What are the roles and tasks of medical physicists in clinical trials?

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What are clinical trials?

- Research studies that explore whether a medical strategy, treatment, or device is **safe and effective for humans**
- Clinical trials follow **strict scientific standards**
- Clinical trials follow **strict ethical rules**
- Clinical trials can result into:
  - Improved patient outcomes, or
  - Offer no benefit, or
  - Cause unexpected harm

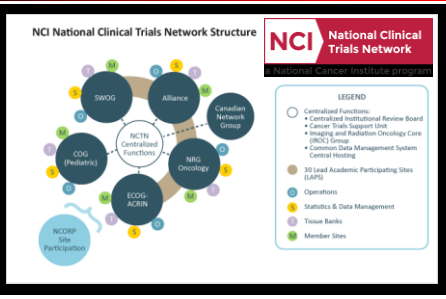
Clinical trial phases

- **Phase I:** test new treatments in small groups of people for safety and side effects
- **Phase II:** looks at how well treatments work and further review these treatments for safety
- **Phase III:** use larger groups of people to confirm how well treatments work, further examine side effects, and compare new treatments with other available treatments.

Single-center vs Multi-center trials

- Phase I, and sometimes Phase II clinical trials are done typically at **single institutions**
  - Institutional Clinical Research Office takes care of the clinical trial logistics
- Phase II and Phase III clinical trials are done at **multiple institutions**
  - One institution takes the lead coordination
  - Pharma via Contract Research Organizations
  - NIH (e.g., NCI) via National Clinical Trials Network (NCTN)

National Clinical Trials Network (NCTN)



Clinical trial protocol

- The clinical trial is led by a **Chair/Principal Investigator,** who prepares the clinical trial protocol
  - The trial might include one or more **Co-Chairs/Co-Principal Investigators**
- **Key information** in a protocol includes:
  - How many patients will take part in the clinical trial;
  - Who is eligible to take part in the clinical trial;
  - What tests patients will get and how often they will get them;
  - What type of data will be collected during the clinical trial; and
  - Detailed information about the treatment plan.

Roles of medical physicists

- **Supporting role:**
  - Execution of study procedures (e.g., RT planning and delivery)
- **Study Co-Chair role:**
  - Oversight of a specific task (e.g., RT prescription, QA)
- **Study Chair role:**
  - Protocol design, write-up, approval, monitoring, regulatory oversight…

Role: Medical Physics Co-Chair

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0825

PHASE III DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE PLUS BEVACIZUMAB VERSUS CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

NCI-Supplied Agent: Bevacizumab (NSC 704865; IND 7921)

Study Chairs (4/15/09)

RTOG Study Chairs (Coordinating Group)*

Principal Investigator/Medical Oncology
Mark R. Gilbert, MD
U. T. M. D. Anderson Cancer Center

Radiation Oncology
Minesh Mehta, MD
University of Wisconsin
Department of Radiation Oncology

Medical Oncology
Deborah T. Blumenthal, MD
Tel Aviv Medical Center

Neurosurgery
Michael A. Vogelbaum, MD, PhD
Brain Tumor Institute
Cleveland Clinic Foundation

Neuropathology/Correlative Biology
Ken Aldape, MD
U.T. M. D. Anderson Cancer Center

Howard Colman, MD, PhD
U.T. M. D. Anderson Cancer Center

Arnab Chakravarti, MD
Department of Radiation Oncology
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Medical Physics
Robert Jeraj, PhD
Departments of Medical Physics, Human Oncology and Biomedical Engineering
University of Wisconsin - Madison

Quality of Life
Terri S. Armstrong, PhD, ANP-BC
University of Texas Health Science Center

Neurocognitive Function
Jeffrey S. Wefel, PhD
U.T. M.D. Anderson Cancer Center

Senior Statistician
Meihua Wang, PhD
Radiation Therapy Oncology Group/ACR

*See next page for NCCTG and ECOG Study Chairs

Radiotherapy specifics

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Allowed
Modality chosen at registration must be used for the entire course of treatment.

Treatment must begin > 3 weeks and ≤ 5 weeks after surgery.

