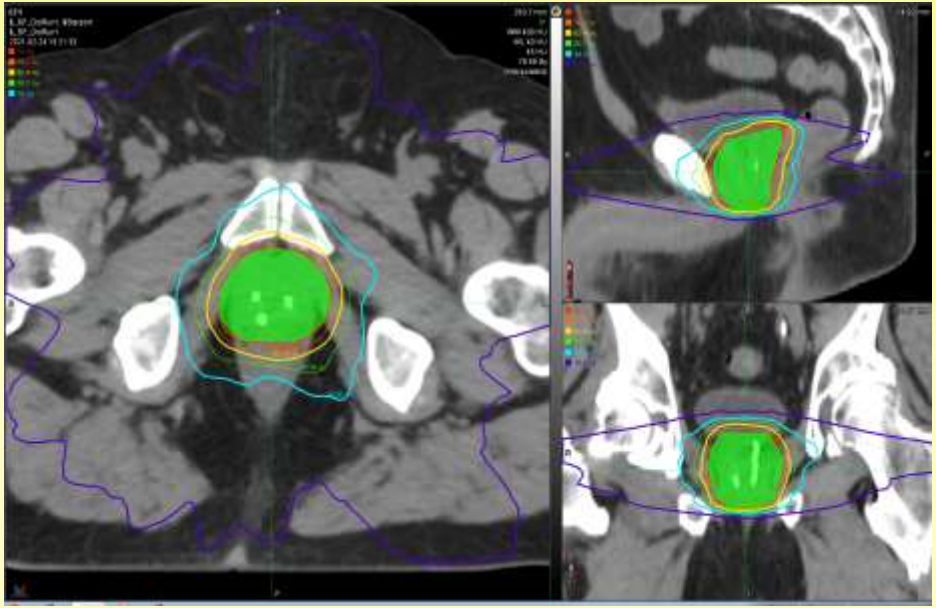
Applies to a multi-center clinical trial: Each site will typically have a clinical research coordinator that is assigned the specific study and works under the direction of the site PI. They are a clinical trial professional that manages many of the day-to-day study operations at the local level.

One Last Definition

"In virtually every research study departures occur from the procedures set forth in the IRB-approved protocol. Various terms are used to describe these departures, including "protocol deviations," "protocol violations," "protocol variances," and "non-compliance." For the purposes of this recommendation, such departures shall be herein referred to as "protocol deviations."

From: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2012-march-30-letter-attachment-c/index.html

Has This Happened to You?



"I'm checking a prostate plan and I see that the proximal seminal vesicle structure doesn't match our standard clinical approach. There is a note about following protocol XYZ. Are we currently enrolling patients on this protocol?"

RO Clinical Trials

Question: What can a Medical Physicist do to ensure the success of a Radiation Oncology clinical trial?

Answer: Prepare in advance, be an expert on the clinical aspects of the protocol, develop a working relationship with the key players, adapt your clinical processes as needed, and implements methods to ensure trial compliance.

Preparation for Clinical Trials

1. Know the Protocol

- Identify where your standard processes differ from the protocol.

- Does your hardware and software meet protocol standards?

Example: Your TPS algorithm

- Step up and lead the way.

Preparation for Clinical Trials

Table 7.4d.1 Description and Naming of Required Target Volumes

Standard Name	Description	Validation Required/Required when applicable
GTV_ddGyxF	GTV to receive dd Gy per fraction for F fractions	**Required**
IGTV_ddGyxF	IGTV to receive dd Gy per fraction for F fractions	**Required**
PTV_ddGyxF	PTV to receive dd Gy per fraction for F fractions	**Required**
PTV20	PTV + 20 mm expansion defined to control intermediate dose spillage	**Required**

e.g., **dd = Gy** and **F = number of fractions**; If plan is for a central lung lesion prescribed to a total of 50 Gy delivered in 5 fractions, the PTV is to be named **PTV_10Gyx5**, where 10 Gy is to be given per fraction, for 5 fractions.

Do you use the same target and OAR nomenclature found in the protocol?

Here are target names from S1914.

Follow the protocol!

Preparation for Clinical Trials

Target and OAR structure definitions are critical

> Int J Radiat Oncol Biol Phys. 2021 Jan 1;109(1):174-185. doi: 10.1016/j.ijrobp.2020.08.034. Epub 2020 Aug 27.

NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes for Intact and Postoperative Prostate Cancer

William A Hall [1], Eric Paulson [2], Brian J Davis [3], Daniel E Spratt [4], Todd M Morgan [5], David Dearnaley [6], Alison C Tree [6], Jason A Efstathiou [7], Mukesh Harisinghani [8], Ashesh B Jani [9], Mark K Buyyounouski [10], Thomas M Pisansky [3], Phuoc T Tran [11], R Jeffrey Karnes [12], Ronald C Chen [13], Fabio L Cury [14], Jeff M Michalski [15], Seth A Rosenthal [16], Bridget F Koontz [17], Anthony C Wong [18], Paul L Nguyen [19], Thomas A Hope [20], Felix Feng [18], Howard M Sandler [21], Colleen A F Lawton [3]

> Radiother Oncol. 2020 Sep;150:30-39. doi: 10.1016/j.radonc.2020.05.038. Epub 2020 Jun 3.

Organ at risk delineation for radiation therapy clinical trials: Global Harmonization Group consensus guidelines

Romaana Mir [1], Sarah M Kelly [2], Ying Xiao [3], Alisha Moore [4], Catharine H Clark [5], Enrico Clementel [6], Coreen Corning [6], Martin Ebert [7], Peter Hoskin [8], Coen W Hurkmans [9], [illegible]grid Kristensen [11], Stephen F Kry [12], Joerg Lehmann [13], Jeff M Michalski [14],

Practice Guideline > Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):e353-62. doi: 10.1016/j.ijrobp.2012.01.023. Epub 2012 Apr 6.

Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas

Hiram A Gay [1], H Joseph Barthold, Elizabeth O'Meara, Walter R Bosch, Issam El Naqa, Rawan Al-Lozi, Seth A Rosenthal, Colleen Lawton, W Robert Lee, Howard Sandler, Anthony Zietman, Robert Myerson, Laura A Dawson, Christopher Willett, Lisa A Kachnic, Anuja Jhingran, Lorraine Portelance, Janice Ryu, William Small Jr, David Gaffney, Akila N Viswanathan, Jeff M Michalski

Review > Radiother Oncol. 2019 Aug;137:1-8. doi: 10.1016/j.radonc.2019.04.012. Epub 2019 Apr 28.

Impact of deviations in target volume delineation – Time for a new RTQA approach?

Samantha Cox [1], Anne Cleves [2], Enrico Clementel [3], Elizabeth Miles [4], John Staffurth [5], Sarah Gwynne [6]

Preparation for Clinical Trials

Pract Radiat Oncol. 2021 Mar 1;S1879-8500(21)00057-6. doi: 10.1016/j.prro.2021.02.007. Online ahead of print.

Rigid and Deformable Image Registration for Radiation Therapy: A Self-Study Evaluation Guide in YYYY Clinical Trial Participation

Yi Rong [1], Mihaela Rosu-Bubulac [2], Stanley H Benedict [3], Yunfeng Cui [4], Russell Ruo [5], Tanner Connell [5], Rojano Kashani [6], Kujtim Latifi [7], Quan Chen [8], Huaizhi Geng [9], Jason Sohn [10], Ying Xiao [9]

Affiliations + expand

PMID: 33662576 DOI: 10.1016/j.prro.2021.02.007

As is Image Registration!

Preparation for Clinical Trials

2. Know The People

- You should know your site principal investigator and, if possible, develop a strong working relationship with them.
  - Work closely with the site clinical study coordinator on documentation, data collection, and data submission. They will keep you up-to-date on enrollments, randomizations, and training.
- If you have questions about the protocol reach out to your local team first, then Medical Physics co-chair or Study PI if needed.

Preparation for Clinical Trials

3. Modify Local Processes / Procedures If Required

- In some cases local processes and procedures could lead to a protocol deviation. You may need to need to modify existing methods and/or possibly develop new ones and then ***train staff***.

Simple example: The trial protocol requires a 2 mm or smaller slice thickness when performing a CT simulation scan. Your current clinical simulation method uses a 2.5 mm slice thickness.

Preparation for Clinical Trials

4. Implement Protocol-Specific Compliance Tools and Templates

- If you can't meet a trial constraint you should know before you approve the plan!

Are there any major violation?

What are acceptable deviations?

Are the margins and dose coverage per protocol?

Are unique structure name and contour requirements followed?

Preparation for Clinical Trials

4. Implement Protocol-Specific Compliance Tools and Templates

PTV Name:

PTV Margin: CTV + **mm axial and** **mm craniocaudal expansion**

☐ Acceptable (5 mm to 7 mm) ☐ Deviation (< 5 mm or > 7 mm)

PTV Coverage (% of Prescription Dose)	PTV Coverage Achieved	Compliance (check one
Minimum V100% >94%	V100% = %	☐ Acceptable ☐ Deviation Unacceptable
V90% > 99.9%	V90% = %	☐ Acceptable ☐ Deviation Unacceptable
Dmax <167%	Dmax = %	☐ Acceptable ☐ Deviation Unacceptable

Parameter	Result	Protocol Score
1. Lung V20 (%)	3.0	ACCEPTABLE
2. Spinal Cord Dose to vol (Gy)	10.7	ACCEPTABLE
2. Spinal Cord Dmax (Gy)	12.4	ACCEPTABLE
3. Esophagus Dose to vol (Gy)	4.7	ACCEPTABLE
3. Esophagus Dmax (Gy)	7.7	ACCEPTABLE
4. Brachial Plexus Dose to vol (Gy)	0.2	ACCEPTABLE
4. Brachial Plexus Dmax (Gy)	0.3	ACCEPTABLE
5. Heart Dose to vol (Gy)	5.1	ACCEPTABLE
5. Heart Dmax (Gy)	9.1	ACCEPTABLE
6. Great Vessel Dose to vol (Gy)	8.3	ACCEPTABLE
6. Great Vessel Dmax (Gy)	15.1	ACCEPTABLE
7. Trachea Dose to vol (Gy)	0.6	ACCEPTABLE
7. Trachea Dmax (Gy)	1.2	ACCEPTABLE
8. Bronchus Dose to vol (Gy)	12.3	ACCEPTABLE
8. Bronchus Dmax (Gy)	24.6	ACCEPTABLE
9. Rib Dose to vol (Gy)	27.8	ACCEPTABLE
9. Rib Dmax (Gy)	52.6	ACCEPTABLE

