Clinical Trials and the Medical Physicist: Design, Analysis, and Our Role

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A National Cancer Institute Comprehensive Cancer Center
BARNES-JEWISH Hospital
Washington University in St. Louis School of Medicine
NCCN National Comprehensive Cancer Network
NCI CCC

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Introduction

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- Clinical research is a systematic investigation designed to contribute to generalizable knowledge (45 CFR 46.102)
- Clinical trials are studies designed to find an answer to a specific, clinically relevant scientific question.
- Development → Testing → Approved Care
- Can come from physicians → "Investigator Instigated Trials"
- Also come from government, industry

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Clinical Trials Pathway

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Pre-Clinical Testing		
Laboratory Testing	Animal Testing	Several Years

↓

Phase 0 / Pilot Study		
Helps determine if treatments do what they are expected to do	Low doses, few subjects	Months

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Phase 1		
Finding the safest dose or mode	Less than 100 participants	Several Months

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Clinical Trials Pathway

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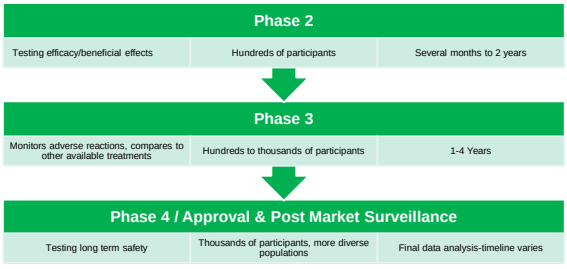

Quality (Ethical) Trials

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- **Value:** Enhance health or knowledge.
- **Scientific Validity**: Methodologically rigorous
- **Fair Subject Selection**: Scientific objectives determine communities selected and inclusion criteria.
- **Favorable Risk-Benefit Ratios:** Potential benefits to individuals and knowledge gained for society must outweigh the risks.
- **Independent Review**: Unaffiliated individuals must review, approve, amend, and/or terminate the research.
- **Informed Consent**: Individuals should be informed about the research and provide their voluntary consent.
- **Respect for Enrolled Subjects:** Subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored.

Emanuel, EJ,et al; JAMA. 2000; 283:2701-2711

Arms and Controls

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- Arms: Any treatment group in a clinical trial.
- 2 is common, but 3 or more possible
- Investigational groups: New treatment or combination of treatments.
- Control groups: Use standard of care.
- Placebo: A treatment with no effect.
  - Useful when no standard of care exists
  - Useful for double blind studies
  - Patients must be informed of its use

Randomization

- "Randomized" Trial: Patients assigned to groups by chance.
- Randomization helps prevent bias.
- No set methodology to randomization
- Any randomization method used should not impart bias itself

Blinding

- Blinding: Helps prevent bias
- Unblinded: Participant and physician know which arm they are in.
- Single-Blinded → Only participant does not know which arm they are in.
- Double-Blinded → Neither participant nor physician know which arm the participants are in until the end of study.
  - Certain other study personnel will be need to know which arm participants are in (i.e. they are unblinded)
- Each study must have a specific procedure for unblinding the study

Sample Size Estimation

- Need to consider primary endpoint.
- Input from previous studies.
- Determine clinically meaningful difference → Difficult
- Basis: Hypothesis Testing
  - Equality vs. Non-superiority vs. Superiority

Example: Superiority

H_0: Investigation Group = Control; H_1: Investigation Group > Control

Decision Taken \ Actual Fact	H_0 is True	H1 is True
Reject H_0	Type I error	No error
Accept H_0	No error	Type II error

Probability (Type I error) = Level of Significance → 0.05 (5%) is typical

Probability (No Type II error) = Power → Typically want ≥80%

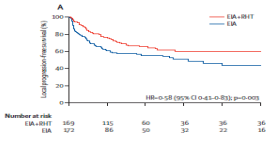
Perspect Clin Res. 2010 Apr-Jun; 1(2): 67–69

Outcomes and Evaluation

- Outcome(s) of interest should be considered when designing studies.
- Survival benefit, reduction of toxicities, etc.
- Study protocols should include a mechanism to end study if risks begin to outweigh benefits.
  - Unexpected toxicities, etc.
- Different parameters and techniques can be used for study evaluation…

Kaplan Meier Statistics

- In clinical trials, would like to know "survival curve" (S(t)) that describes the occurrence of an outcome over time in a population
- Kaplan-Meier statistics can estimate S(t) by:



$$\hat{S}(t) = \prod_{t_i < t} S_i(t_i) = \prod_{t_i < t} \frac{n_i - d_i}{n_i}$$

- **n_i = number of participants at time t_i**
- **d_i = events (deaths) at time t_i**

- Necessity → Data is not normal, contains "censored" data.
  - Censored = "survival" past the end of study, drop outs, lost follow ups, etc.

