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

Michael B. Altman, Ph.D.
Washington University – St. Louis School of Medicine

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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Introduction

- 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

Clinical Trials Pathway

<table>
<thead>
<tr>
<th>Pre-Clinical Testing</th>
<th>Laboratory Testing</th>
<th>Animal Testing</th>
<th>Several Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Phase 0 / Pilot Study

<table>
<thead>
<tr>
<th>Helps determine if treatments do what they are expected to do</th>
<th>Low doses, few subjects</th>
<th>Months</th>
</tr>
</thead>
</table>

Phase 1

<table>
<thead>
<tr>
<th>Finding the safest dose or mode</th>
<th>Less than 100 participants</th>
<th>Several Months</th>
</tr>
</thead>
</table>

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Clinical Trials Pathway

Phase 2
- Testing efficacy/beneficial effects
- Hundreds of participants
- Several months to 2 years

Phase 3
- Monitors adverse reactions, compares to other available treatments
- Hundreds to thousands of participants
- 1-4 Years

Phase 4 / Approval & Post Market Surveillance
- Testing long term safety
- Thousands of participants, more diverse populations
- Final data analysis/timeline varies

Quality (Ethical) Trials

- **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.

Arms and Controls

- **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 the 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

\[ H_0: \text{Investigation Group} = \text{Control}; \quad H_1: \text{Investigation Group} > \text{Control} \]

<table>
<thead>
<tr>
<th>Decision Taken</th>
<th>Actual Fact</th>
<th>H(_0) is True</th>
<th>H(_1) is True</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reject H(_0)</td>
<td>Type I error</td>
<td>No error</td>
<td>No error</td>
</tr>
<tr>
<td>Accept H(_0)</td>
<td>No error</td>
<td>Type I error</td>
<td></td>
</tr>
</tbody>
</table>

Probability (Type I error) = Level of Significance → 0.05 (5%) is typical
Probability (No Type II error) = Power → Typically want ≥80%
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:
  \[ \hat{S}(t) = \prod_{t_i < t} \frac{n_i - d_i}{n_i} \]
  - \( n_i \) = 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.

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 @ \( t \))
  \[ h(t) = \lim_{\Delta t \to 0} \left( \frac{\text{observed events}(t + \Delta t)/N(t)}{\Delta t} \right) = -\ln(S(t)) \]
• 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.
  \[ HR = \frac{P_1}{P_2} \Rightarrow P_1 = \frac{HR}{1 + HR} \cdot P_2 \]
  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
    - X²(log rank) = \( \frac{(O_i - E_i)^2}{E_i} \) + \( \frac{(O_j - E_j)^2}{E_j} \)
    - Assumes \( X^2 \) distribution
  - Cox Regression (Proportional Hazard Model)
    - Allows testing in subgroups
    - No specified underlying distribution
- Both methods assume “proportional hazards”, i.e. HR is constant across whole study
  - Caution: Not always a valid assumption!

Odds Ratio

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

<table>
<thead>
<tr>
<th>Investigational Group</th>
<th>Affected</th>
<th>Unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A_I</td>
<td>U_I</td>
</tr>
<tr>
<td>Control Group</td>
<td>A_C</td>
<td>U_C</td>
</tr>
</tbody>
</table>

\[ OR = \frac{A_I}{U_I} \div \frac{A_C}{U_C} \]

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

Odds Ratio: Example

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

\[ OR = \frac{A_I}{U_I} \div \frac{A_C}{U_C} = \frac{34/15}{23/26} = \frac{2.27}{0.88} = 2.56 \]
**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.

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**Absolute Risk: Example**

\[
\begin{align*}
A_I &= 34 \\
N_I &= 49 \Rightarrow A_I + U_I \\
U_I &= 15 \\
A_C &= 23 \\
N_C &= 49 \Rightarrow A_C + U_C \\
U_C &= 26 \\
RD &= \frac{A_I - A_C}{N_I/N_C} = \frac{34 - 23}{49} = 0.69 - 0.47 = 0.22
\end{align*}
\]


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**Relative Risk: Example**

\[
\begin{align*}
A_I &= 34 \\
N_I &= 49 \Rightarrow A_I + U_I \\
U_I &= 15 \\
A_C &= 23 \\
N_C &= 49 \Rightarrow A_C + U_C \\
U_C &= 26 \\
RR &= \frac{A_I/N_I}{A_C/N_C} = \frac{34/49}{23/49} = 0.69/0.47 = 1.48
\end{align*}
\]

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

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Xofigo Double-Blind Study

- **Xofigo** (Bayer Healthcare) = $^{223}\text{Ra} \rightarrow ^{207}\text{Pb}$ 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

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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

- 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

- **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 Haila, Ph.D.
  - M. Matyszak, 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

PTV Overlap with Parallel Or PTV Overlap with Serial Org

Total PTV volume = 103 cc

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.
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Bibliography


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