Preparation for Clinical Trials

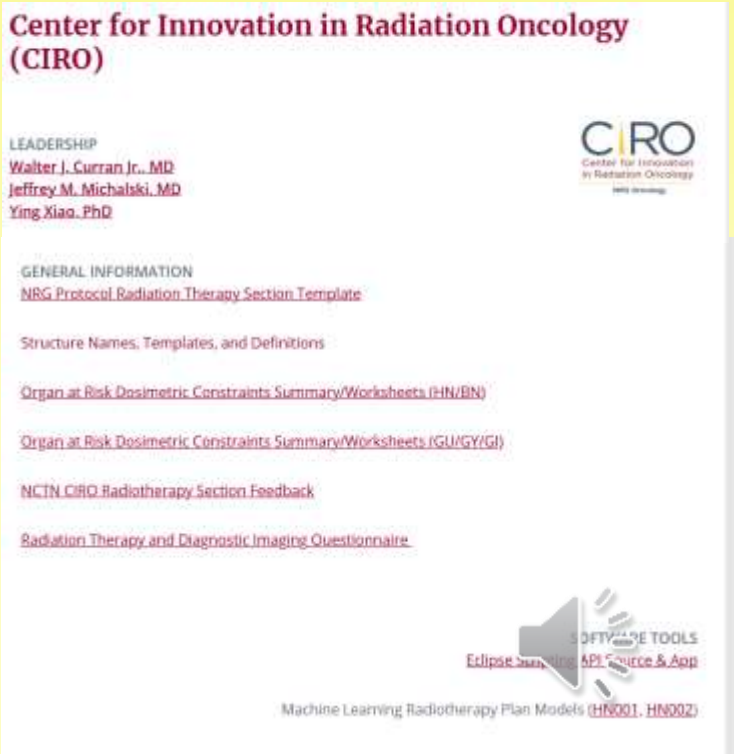

MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

Technical Note | Full Access

Technical Note: A standardized automation framework for monitoring institutional radiotherapy protocol compliance

Sarah Quirk, Jordan Lovis, Kailyn Stenhouse, Lukas Van Dyke, Michael Roumeliotis, Kundan Thind

First published: 23 February 2021 | https://doi.org/10.1002/mp.14797


Center for Innovation in Radiation Oncology (CIRO)

LEADERSHIP
Walter J. Curran Jr., MD
Jeffrey M. Michalski, MD
Ying Xiao, PhD

GENERAL INFORMATION
NRG Protocol Radiation Therapy Section Template

Structure Names, Templates, and Definitions

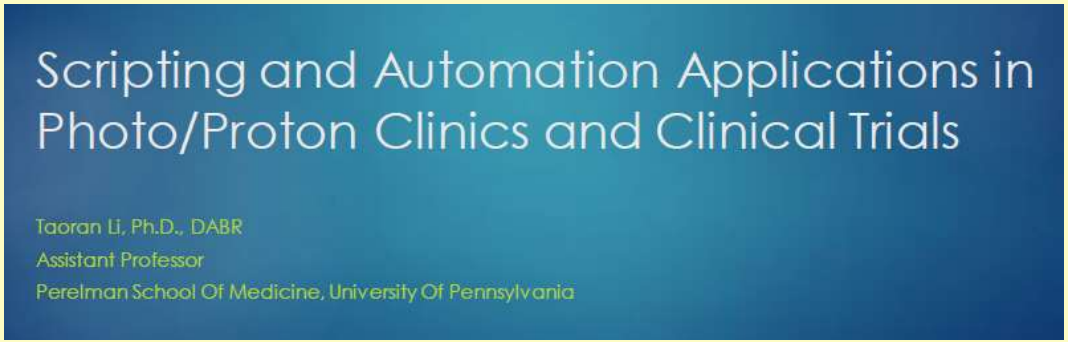
Organ at Risk Dosimetric Constraints Summary/Worksheets (HN/BN)

Organ at Risk Dosimetric Constraints Summary/Worksheets (GU/GY/GI)

NCTN CIRO Radiotherapy Section Feedback

Radiation Therapy and Diagnostic Imaging Questionnaire

Machine Learning Radiotherapy Plan Models (HN001, HN002)


Scripting and Automation Applications in Photo/Proton Clinics and Clinical Trials

Taoran Li, Ph.D., DABR
Assistant Professor
Perelman School Of Medicine, University Of Pennsylvania

Preparation for Clinical Trials

TRIAD
ACR IMAGE AND INFORMATION EXCHANGE

Clinical Trials

TRIAD securely moves DICOM images, structured and unstructured reports, and DICOM RT objects across the Internet.

https://triadhelp.acr.org/

Know How to Prepare Trial Data

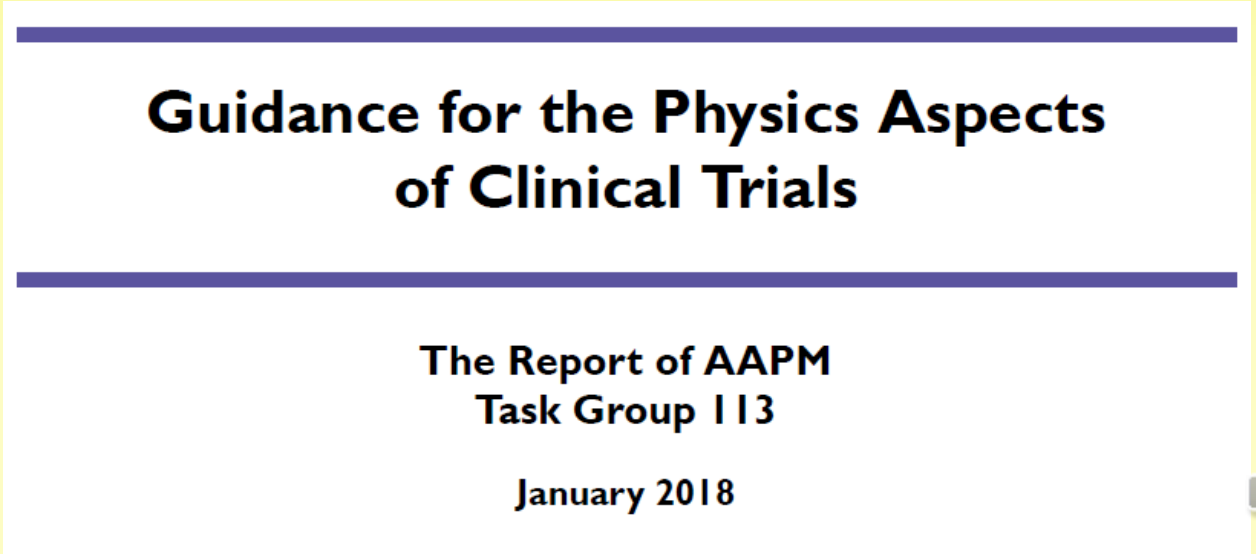
- Many clinical trials require the submission of RT treatment plans and treatment records.
- The Medical Physicist often oversees the data preparation and submission. *Follow the instructions referenced in the protocol.*

Preparation for Clinical Trials

If you are going to become involved in a trial, then you should strive to be the site expert on implementing the protocol in your clinic!

Preparation for Clinical Trials

Your homework: Read and Follow the AAPM Task Group Report



Preparation for Clinical Trials

FLASHBACK: BEFORE YOU ENROLL PATIENTS

Credentialing

Paige Taylor from IROC @ MD Anderson will tell you everything you need to know about credentialing and will also discuss key organizations and resources for aspiring trial physicists.

Introduction

- Paige Taylor, MS, DABR
- Medical Physicist at IROC's Houston Office
- Focus: radiation therapy

pataylor@mdanderson.org

@mpPaigeTaylor

Session Learning Objectives

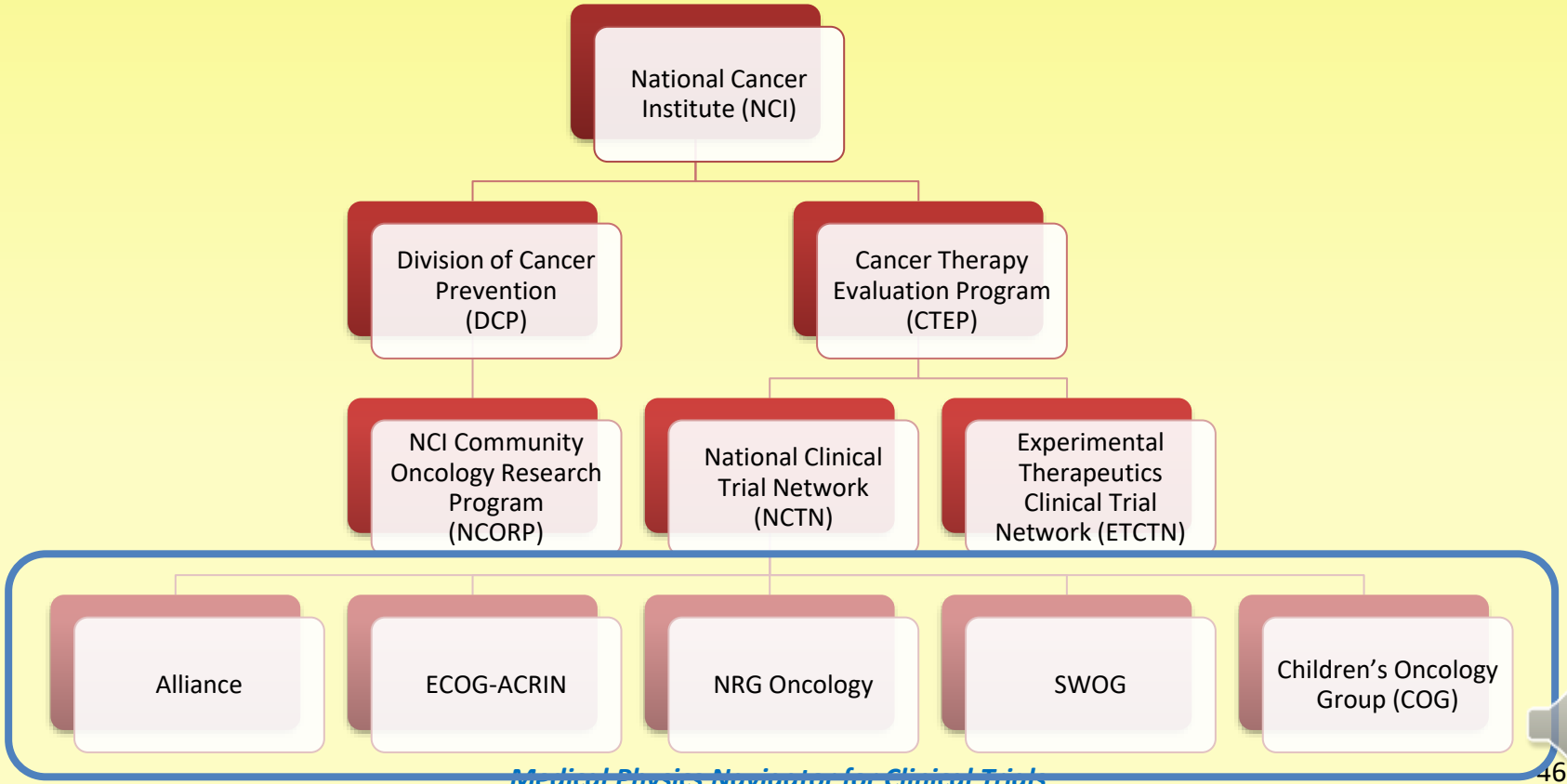
- Distinguish the different types of clinical trials, identify their important elements, and identify key personnel involved in trial success.
- ***Understand the steps involved in clinical trial credentialing.***
- Identify how medical physicists can contribute to clinical trials.