6.1 Dose Specifications and Schedule

For both IMRT and 3D-CRT plans, one treatment of 2 Gy will be given daily 5 days per week for a total of 60 Gy over 6 weeks. All portals shall be treated during each treatment session. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are necessary to make this selection.

6.2 Technical Factors

Treatment shall be delivered with megavoltage machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy (ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle, or implant boost is not permissible. IMRT delivery will require megavoltage radiation therapy machines of energy ≥ 6 MV.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device to ensure adequate immobilization during therapy and ensure reproducibility is strongly recommended. Simulation may include a dedicated radiotherapy simulator or a virtual simulation using a treatment planning CT. Fusion with MR images is strongly recommended, whenever feasible.

Target volume definitions

6.4 Treatment Planning/Target Volumes

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. Intensity-modulated inverse-planned approaches are permitted. Any of the methods of IMRT (including tomotherapy) may be used, subject to protocol localization and dosimetry constraints. CT-based treatment planning is necessary to assure accuracy in the selection of field arrangements. MRI-fusion for accurate target delineation is strongly recommended.

6.4.1 **Initial Target Volume**: Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. Two planning target volumes (PTV) will be defined, as outlined below. The initial gross tumor volume (GTV1) will be defined by either the T2 or the FLAIR abnormality on the post-operative MRI scan. This must also include all postoperative-enhanced MRI enhancement, and the surgical cavity. The initial clinical target volume (CTV1) will be the GTV plus a margin of 2 cm. If no surrounding edema is present, the initial planning target volume (PTV1) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 2.5-cm margin. The CTV1 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The initial planning target volume (PTV1) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV1 and the particular PRV of concern, may be created. Dose to the $PTV_{Overlap}$ must be as close as permissible to 46 Gy while not exceeding the OAR dose limit.

Dose prescription

6.4.2 **Boost Target Volume**: The boost gross tumor volume (GTV2) will be defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan. This must also include the surgical cavity margins. The boost clinical target volume (CTV2) will be the GTV plus a margin of 2 cm. The CTV2 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The boost planning target volume (PTV2) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined , along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV2 and the particular PRV of concern, may be created (the overlap is the intersection between the PTV1 and the PRV). Dose to the $PTV_{overlap}$ must be as close as permissible to 14 Gy while not exceeding the OAR dose limit.

6.4.3 **Dose Guidelines**: The initial target volume will be treated to 46 Gy in 23 fractions. After 46 Gy, the conedown or boost volume will be treated to a total of 60 Gy, with seven additional fractions of 2 Gy each (14 Gy boost dose).

Isodose distributions for the initial target volume (PTV1) and the conedown target volume (PTV2) are required on all patients. A composite plan is required showing the respective target volumes. The following composite isodose lines should be included: 66 Gy (when 66 Gy dose regions exist in the tumor), 60 Gy, 57 Gy, 48 Gy, 44 Gy and 40 Gy. The inhomogeneity within the target volume shall be kept to ± 10% of the prescribed dose.

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are encouraged to make this selection. The use of vertex fields requires either a diagram or a photograph of the treatment position to be submitted to RTOG Headquarters.

Finally - An impactful publication

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, M.D., Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieber, M.D., David G. Brachman, M.D., Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. Sulman, M.D., Kenneth D. Aldape, M.D., Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

Roles of medical physicists

- **Supporting role:**
  - Execution of study procedures (e.g., RT planning and delivery)
- **Study Co-Chair role:**
  - Oversight of a specific task (e.g., RT prescription, QA)
- **Study Chair role:**
  - Protocol design, write-up, approval, monitoring, regulatory oversight…

Role: Imaging Co-Chair

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

EA8153

Cabazitaxel with Abiraterone versus Abiraterone alone
Randomized Trial for Extensive Disease following
Docetaxel: the CHAARTED2 Trial

STUDY CHAIR: Christos Kyriakopoulos, M.D.
STUDY CO-CHAIR: Glenn Liu, M.D.
STUDY STATISTICIAN: Yu-Hui Chen, MPH, M.S.
IMAGING STATISTICIAN: Fengshi Yuan, Ph.D.
IMAGING CO-CHAIR: Robert Jeraj, Ph.D.
TRANSLATIONAL SCIENCE CO-CHAIR: Emmanuel Antonarakis, M.B.B.Ch.
PATIENT-CENTERED OUTCOMES CO-CHAIR: Alicia Morgans, M.D., MPH
PATIENT OUTCOMES AND SURVIVORSHIP COMMITTEE CHAIR: Lynne Wagner, Ph.D.
PROSTATE SUB-COMMITTEE CHAIR: Glenn Liu, M.D.
GU COMMITTEE CHAIR: Michael Carducci, M.D.