Figure from: Issa et al., Lancet. 2010, p. 561-570

Hazard Rates and Ratio

- Hazard rate: Probability that, if an event has not occurred at time t, it will occur at time t
- Related to survival function (N(t) is # subjects @ t)

$$h(t) = \lim_{\Delta t \to 0} \left(\frac{observed\ events(t + \Delta t) / N(t)}{\Delta t} \right) = -\ln(S(t))$$

- Hazard ratio (HR) = ratio of hazard rates between two arms.
  - Control is typically the denominator
  - Risk of event in two different populations
  - Probability (P) that an individual in group with a higher hazard reaches that hazard first.

$$HR = \frac{P}{1-P} \Rightarrow P = \frac{HR}{1+HR};\ HR = 3 \Rightarrow P = 0.75;$$

75% chance someone in treatment arm survives vs. control at time t

Analysis of Survival Curves

- Two ways studies compare survival curves:

➢ Log-Rank Test
  - Compare two curves
  - Assumes X^2 distribution

$$X^2(\log\ rank) = \frac{(O_1 - E_1)^2}{E_1} + \frac{(O_2 - E_2)^2}{E_2}$$

$$E_1 = \sum_{i=1}^{k} \frac{d_i}{n_i} n_{i,Arm1}$$

- O_i = observed events
- E_i = estimated events
- n_i , d_i as above
- $n_{i,Arm1}$ = participants at time t_i in Arm 1 only

➢ Cox Regression (Proportional Hazard Model)
  - Allows testing in subgroups
  - No specified underlying distribution

$$\ln\left[\frac{h(t)}{h_0(t)}\right] = \sum_{j=1}^{p} a_j x_j$$

- $h_0(t)$= "baseline" hazard
- x_j = explanatory variables
- a_j = coefficients for different factors
- p = total # factors modeled

- Both methods assume "proportional hazards", i.e. HR is constant across whole study
  - Caution: Not always a valid assumption!

Critical Care 2004, 8:389-394

Odds Ratio

- Determines how strongly presence or absence of one property or outcome is associated with another within a population.

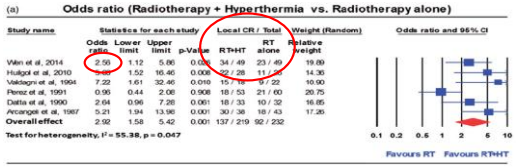
	Affected	Unaffected
Investigational Group	A_I	U_I
Control Group	A_C	U_C

- A_x = Number Affected
- U_x = Number Unaffected
- $N_x = A_x + U_x$

$$OR = \frac{A_I / U_I}{A_C / U_C}$$

- OR ≠ 1 implies association.
- Association does not guarantee causality, however.

Odds Ratio: Example



$A_I = 34$ $A_C = 23$

$N_I = 49 = A_I + U_I$ $N_C = 49 = A_C + U_C$

$U_I = 15$ $U_C = 26$

$$OR = \frac{A_I / U_I}{A_C / U_C} = \frac{34/15}{23/26} = \frac{2.27}{0.88} = 2.56$$

Datta NR *et al. Int J of Hyperthermia (2015).* Early Online 1-10.

Risk: Relative and Absolute

- Absolute Risk: Probability of an event occurring in any one group.
- Absolute Risk Reduction or Risk Difference (RD) or Absolute Effect: The difference in absolute risk between two groups.

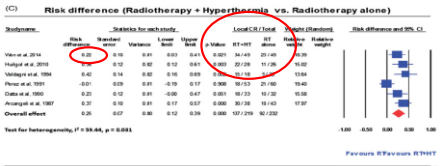
$$RD = \frac{A_I}{N_I} - \frac{A_C}{N_C}$$

- Relative Risk or Risk Ratio (RR): Ratio of probability of an event occurring in the investigational group to the control group.

$$RR = \frac{A_I / N_I}{A_C / N_C}$$

- RR is similar conceptually to HR, but has no time component → includes information from entire trial.

Absolute Risk: Example

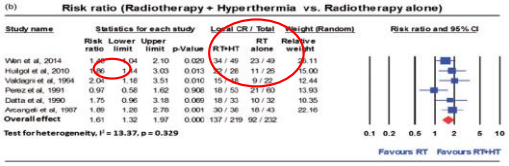


$A_I = 34$ $A_C = 23$
$N_I = 49 = A_I + U_I$ $N_C = 49 = A_C + U_C$
$U_I = 15$ $U_C = 26$

$$RD = \frac{A_I}{N_I} - \frac{A_C}{N_C} = \frac{34}{49} - \frac{23}{49} = 0.69 - 0.47 = 0.22$$

Datta NR *et al. Int J of Hyperthermia (2015).* Early Online 1-10.

Relative Risk: Example



$A_I = 34$ $A_C = 23$
$N_I = 49 = A_I + U_I$ $N_C = 49 = A_C + U_C$
$U_I = 15$ $U_C = 26$

$$RR = \frac{A_I / N_I}{A_C / N_C} = \frac{34/49}{23/49} = \frac{0.69}{0.47} = 1.48$$

Datta NR *et al. Int J of Hyperthermia (2015).* Early Online 1-10.