So. Many. Acronyms.

Let's start with some basic org charts and common acronyms you'll hear in the clinical trials space

https://makeameme.org/meme/acronyms-acronyms-everywhere-5981993604

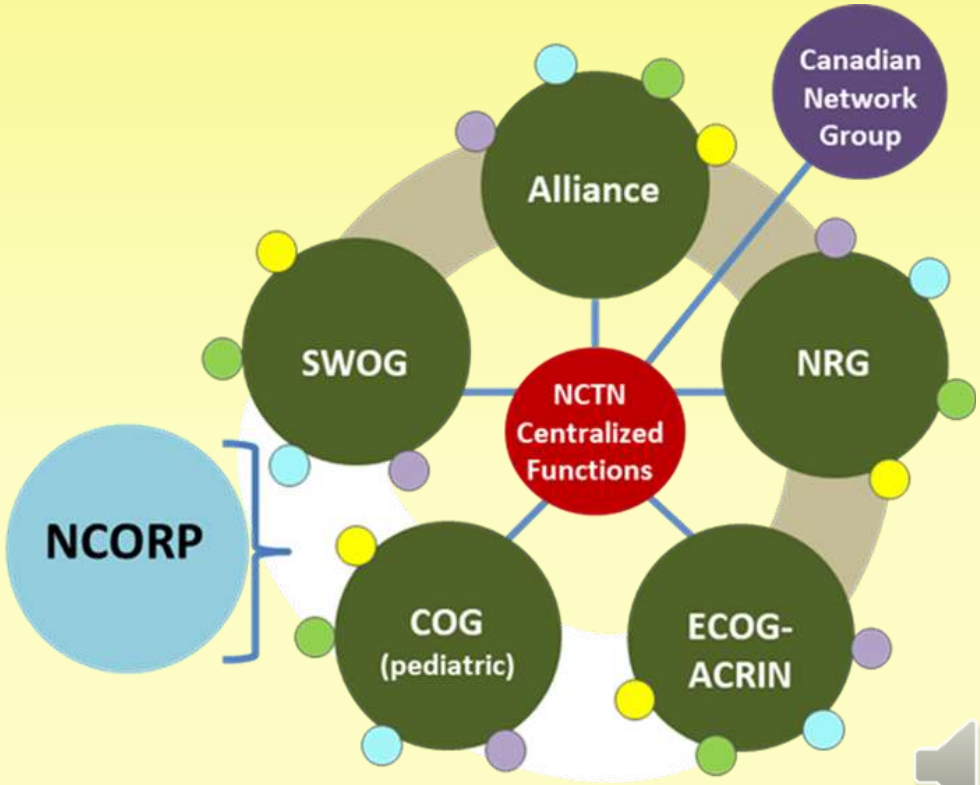
NCI Trial Organizations



Key Organizations: NCTN

LEGEND:

- **Central Functions:**
  - CIRB
  - CTSU
  - IROC
  - Common Data System/Hosting
  - Network Accrual Team
- 30 LAPS
- Tumor Banks
- Operations Centers
- Member Sites
- Statistics/Data Ctrs



Key Organizations: International Trial Groups

- Canadian Cancer Trials Group (CCTG)
- European Organisation for Research and Treatment of Cancer (EORTC)
- Japan Clinical Oncology Group (JCOG)
- UK's National Institute for Health Research (NIHR)
- Trans-Tasman Radiation Oncology Group (TROG)

Key Organizations: IROC

NCI Clinical Trial Support

IROC®
IMAGING AND RADIATION ONCOLOGY CORE
Global Leaders in Clinical Trial Quality Assurance

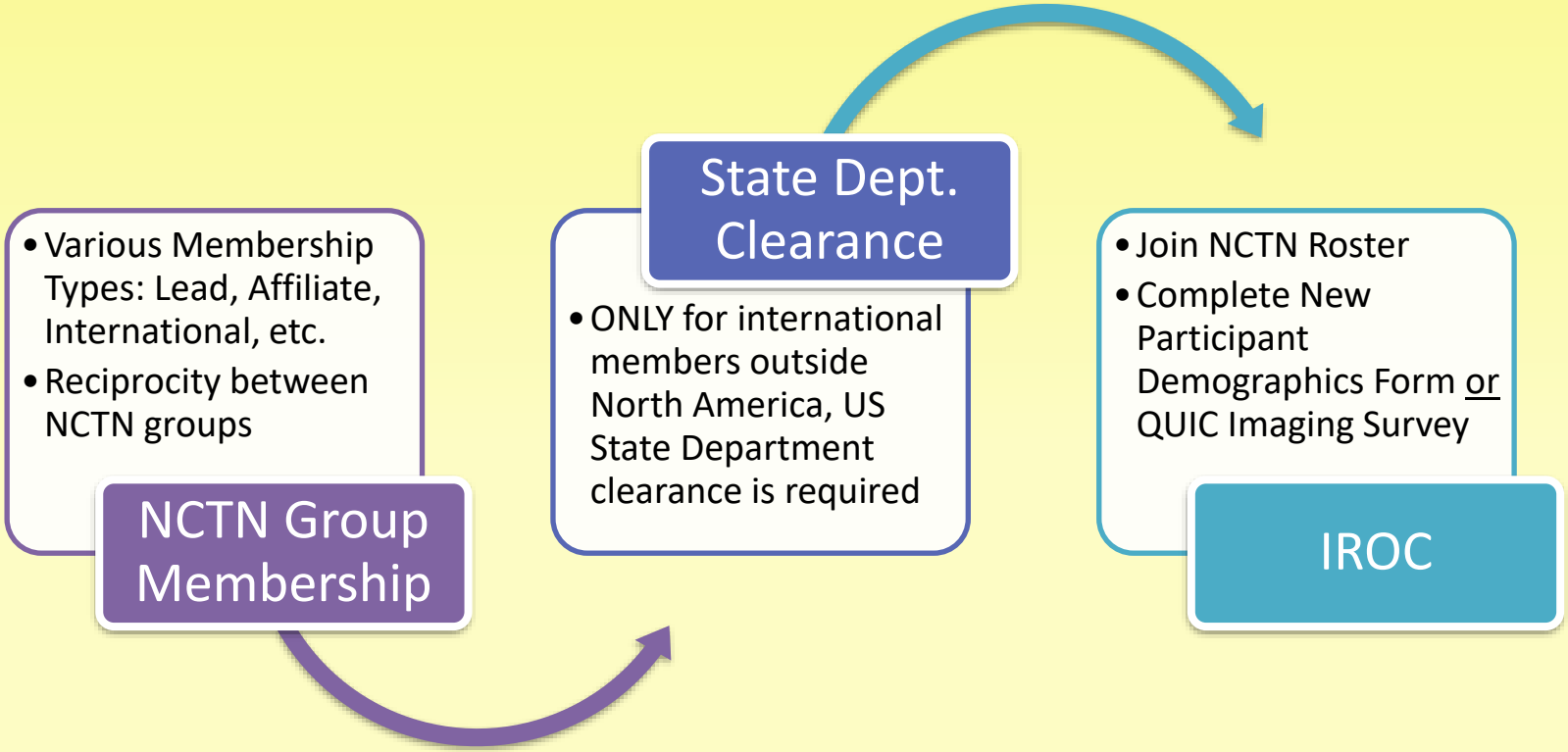
1. Site Qualification
2. Trial Design Support
3. Credentialing
4. Data Management
5. Case Review

Clinical Trial Group Membership

Membership: NCTN

- Each clinical trial group within the NCTN has its own membership process
  - Alliance: https://www.allianceforclinicaltrialsinoncology.org/main/public/standard.xhtml?path=%2FPublic%2FBecome-Member
  - COG: https://childrensoncologygroup.org/index.php/joiningcog
  - ECOG-ACRIN: https://ecog-acrin.org/about-us/membership
  - NRG: https://www.nrgoncology.org/About-Us/Membership
  - SWOG: https://www.swog.org/about/join-swog-cancer-research-network
  - CCTG: https://www.ctg.queensu.ca/public/become-member