Version Date: April 5, 2017

STUDY PARTICIPANTS ***ACTIVATION DATE***
ALLIANCE / Alliance for Clinical Trials in Oncology

Imaging rationale

1.4.2 Characterize the pharmacodynamic changes and response to treatment using NaF PET/CT.

The clinical course of metastatic prostate cancers is largely restricted to bone, with predominantly osteoblastic metastases. However, there is currently no validated tool to assess treatment response in patients with metastatic prostate cancer to the bone. One of the most promising PET imaging agents for detection of bone metastasis in prostate cancer is ^{18}F-Sodium fluoride (NaF). NaF PET/CT is a more specific and sensitive tool that allows quantitative determination of change in functional disease burden to therapy. NaF PET/CT repeatability and responsiveness in patients with metastatic castration-resistant prostate cancer to bone treated with an antimicrotubule directed agent or AR-directed therapies has been previously evaluated [20]. In this study, we will prospectively examine whether the addition of cabazitaxel to abiraterone acetate can improve the overall response as well as the percentage of responding lesions compared to abiraterone acetate alone in support of our hypothesis. NaF PET/CT scans will be analyzed with innovative image analysis technique, termed Quantitative Total Bone Imaging (QTBI), developed at the University of Wisconsin [21, 22].

Imaging endpoints/eligibility criteria

2.4.2 Imaging Objectives

2.4.2.1 To assess if the changes in total tumor burden from baseline to week 12 as assessed with NaF PET/CT will differ between two arms.

2.4.2.2 To correlate total tumor burden at the baseline as assessed with NaF PET/CT with the PFS.

2.4.2.3 To correlate heterogeneity of response from baseline to week 12 as assessed with NaF PET/CT with the PFS.

3.2 NaF PET/CT Optional Sub-Study Eligibility Criteria

3.2.1 Inclusion Criteria

3.2.1.1 Ability to lie still for imaging.

3.2.1.2 Weight ≤ 300 lbs. (due to equipment specifications)

Imaging procedure specifics

10. Imaging Research Study

All NaF PET/CT images are to be submitted via TRIAD as outlined in Section 4.6.4

10.1 NaF PET/CT Imaging

The overall goal of this study is to examine whether the addition of cabazitaxel to abiraterone acetate can improve the overall response as well as the percentage of responding lesions compared to abiraterone acetate alone in support of our hypothesis. We expect a total of 50 eligible patients will be accrued in the sub-study. All participants will receive two imaging studies according to study protocol: **pre-treatment NaF** PET/CT at baseline **and a mid-treatment NaF** PET/CT at week 12. Eligible participants who have consented to this study will be actively involved in the trial and will be followed for treatment outcomes per protocol.

10.1.1 Imaging Schedule

Pre-treatment NaF PET/CT Imaging: this imaging study should be completed prior to treatment start.

Mid-Treatment NaF PET/CT Imaging: this imaging study should be completed during week 12 of the study treatment.

Imaging endpoint statistics

10.1.4 Imaging Aims and Statistics

There are three imaging aims in this correlative study.

10.1.4.1 *To assess if the changes in total tumor burden from baseline to week 12 as assessed with NaF PET/CT will differ between two arms.*

For the imaging Aim 1, we assume the mean percentage of SUVtotal decrease was 30% in the abiraterone acetate alone arm [43] and 60% (i.e., doubled) in the combination of cabazitaxel and abiraterone acetate arm, respectively, while the percentage of decrease is defined as (post SUVtotal – pre SUVtotal)/pre SUVtotal * 100%. The standard deviation was assumed to be 40% for both groups. Under the type I error 0.10 (two-sided), the sample size of 50 (25 in each arm) can achieve 83% power to detect the difference between two arms. Two-sample t-test assuming equal variance in PASS 14 was used for the computation.