Physicists' Role

- Design
  - Workflow, limitations, among other considerations.
  - Example: Many RTOG studies include physicists among the authorship
- Implementation
  - Clinical physicists perform many tasks integral to certain trials
  - Heavy involvement or tangential
- Analysis
  - No biostatistician → tasked with analysis

Xofigo Double-Blind Study

- Xofigo (Bayer Healthcare) = ^{223}Ra → ^{207}Pb alpha-emitter (95% decay, 5.0-7.5 MeV), $T_{1/2}$ = 11.4 days.
- FDA approved → bone metastasis of prostate patients
- Treatment Mechanism: Calcium mimetic, forms complexes with bone mineral at metastases site.
- Industry driven double-blind trial to test use of Xofigo at standard dosing scheme vs. placebo for bone metastasis of breast cancer patients.
- 1.49 mCi/kg for 6 treatments at 4 week intervals.
- Liquid, delivered through IV injection

Xofigo Study: Physics Role

- Physics involvement: design, implementation
- Design: Helped create workflow which would protect double-blind nature of study
  - Physics are among those unblinded
  - Both active dose and placebo workflow and delivery must look the same to all blinded personnel (including MD)
  - Keep as few unblinded individuals as possible
- Implementation: Physics performing the assays, analyzing delivered dose, performing surveys




Xofigo Study: Physics Role

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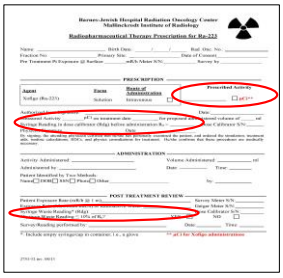

Xofigo Study: Physics Role

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- Need ways to maintain areas as “blinded” when study activities are being performed.
- Turn Geiger counters and other meters into silent mode.
- Keep interaction between patient / subject and unblinded personnel to a minimum.

NRG-BR001

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NRG ONCOLOGY

NRG-BR001

A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

SCHEMA

Patients with metastatic breast, adenocarcinoma of the prostate or non-small cell lung cancer with ≤ 4 metastases, all metastases not resected must be amenable to SBRT

See Section 3.2 for details

REGISTER

SBRT (in 3 or 5 fractions) to all existing metastases in 1-3 weeks

See Table 6-1 in Section 6.1 for dose levels and Table 13-1 in Section 13.3 for Dose Limiting Toxicities (DLTs)

See Section 5.0 for pre-registration requirements and Section 6.3 for details of radiation therapy planning and delivery.

Table 6-1

Prescription Doses

Metastatic Locations	Initial Starting Dose	Decreased DLT Dose
Lung–Peripheral	45 Gy (3 fractions)	42 Gy (3 fractions)
Lung–Central	50 Gy (5 fractions)	47.5 Gy (5 fractions)
Mediastinal/Cervical Lymph Node	50 Gy (5 fractions)	47.5 Gy (5 fractions)
Liver	45 Gy (3 fractions)	42 Gy (3 fractions)
Spinal/Paraspinal	30 Gy (3 fractions)	27 Gy (3 fractions)
Osseous	30 Gy (3 fractions)	27 Gy (3 fractions)
Abdominal-pelvic metastases (lymph node/adrenal gland)	45 Gy (3 fractions)	42 Gy (3 fractions)

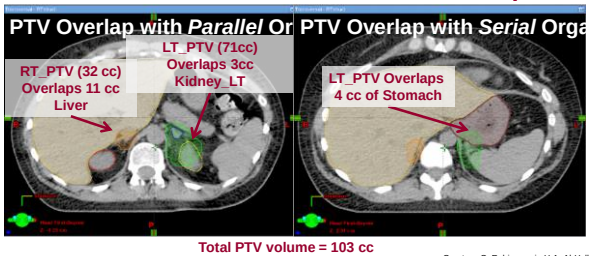
- **Hypothesis**: 3-4 metastases and 2 anatomically close metastases can be safely treated with established SBRT doses
- **Objective:** Determine the recommended dose location
- Metastatic NSCLC, Breast, and Prostate.
- 2 Physics Co-chairs
  - H. Al Hallaq, Ph.D.
  - M. Matuszak, Ph.D.

NRG-BR001

- Physics involvement : Planning, Implementation
- Requires typical credentialing for SBRT trials
  - Facility questionnaire
  - Phantom irradiation (if not previously met for other trials)
    - IMRT credentialing grandfathers in for 3D-CRT SBRT
    - FFF, Tomo, CyberKnife credentialed separately
  - IGRT verification study
- Also requires planning of a benchmark case (2 adrenal metastases).
  - Local physics / dosimetry determine how to plan
- Pre-treatment review of first case.
- All subsequent plans: local physics planning or QA.

NRG-BR001: Benchmark Case

Bi-lateral Adrenal Metastases < 5 cm Apart



Total PTV volume = 103 cc

Courtesy C. Robinson via H.A. Al-Hallaq

Summary

- Clinical trials are studies designed to answer a specific clinical question.
- Statistics for clinical trials need to analyze survival data w/ censoring.
- Many different aspects determine how clinical trials are designed and analyzed
- Medical physicists are increasingly involved in trials in design, implementation, and analysis.

Acknowlegements

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Thank You!

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