Membership: NCTN



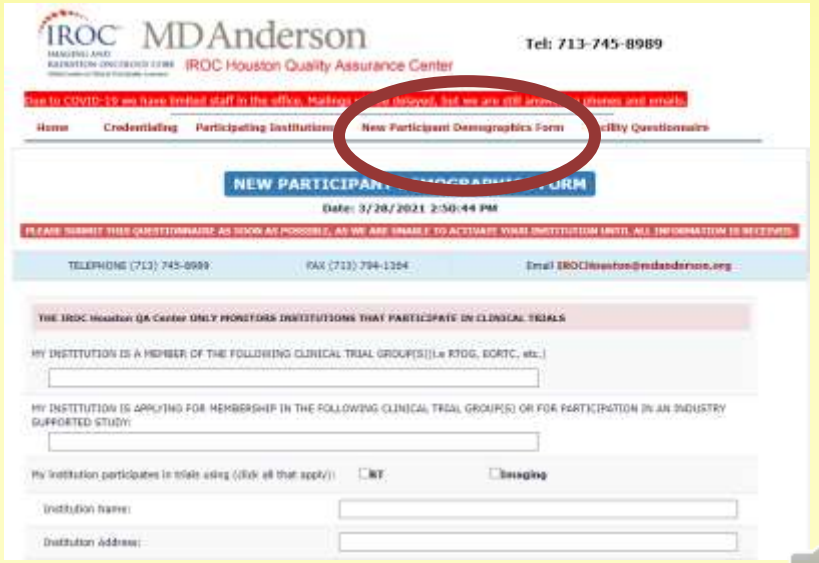
Membership: NCTN Roster

- IROC, CTEP and CTSU are creating a new NCTN Member Roster for Imaging and Radiation Therapy Facilities participating in Network trials
- Roster includes Imaging and Radiation Therapy Facilities at non-enrolling sites as well as those at enrolling site institutions

Membership: NCTN Roster

quic.acr.org

irochouston.mdanderson.org



Clinical Trial Resources

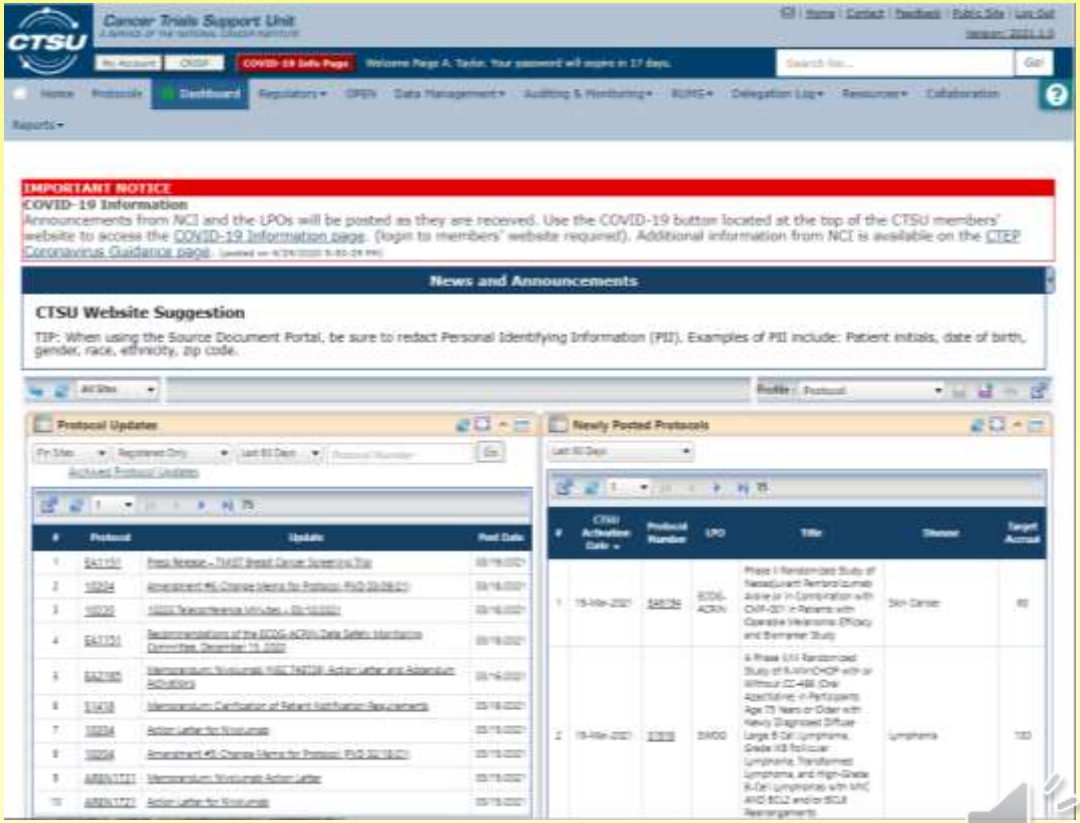
Resources: CTSU

CTSU Website: www.ctsu.org

- **Protocol** and **protocol-related documents**
- Funding information for studies under the NCI National Clinical Trials Network (NCTN)
- NCI Central Institutional Review Board (CIRB) documents for sites participating in the CIRB initiative
- Links to Medidata Rave® and the Oncology Patient Enrollment Network (OPEN)
- Access to the Data Quality Portal, Site Audit Portal, and accrual information
- Information on regulatory submissions
- Educational materials
- E-mail notification on protocol updates

Resources: CTSU

In order to get access to CTSU website, need to register for CTEP IAM account: https://ctepcore.nci.nih.gov/iam



Resources: TRIAD

- TRIAD is the American College of Radiology's (ACR) image exchange application
- New NCTN trials use TRIAD for dosimetry digital treatment data submission

- Need help with TRIAD?

https://triadhelp.acr.org

703-390-9858

Triad-Support@acr.org

Resources: Contouring Atlases

NCTN has contouring atlases for:

- Brain
- Breast
- Extremity Soft Tissue Sarcoma
- GI
- GU
- GYN
- H&N
- Lung
- Male Normal Pelvis
- Upper abdomen

CIRO
Center for Innovation in Radiation Oncology
NRG Oncology

https://www.nrgoncology.org/ciro-contouring-atlases-templates-and-tools

Resources: Physics Committees

Many clinical trial groups have medical physics committees. These are a great resource for trial information

- NRG Oncology Medical Physics Subcommittee
- COG Medical Physics Committee
- AAPM Work Group on Clinical Trials (us!)

Clinical Trial Credentialing

Importance of Credentialing

Goal of credentialing: ensure comparability and consistency across centers participating in trials

Peters, *et al.* found that noncompliant RT resulted in a **40% decrease in Overall Survival**

Journal of Clinical Oncology > List of Issues > Volume 28, Issue 18 >

ORIGINAL REPORTS | Head and Neck Cancer

Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques BernierJean Bourhis, Kally Yuen, Richard Fisher, Danny Rischin

From the Departments of Radiation Oncology and Medical Oncology, and Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre; University of Melbourne, Melbourne, Australia; Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada; Department of Radiation Oncology, Hospital General Vall d'Hebron, Barcelona, Spain; Department of Radiation Oncology, University of Massachusetts Medical Center, North Worcester, MA; Department of Radiation Oncology, H. Lee Moffitt Cancer Center, Tampa, FL; Department of Radiation Oncology, Genolier Swiss Medical Network, Geneva, Switzerland; Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; Quality Assurance Review Center, Providence, RI.

Importance of Credentialing

Weber, *et al.* found that a majority of RT trials had a primary end-point negatively impacted by protocol deviations

Clinical trial credentialing helps minimize uncertainty and reduce these deviations

ELSEVIER

Radiotherapy and Oncology

Volume 105, Issue 1, October 2012, Pages 4-8

Systematic review

QA makes a clinical trial stronger: Evidence-based medicine in radiation therapy

Damien C. Weber [a, e], Milan Tomsej [b], Christos Melidis [c], Coen W. Hurkmans [d, e]

Show more

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https://doi.org/10.1016/j.radonc.2012.08.008

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Importance of Credentialing

- Credentialing is very important in the context of new technologies in clinical trials
  - Proton therapy
  - Adaptive RT
  - MR-linacs
  - Targeted radionuclide therapy

- If our goal is comparability and consistency, credentialing is a great way to verify that for new techniques

Image from https://www.pennmedicine.org/cancer/navigating-cancer-care/programs-and-centers/roberts-proton-therapy-center

What does credentialing involve?

Credentialing

IROC is the main credentialing body for the NCI

IROC®
IMAGING AND RADIATION ONCOLOGY CORE
Global Leaders in Clinical Trial Quality Assurance

1. Site Qualification
   FQs, ongoing QA, proton approval
2. Trial Design Support/Assistance
   protocol review, help desk
3. **Credentialing**
   phantoms, IGRT, knowledge assessments, benchmarks
4. Data Management
   pre-review, use of TRIAD, post-review for analysis
5. Case Review
   pre-, on-, post-treatment clinical reviews

Credentialing

- Types of credentialing:
  - Phantoms
  - IGRT
  - Scanner qualification
  - Knowledge assessments
  - Benchmarks
  - pre-, on-, post-treatment clinical reviews

Credentialing

Where can you find credentialing information?