Roles of medical physicists

- **Supporting role:**
  - Execution of study procedures (e.g., RT planning and delivery)
- **Study Co-Chair role:**
  - Oversight of a specific task (e.g., RT prescription, QA)
- **Study Chair role:**
  - Protocol design, write-up, approval, monitoring, regulatory oversight…

Role: Study Chair

ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAI141

Early Assessment of Treatment Response in AML using FLT PET/CT Imaging

STUDY CHAIR:	Robert Jeraj, PhD
STUDY CO-CHAIR:	Ryan J. Mattison, MD
MODALITY CO-CHAIR(S):	Lale Kostakoglu, MD, PhD
STUDY STATISTICIAN:	Fenghai Duan, PhD
EXPERIMENTAL IMAGING SCIENCES COMMITTEE CHAIR:	David Mankoff, MD, PhD
DISEASE-ORIENTED COMMITTEE CHAIR:	Mark Litzow, MD
PATHOLOGY CO-CHAIR:	Daniel Arber, MD
LABORATORY CO-CHAIR:	Elisabeth Paietta, PhD

Version Date: July 14, 2016
Update Date: October 7, 2015

STUDY PARTICIPANTS	*ACTIVATION DATE*
ALLIANCE / Alliance for Clinical Trials in Oncology	December 9, 2015

Rev. 10/16

How it usually starts…

HO04409

A Pilot Study for Using ^{18}F-FLT PET Imaging for Early Assessment of Treatment Response in Acute Myeloid Leukemia (AML)

Study Chair	Robert Jeraj, Ph.D.
Study Co-Chair	Mark Juckett, M.D.
Investigators	Brad Kahl, M.D. Scott Perlman, M.D. Jerry Nickles, Ph.D. Minesh Mehta, M.D. Deepak Khuntia, M.D.
Statistician	Richard Chappell, Ph.D.
Study Coordinator	Nancy Turman

August, 2005
Version 4

The problem..

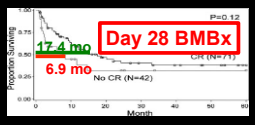


TABLE II. Predictive Utility of Day 14 BM on Day 28 Complete Remission Rate

Day 14 BMBx

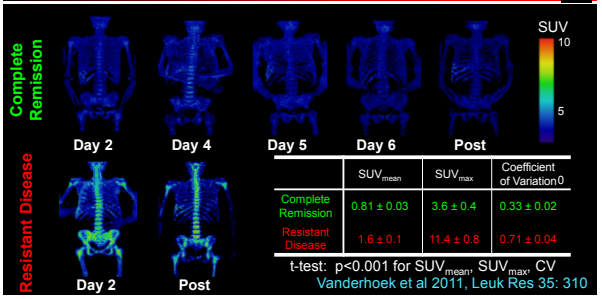
	Day 28 BMBx	
Day 14 BMBx	≤5%	>5%
≤5%	46	12
>5%	5	9
	51	21

	58	
	14	
	72[a]	

Specificity = 43%
NPV = 64%

Hussein et al 2008, Am J Hemat, 83(6): 446

High NPV of FLT PET for predicting CR

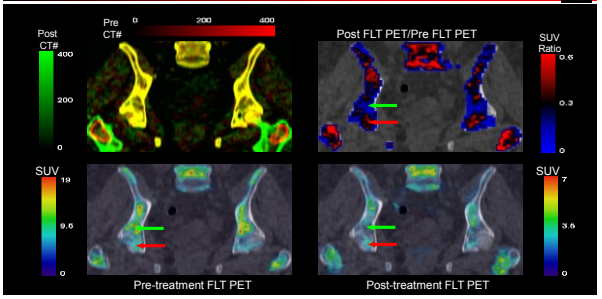


	SUV_{mean}	SUV_{max}	Coefficient of Variation
Complete Remission	0.81 ± 0.03	3.6 ± 0.4	0.33 ± 0.02
Resistant Disease	1.6 ± 0.1	11.4 ± 0.8	0.71 ± 0.04

