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

Robert Jeraj
Professor of Medical Physics, Human Oncology, Radiology and Biomedical Engineering
University of Wisconsin Carbone Cancer Center, Madison, WI, USA
rjeraj@wisc.edu

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

Radiotherapy specifics
8/2/2017

Target volume definitions

Dose prescription

Finally - An impactful publication

The NEW ENGLAND JOURNAL of MEDICINE

FEBRUARY 20, 2014

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Todd S. Armstrong, Ph.D., A. N. P. C., Jeffrey S. Weber, Ph.D., Debra P. Blumenthal, M.D., Michael A. Veh总裁, M.D., Ph.D., Howard Colman, M.D., Ph.D.,

Arvind Chhatwal, M.D., Stephanie Fung, Ph.D., Mohsen Honar, M.A., Bondurant B. Shuman, Ph.D., Paul P. Gillman, M.D.,

Krishna B. Kondaveeti, M.D., Susan M. Miller, M.D., Jennifer M. Andrews, M.D.,

Mark W. Month, M.D., Ivan W. Trompette, M.A., D. P. S. G. S., M.D., Kenneth D. Aldiges, M.D.,

Valerie D. V. D. M., and Ming-Hsi R. V. M. H., 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**

Image with study information.

---

**Imaging rationale**

1.4.2 Characterize the pharmacodynamic changes and response to treatment using 18F-PET/CT.

The clinical course of metastatic prostate cancers is largely restricted to bone, with predominantly osteolytic 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 18F-PET imaging agents for detection of bone metastases in prostate cancer is 18F-deoxyglucose ([18F]FDG). 18F-PET/CT is a more specific and sensitive tool that allows quantitative determination of change in functional disease burden to therapy. 18F-PET/CT is feasible and reproducible in patients with metastatic castration-resistant prostate cancer to bone treated with an androgenic modulated hormone agent or all directed therapies that have been previously evaluated [23]. In this study, we prospectively examine whether the addition of abiraterone acetate can improve the diagnostic accuracy of 18F-PET/CT by comparing lesion counts compared to abiraterone acetate alone in support of our hypothesis. 18F-PET/CT scans will be analyzed with innovative image analysis technique, termed Quantitative Total Bone Imaging (QTB), developed at the University of Wisconsin [24, 33].
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 Half 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 > 70 lb (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 6.5.4.

10.1 NaF PET/CT Imaging
The overall goal of this study is to examine whether the addition of capecitabine 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. The expected 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 real-time 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 difference was 30% in the abiraterone acetate arm and 15% in the control arm. We assume the percentage of capecitabine and abiraterone acetate arm, respectively, the percentage of decrease is defined as [post SUVTotal – pre SUVTotal] / SUVTotal * 100%. The standard deviation was assumed to be 40% for both groups. Under the type I error 0.05 (two-sided), the sample size of 50 (20 in each arm) can achieve 80% 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

![Image of ECOG-ACRIN study protocol](ECOG-ACRIN_Early_Assessment_of_Treatment_Response_in_AIR.png)

**How it usually starts...**

![Image of study proposal](Study_Proposal.png)
The problem...

Specificity = 43%
NPV = 64%


High NPV of FLT PET for predicting CR

Complete Remission

Resistant Disease

Day 2
Day 4
Day 5
Day 6
Post

SUV max
SUV mean

Coefficient of Variation

Complete Remission
0.81 ± 0.03
8.8 ± 0.4
0.37 ± 0.02

Resistant Disease
1.6 ± 0.1
11.4 ± 0.8
0.71 ± 0.04

Significantly different by t-test: p<0.001 for SUV max, SUV mean, CV

Vanderheuk et al 2011, Leuk Res 35:310

Treatment response heterogeneity
Long path to an NCTN trial...

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
  - Mauro Namias
  - Tim Perk
  - Matt Scarpelli
  - Mark Simoncic
  - Urban Simoncic
  - Marusa Turk
  - Damijan Valentinuzzi
  - Amy Weisman
  - Former students and postdocs...

- Medical Physics Research Group (Slovenia)

- Funding
  - ONRH, Medivation, MVI, Pfizer, UWCCC, State of Wisconsin

- Medical Oncology/Hematology
  - Glenn Liu
  - Doug McNeel
  - Ryan Medison
  - Ruth O'Regan
  - Anne Traynor
  - Bert van der Kogel

- Radiology
  - Scott Perlman
  - Tyler Bedtknow
  - Chris Jackowski

- Human Oncology
  - Paul Harari

- Medical Physics
  - Ed Jackson

- UWCCC TIR, CTD2, DOTS
  - UW WOIX, WIX