The protocol

(check www.ctsu.org)

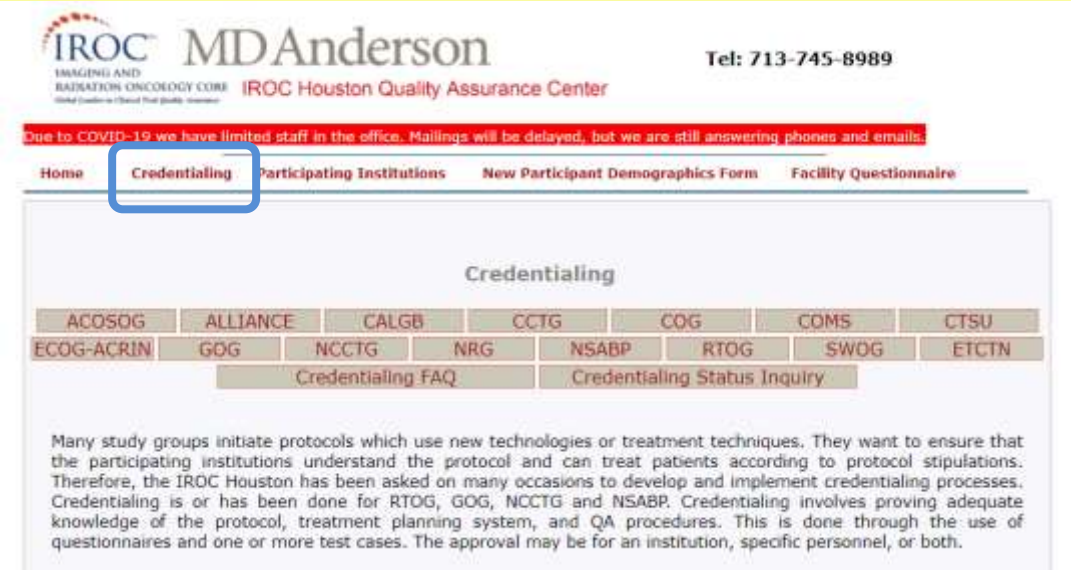
RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org			
	Treatment Modality			Key Information
	SBRT	IMRT	Proton	
Facility Questionnaire	X	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	X	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	X	X	X	A liver phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that only the most sophisticated technique needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used. VMAT, Tomotherapy, Cyberknife and proton treatment delivery modalities must be credentialed individually.
IGRT Verification Study	X	X	X	The institution must submit a sample of verification images showing their ability to reproducibly register daily IGRT information with a planning CT dataset (i.e., the GTV falls within the CT simulation defined PTV). The patient ("as if patient") used for this study must have a target (or mock target) in the liver. The information submitted must include 2 IGRT datasets (from 2 treatment fractions) for a single patient and must employ the method(s) that will be used for respiratory control for patients entered from a particular institution (e.g. abdominal compression, breath hold, etc...). This information with a spreadsheet (the spreadsheet is available on the IROC Houston web site, http://irochouston.mdanderson.org
Pre-Treatment Review	X	X	X	The first patient to be enrolled from each institution will be planned per NRG-GI001 specifications and submitted via TRIAD for evaluation by the IROC Houston QA Center and the trial PI or designee. Feedback will be given to the institution within 3 business days regarding any concerns prior to the patient being treated. Any required treatment plan modifications must be resubmitted for evaluation prior to treatment.
Credentialing Notification Issued to:				
Institution				IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

Credentialing

Where can you find credentialing information?

IROC website

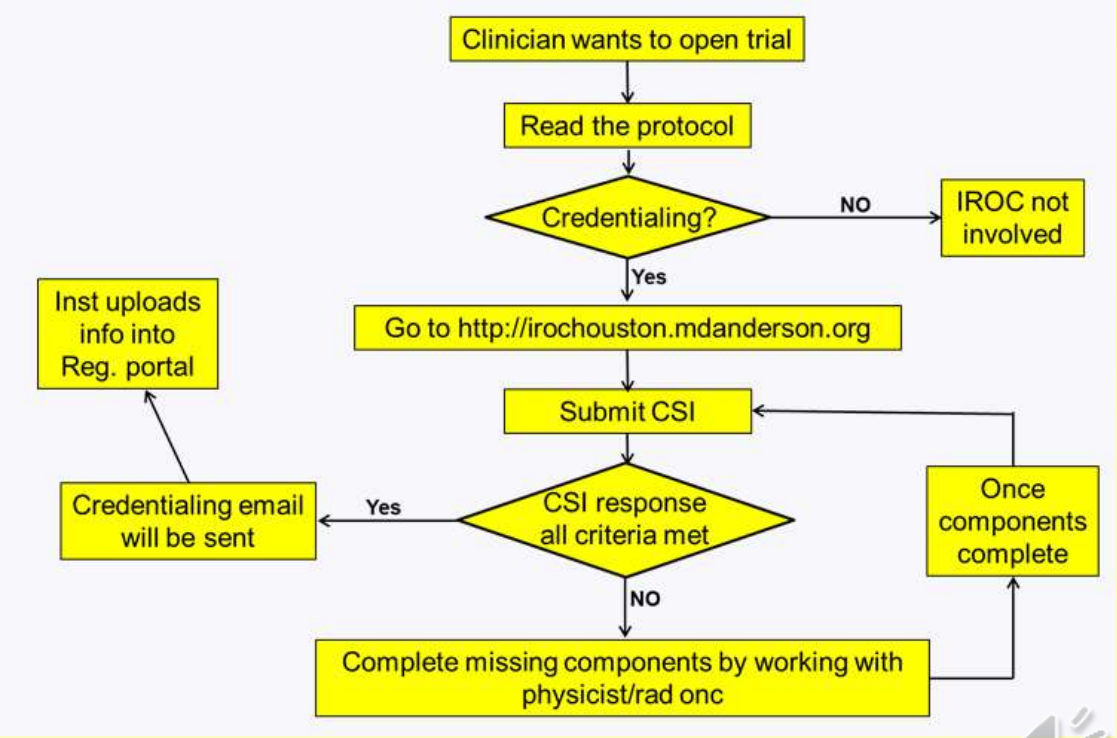
(www.irochouston.mdanderson.org)



Credentialing

Here's a little cheat sheet for figuring out credentialing for your center for a clinical trial

Best place to start:
Credentialing Status Inquiry Form (CSI)
On IROC website



Credentialing: Phantoms

H&N

Lung

Liver

SRS

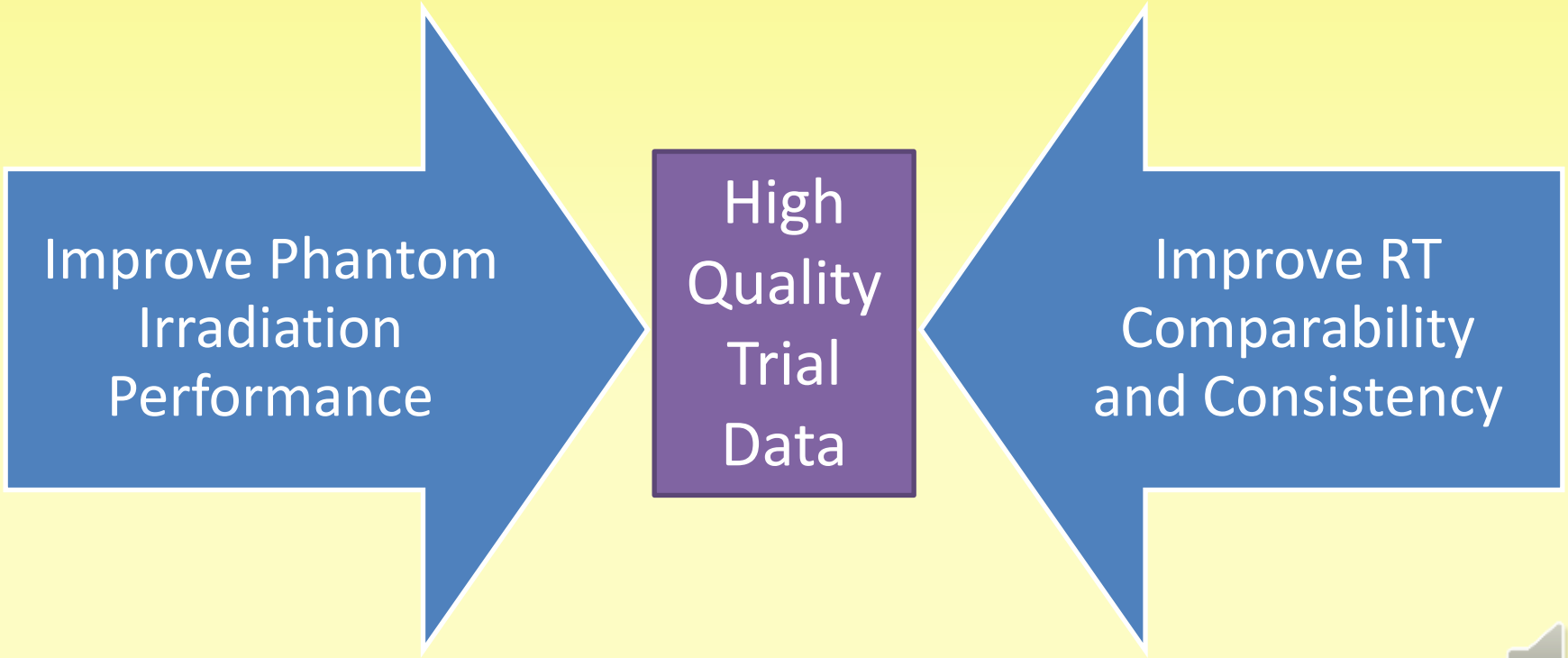
Spine

Prostate

Phantoms are an effective end-to-end test of an institution's RT treatment abilities

Phantom are used for credentialing in a majority of NCTN RT trials

Credentialing: Phantoms



Credentialing: Phantoms

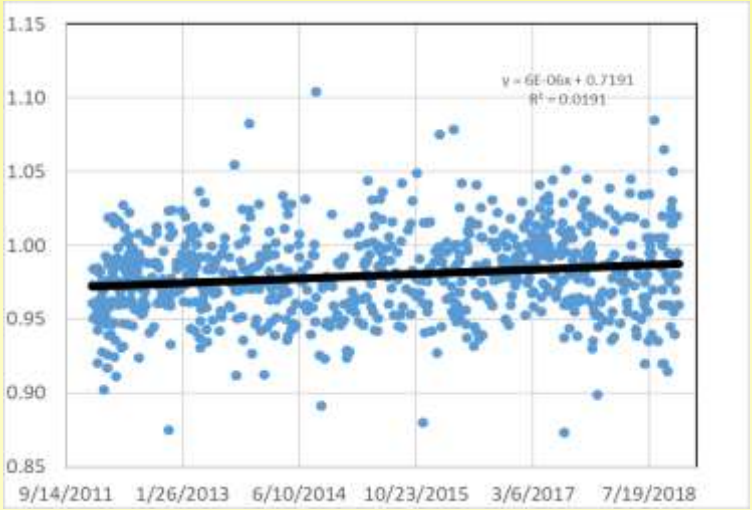
IROC SRS Phantom

- Simulates 1.9 cm brain lesion
- Rx: 30 Gy
- Acceptance Criteria: ±5% TLD, 5%/3mm film

Credentialing: Phantoms

SRS Phantom TLD:TPS vs Irradiation Date

- Significant improvement with time (p<<0.01)
  - Improved small field dosimetry
  - Improved beam modeling in TPS
- 2012, average TLD ratio: 0.972
- Present, average TLD ratio: 0.987
- Before the end of 2023, average TLD ratio will reach 1.000!