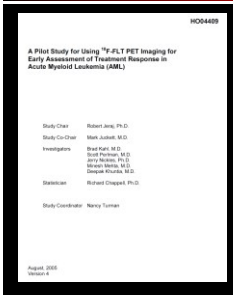
t-test: p<0.001 for SUV_{mean}, SUV_{max}, CV

Vanderhoek et al 2011, Leuk Res 35: 310

Treatment response heterogeneity



Long path to an NCTN trial…

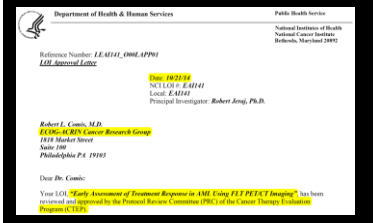


HO04409

A Pilot Study for Using ^{18}F-FLT PET Imaging for Early Assessment of Treatment Response in Acute Myeloid Leukemia (AML)

Study Chair: Robert Jenq, Ph.D.
Study Co-Chair: Mark Juckett, M.D.
Investigators: Brad Kahl, M.D. Scott Perlman, M.D. Jerry Noble, Ph.D. Monish Mehta, M.D. Deepak Khuntia, M.D.
Statistician: Richard Chappell, Ph.D.
Study Coordinator: Nancy Turman

August, 2005
Version 4



Department of Health & Human Services — Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Reference Number: *LEAI141_000LAPP01*
LOI Approval Letter

Date: *10/21/14*
NCI LOI #: *EAI141*
Local: *EAI141*
Principal Investigator: *Robert Jenq, Ph.D.*

Robert L. Comis, M.D.
ECOG–ACRIN Cancer Research Group
1818 Market Street
Suite 100
Philadelphia PA 19103

Dear *Dr. Comis:*

Your LOI *"Early Assessment of Treatment Response in AML Using FLT PET/CT Imaging"* has been reviewed and approved by the Protocol Review Committee (PRC) of the Cancer Therapy Evaluation Program (CTEP).

Multiple roles

- **Protocol design and write-up** (~months)
  - Initial protocol write-up/modification/clean-up
  - Protocol forms preparation
  - Protocol modifications/amendments
- **Protocol approval (5+ committees + IRBs)**
  - Issue resolutions (multiple IRBs different views)
  - Site recruitment

Multiple roles

- **Protocol execution**
  - Constant oversight, issue resolution; need prompt responses
  - 50+ emails/month, weekly updates, monthly calls, semi-annual meetings, …
- **Data analysis**
  - Best part of the study, but nerve-wrecking ☺
- **Publishing**

Summary

- Clinical trials are complex, difficult, long, lots of work, but very exciting – **directly testing clinical impact**
- Medical physicists should be **involved much more**
- Medical physics roles **very diverse**:
  - Supporting role
  - Co-Chair role(s)
  - Chair role

Thanks to:

- **Image-guided Therapy Group (UW)**
  - Enrique Cuna
  - Peter Ferjancic
  - Daniel Huff
  - Christie Lin
  - Mauro Namias
  - Tim Perk
  - Alison Roth
  - Matt Scarpelli
  - Urban Simoncic
  - Marusa Turk
  - Damijan Valentinuzzi
  - Amy Weisman
  - Former students and postdocs…
- **Medical Physics Research Group (Slovenia)**
- **Funding**
  - DCF, NIH, Medivation, MVI, Pfizer, UWCCC, State of Wisconsin
- **Medical Oncology/Hematology**
  - Glenn Liu
  - Doug McNeel
  - Ryan Mattison
  - Mark Albertini
  - Anne Traynor
  - Ruth O'Regan
- **Radiology**
  - Scott Perlman
  - Tyler Bradshaw
  - Chris Jaskowiak
- **Human Oncology**
  - Paul Harari
  - Bert van der Kogel
- **Medical Physics**
  - Ed Jackson
- **UWCCC TIR, CTD2, DOTs**
- **UW WONIX, NIX**