Slide courtesy of Stephen Kry

Credentialing: Phantoms

Sources of SRS Phantom Errors:

- Incorrect Cone factors/output factors
  - TRS-483 is great for improving measurement
  - Modeling can be a separate issue
- Incorrect TMR in TPS
- Incorrect HU-electron density conversion
- Incorrect reference specification in TPS
- Incorrect manual adjustment of output factors

- Minimize errors by following best clinical practice

Slide courtesy of Stephen Kry

Credentialing: Phantoms

SRS Phantom Resources

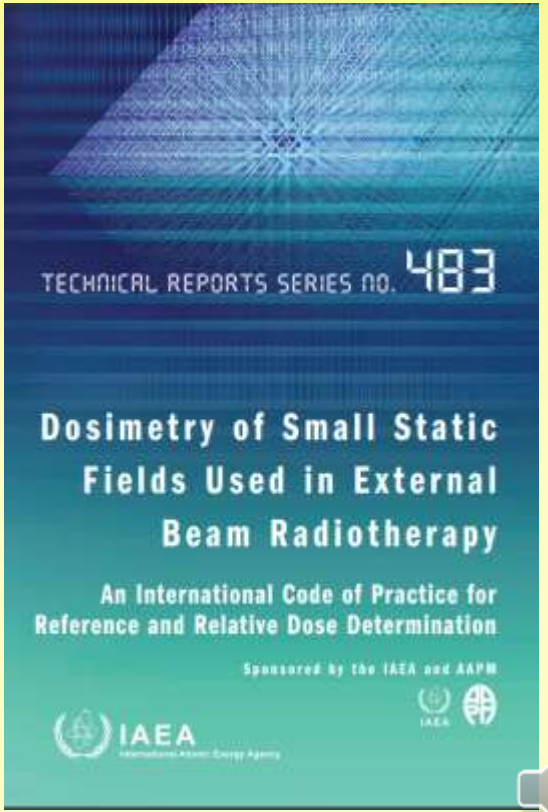
JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, VOLUME 13, NUMBER 5, 2012

The Radiological Physics Center's standard dataset for small field size output factors

David S. Followill,[1a] Stephen F. Kry,[1] Lihong Qin,[2] Jessica Leif,[1] Andrea Molineu,[1] Paola Alvarez,[1] Jose Francisco Aguirre,[1] and Geoffrey S. Ibbott[1]

Department of Radiation Physics,[1] Radiological Physics Center, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA; Department of Therapeutic Radiology,[2] University of Minnesota, Minneapolis, MN, USA
dfollowi@mdanderson.org

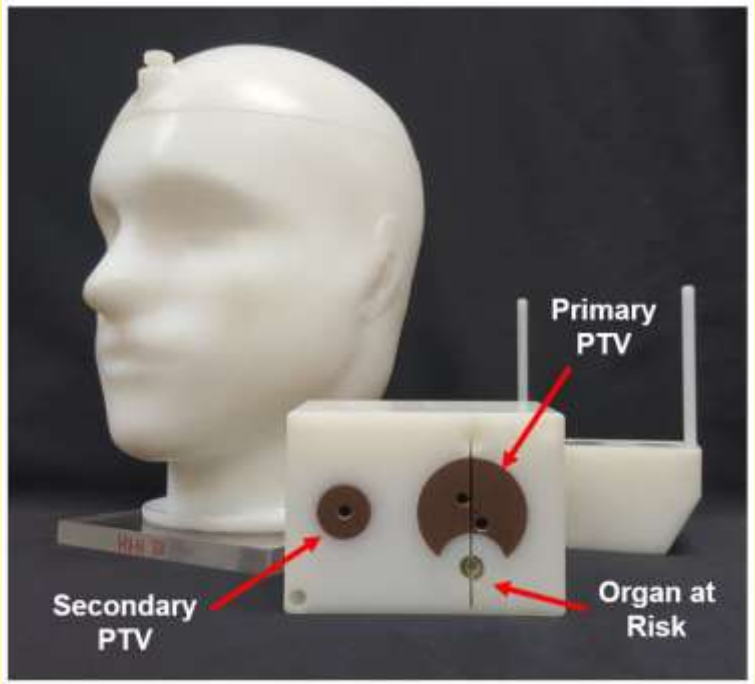
Received 4 March, 2012; accepted 30 May, 2012



Credentialing: Phantoms

IROC H&N Phantom

- Simulates nasopharyngeal lesion with nodal involvement
- Acceptance Criteria: ±7% TLD, 7%/4mm film



Credentialing Phantoms

Main sources of H&N phantom errors:

- Systematic dose
- Setup
- Local
- Global


MEDICAL PHYSICS
The International Journal of Medical Physics Research and Practice

Therapeutic interventions | Open Access

Examining credentialing criteria and poor performance indicators for IROC Houston's anthropomorphic head and neck phantom

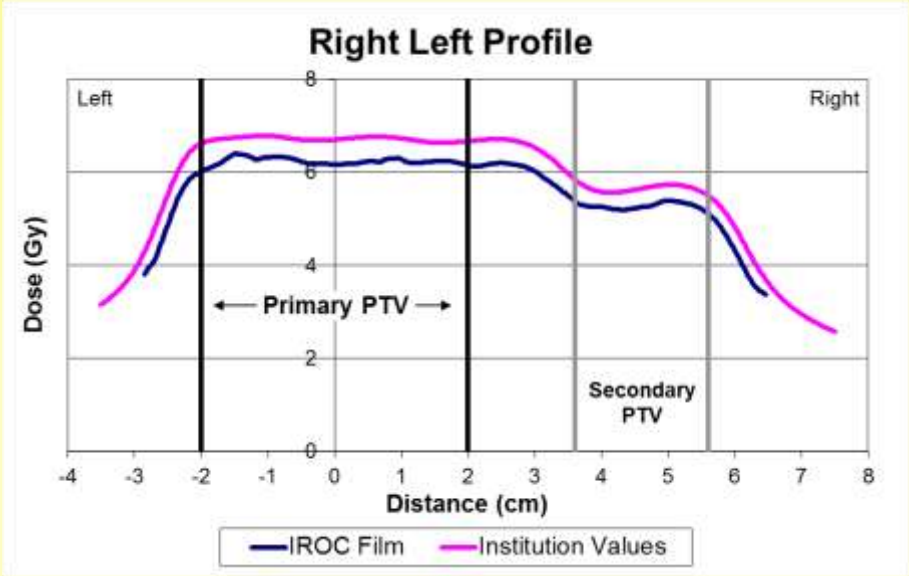
Mallory E. Carson, Andrea Molineu, Paige A. Taylor, David S. Followill, Francesco C. Stingo, Stephen F. Kry

First published: 11 November 2016 | https://doi.org/10.1118/1.4967344 | Citations: 27

Credentialing Phantoms

69% of H&N phantoms failures were due to:

Systematic errors in the TPS dose calculation



Carson, et al. *Med. Phys.* 2016.

Credentialing Phantoms

Phantoms with motion: lung & liver

Can you guess the number one source of error in these phantoms??

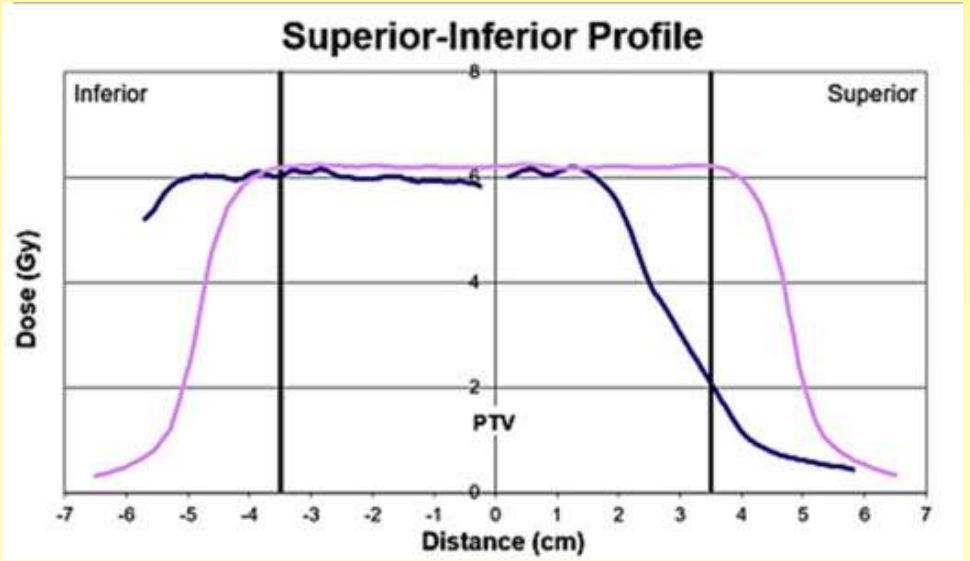
Lung Phantom

Liver Phantom

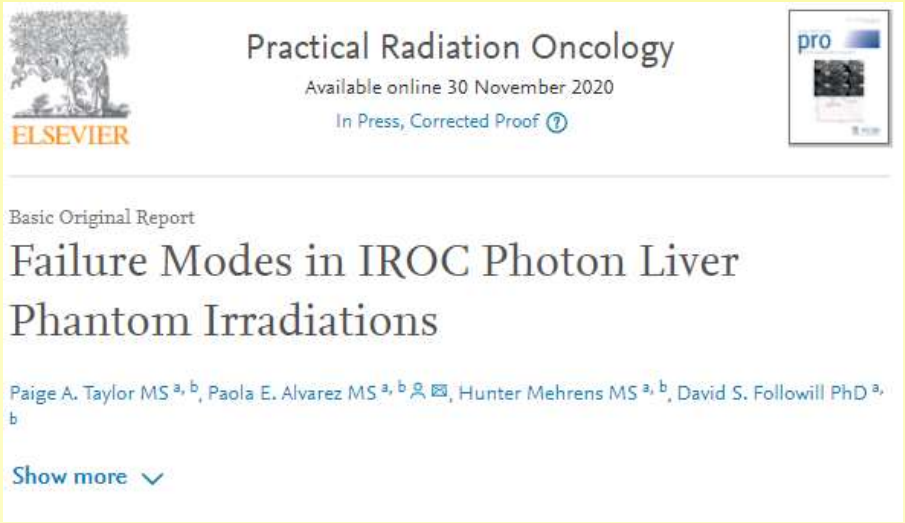
Credentialing Phantoms

Top error in lung and liver phantoms:

Localization error in the direction of motion



Credentialing Phantoms



Practical Radiation Oncology
Available online 30 November 2020
In Press, Corrected Proof

Basic Original Report

Failure Modes in IROC Photon Liver Phantom Irradiations

Paige A. Taylor MS [a, b], Paola E. Alvarez MS [a, b], Hunter Mehrens MS [a, b], David S. Followill PhD [a, b]

Show more

Practical Radiation Oncology
Volume 10, Issue 5, September–October 2020, Pages 372-381

Basic Original Report

Differences in the Patterns of Failure Between IROC Lung and Spine Phantom Irradiations

Sharbacha S. Edward BS [a, b, c], Paola E. Alvarez MS [b, c], Paige A. Taylor MS [a, b, c], H. Andrea Molineu MS [b, c], Christine B. Peterson PhD [a, d], David S. Followill PhD [a, b, c], Stephen F. Kry PhD [a, b, c]

Credentialing Phantoms

Second most common error in lung phantoms:

Systematic dose error

Typically a result of less sophisticated algorithms

Pencil beam algorithms not allowed for photons or protons on NCTN lung protocols anymore

Credentialing: IGRT

IGRT Credentialing

- Typically required for trials that allow reduced treatment margins (<5 mm)

2 Types

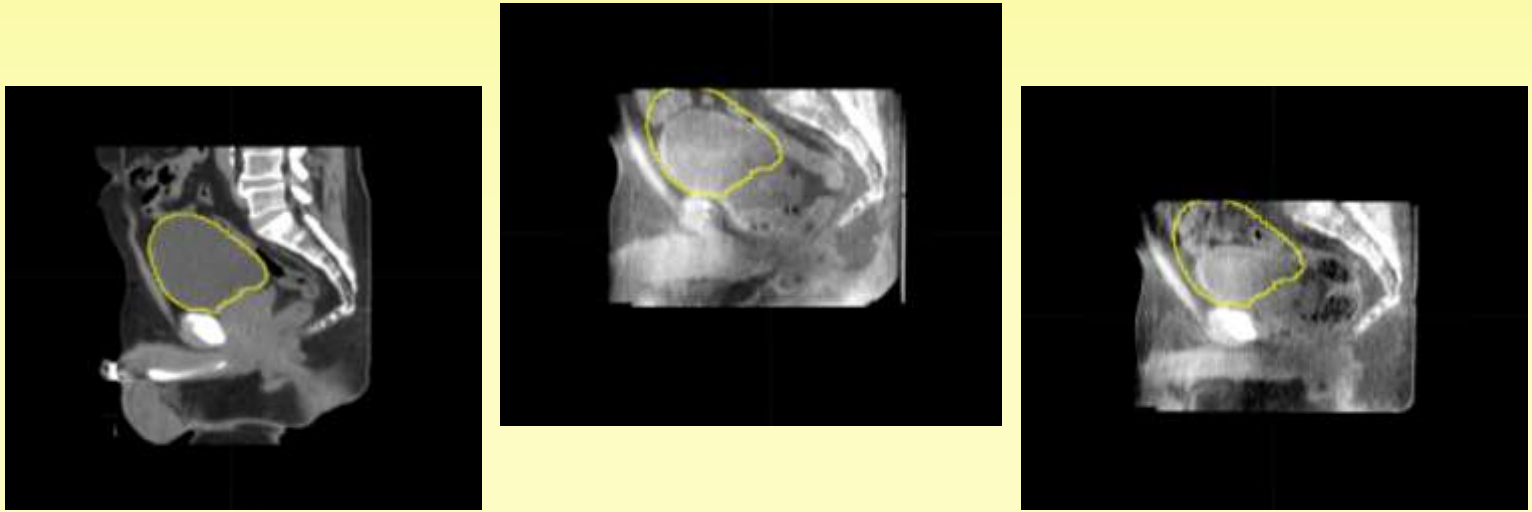
- Boney
  H&N/brain + pelvis
- Soft Tissue
  Lung/liver/pancreas + pelvis

Submission Requirements

- Planning CT (DICOM) for 1 patient
- DICOM RT Structures
- DICOM RT Plan
- DICOM RT Dose
- DICOM localization images (e.g. CBCT or MRI) for 2 fx
- DICOM spatial registration file
- Completed DDSI
- Completed Online IGRT Questionnaire

Credentialing: IGRT

Potential pitfall: inconsistent bladder filling



Slide courtesy of Andrea Molineu

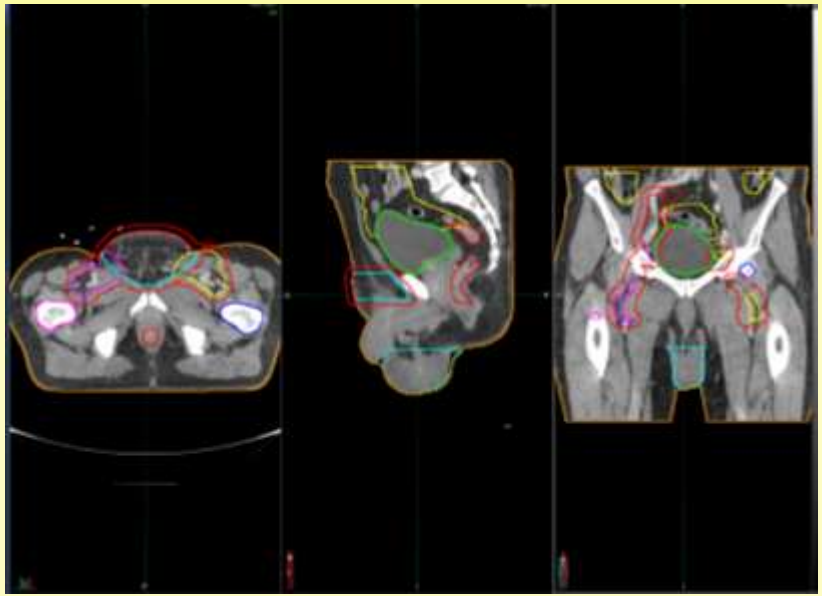
Credentialing: Imaging Scanners

https://www.biodex.com/nuclear-medicine/products/pet-positron-emission-tomography/pet-phantoms/flangeless-deluxe-pet-and-sp

- Credentialing required for some imaging modalities, like PET/CT
- Might be required multiple times during protocol, e.g. PET credentialing required annually for NRG GY006 protocol

Credentialing: Benchmarks

- Benchmark plans provide single data set for every institution to practice on
- Credentialing reviews:
  - Contouring
  - Planning
  - Both



Slide courtesy of Jessica Lowenstein

Credentialing: Patient Plan Reviews

- Pre-treatment
  - Must be reviewed rapidly before patient is treated
  - Biggest impact, but lots of pressure
- On-treatment
  - Relieves some of the time pressure, but allows PIs insight into common planning deviations
  - Opportunity to discuss with co-investigators while the trial is accruing
- Post-treatment
  - Done for most trials to check if trial constraints were met

Credentialing: Knowledge Based Planning

- Becoming more popular for clinical use
- Also employed in a few clinical trials (e.g. NRG GY006)
  - Institution's plan run through KBP program
  - Recommendations to institution about possible ways to improve their plan

Credentialing: Patient Plan Reviews

Review Type	Major Deviation Rate 2018
Benchmark	16%
Pre-treatment	21%
Post-treatment	9%

Slide courtesy of Jessica Lowenstein

Credentialing

- Credentialing → reduce deviations
- We hope you can use some of these tips and tricks to help you on your own credentialing journey
- Don't hesitate to reach out if you ever have questions!

pataylor@mdanderson.org

@mpPaigeTaylor

And once all the credentialing is done…

You can pass the torch to your physician colleagues!

Now for the clinician perspective on clinical trials, from Shruti Jolly, M.D.

Professor and Associate Medical Director of Strategic Planning & Business Development, University of Michigan

The Physician's Perspective

Shruti Jolly MD
Professor, Department of Radiation Oncology
University of Michigan, Ann Arbor, MI

Outline

- **Clinical Research Overview**
- **Radiation Oncologist's Role**
- **Role in trial development and leadership**
- **Recruitment strategies**
- **Case scenarios**

Defining clinical research

- The study of human beings in a systematic investigation of human biology, health, or illness, designed to develop or contribute to generalizable knowledge
- Inclusive of a set of activities that are meant to test a hypothesis, formed on particular treatments/diagnostics/medical devices...
- The conclusions drawn from such research, thereby contribute to generalizable knowledge which will be used to improve medical care or the public health and thus serve the common or collective good.

Defining physician's role

- **Investigator in clinical trials**
  - Enroll patients of clinical practice into clinical trials
- **Tailor studies independently**
  - Helps in understanding and revising the modes of practice
- **Industry**
  - Medical monitor, clinical administrator, medical advisor, CMO

Role in trial development & leadership

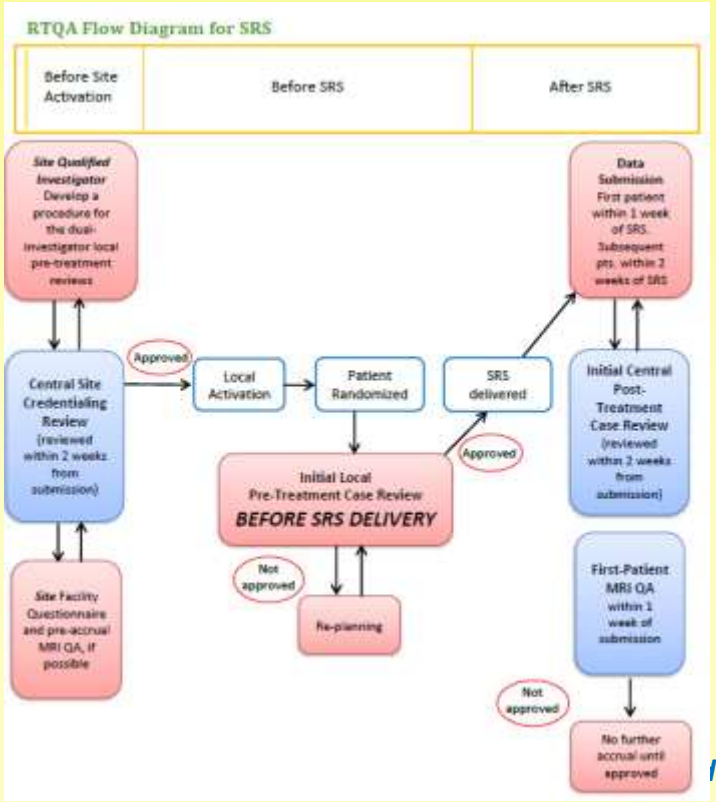
- **Designing of investigator initiated trial**
  - **Clinical**
  - **Biomarker driven**
  - **Drug design**
- **Multi-institutional collaborative clinical trial**
  - **NRG, SWOG**
  - **Various subcommittees and trials of NRG led by physicists**
- **Prospective registry data**
- **NIH, Industry**

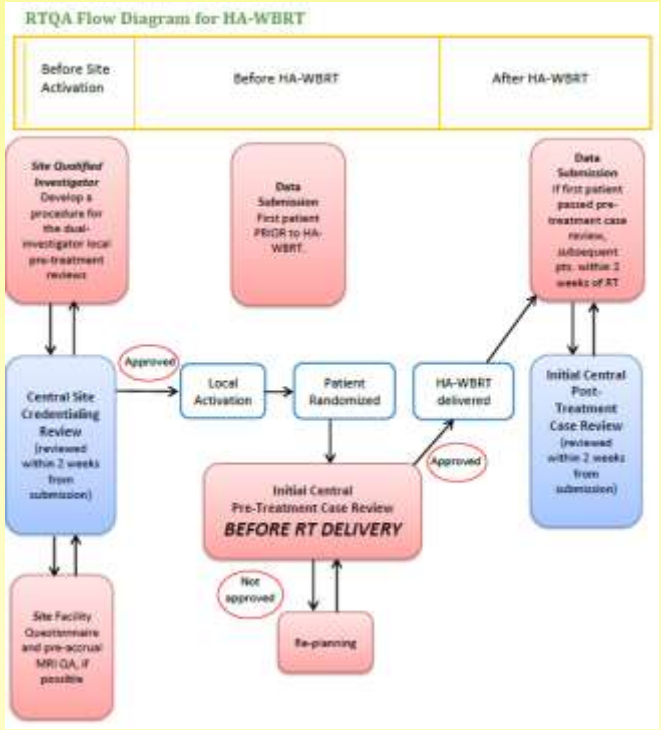
Clinical Trial Recruitment

- **Recruitment strategies**
  - **Sharing with other health care providers (locally and nationally)**
  - **Connecting with patient advocates**
  - **Recruitment campaigns (social media)**
  - **Screening for multiple trials at a time**
  - **Patient convenience**
  - **Incentives**

CCTG-CE-7: A Phase III Trial of Stereotactic Radiosurgery Compared with Whole Brain Radiotherapy (WBRT) for 5-15 Brain Metastases

Case scenario 1





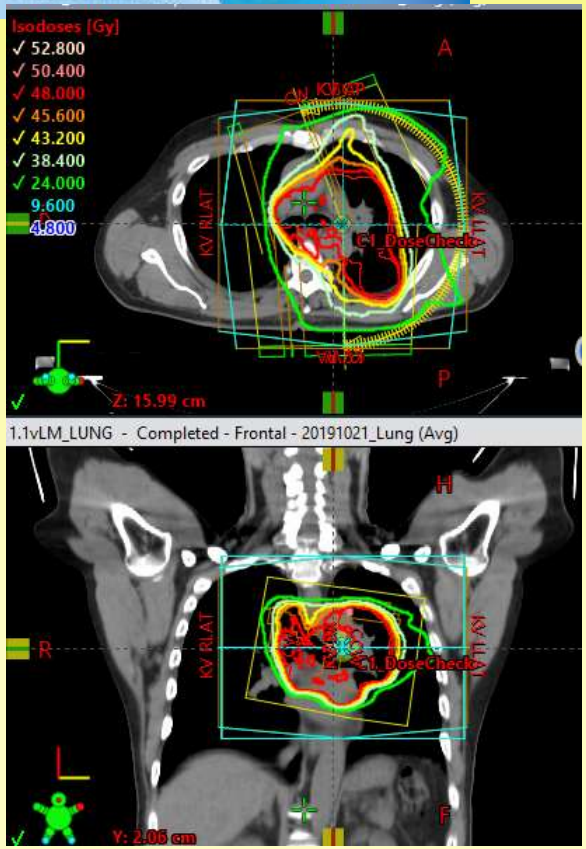
RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org		
	Treatment Modality		Key Information
	SRS	HA-WBRT	
Facility Questionnaire	✓	✓	The IROC electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ go to http://irochouston.mdanderson.org/questionnaires.
Credentialing Status Inquiry Form	✓	✓	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	✓	✓	An IROC Houston anthropomorphic phantom must be successfully completed if the institution has not previously met this credentialing requirement. Flattening-filter-free (FFF) photon beam delivery, CyberKnife, and GammaKnife treatment delivery modalities must be credentialed individually and separately from standard c-arm linac beams. Instructions for requesting and irradiating the phantom are available on the IROC Houston website under credentialing (http://irochouston.mdanderson.org)
MRI QA (SRS)	✓		Documentation of MRI phantom geometric QA, or submission of both planning CT and MRI for a non-protocol (e.g. previous) patient, or for the first enrolled patient on study. See RTQA Manual (section 2.4) for requirements. Note: this differs from case review of HA-WBRT using MRI-only treatment planning (see section 3.2)
Benchmark Testing	✓	✓	Benchmark cases are to be downloaded and completed by each institution before submission to via TRIAD. *NOTE: Before a benchmark can be submitted the site must have IRB Approval and remaining steps of SRS and HA-WBRT credentialing in progress or completed. See below for more details.*
Credentialing Issued to:			
Institution			IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met. It is the institution's responsibility to forward this information to the CTSU Regulatory Office.

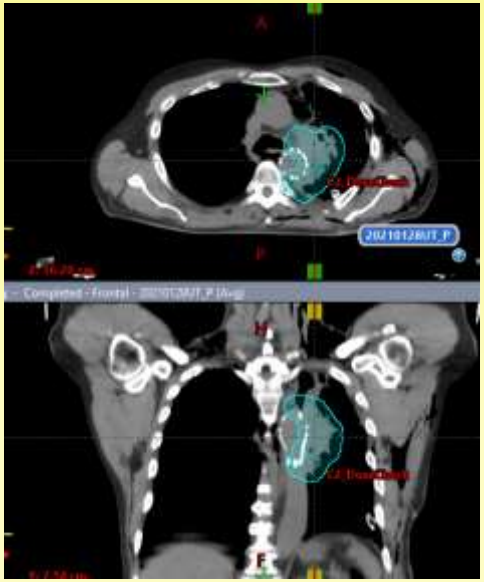
Case scenario 2

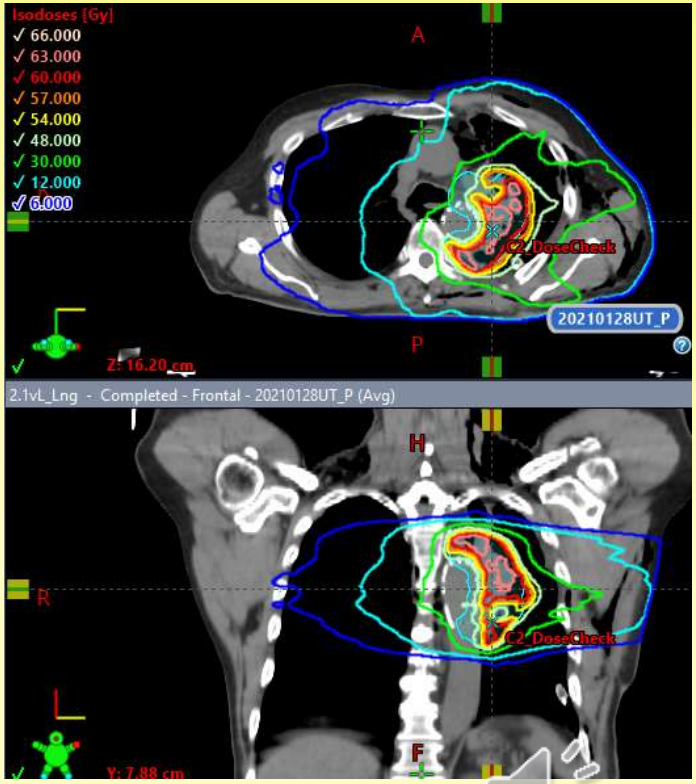
- **UM IIT study (UMCC 2015.035) Individualization of Lung cancer Treatment – using radiographic and biological biomarkers**
  - **PO1 funding, clinical protocol design**
  - **Frequent research team meetings to evaluate accrual, adverse events and logistical issues**
    - **Evaluate lung toxicity, and tumor failures**
  - **Trial analyses, abstracts/manuscripts**
  - **Decide on next steps and ways to obtain additional funding to continue building upon work**

Case scenario 3

- **SPRINT study (Merck sponsored multisite study, Ohri et al.) –**
  - **Locally Advanced NSCLC patients with high PDL1 undergo 3 cycles of Pembrolizumab then PET adaptive radiation (no chemo)**
  - **1 year later, patient presented with hemoptysis and was found to have local recurrence. Restaging scans were otherwise negative.**







2.4 Gy in 20 fxs to 48 Gy per protocol

Local Recurrence treated in 15 fractions

Conclusions

- **Partnership of radiation oncologist with medical physicist is vital to the success of clinical trials in the radiation oncology clinic**