Selection of comparators and outcomes

Mark V. Mishra, MD
Assistant Professor
Associate Director, Radiation Oncology
Clinical Research
Disclosures

• PCORI Patient Engagement Advisory Board Member (2015-Present)

• Funding:
  – American Society of Radiation Oncology
  – PCORI
  – Keep Punching Brain Tumor Foundation
Objectives

• Describe the importance of patient engagement in selecting study comparators and outcomes

• Describe methods for effective patient engagement in selecting comparators and outcomes

• Discuss a real-world example of patient engagement in pragmatic randomized clinical trial

• Understand the patient perspective on choosing comparators and outcomes

• Understand the industry perspective on patient engagement
University of Maryland 10-STEP FRAMEWORK FOR CONTINUOUS PATIENT ENGAGEMENT IN RESEARCH*

A. PLANNING RESEARCH
   1. Topic Solicitation
   2. Prioritization
   3. Framing the Question

B. DOING IT
   4. Selection of Comparators and Outcomes
   5. Creation of Conceptual Framework
   6. Analysis Plan
   7. Data Collection

C. DELIVERING SOLUTIONS
   8. Reviewing & Interpreting Results
   9. Translation
  10. Dissemination

Most crucial part of study design?
Most crucial step for meaningful patient engagement

Benefits of patient engagement: Step 4

Patient interest in study comparators
◦ Are we addressing real-world decisions?
◦ Improved enrollment

Patient interest in outcomes
◦ Answering questions that patients will care about → practice changing
Choosing comparators for a CER study

- Established efficacy?
- Treatments used in the real world?
- Practice patterns vary?
- Is there equipoise?
Choosing comparators for a CER study

- Treatments that patients consider in ‘real-world’?
- Do patients care if there is a difference?
- Patient-perceived equipoise?
Example: Breast Cancer

Radiation therapy is a standard part of treatment for patients with localized breast cancer

**Benefits**

- Improved survival
- Reduced recurrence

**Risks**

- Side effects during treatment
- Side effects after treatment
Real world patient dilemma: Two treatment options

Patient Stories:

Twenty-nine year old patient diagnosed with locally-advanced breast cancer after palpating a mass in her left breast

- Surgery: Mastectomy and lymph node dissection
- Chemotherapy: 6 months of chemotherapy
  - Improve chances of cure but potential damage to heart
- Referred for radiation therapy to her chest wall and lymph nodes
Real world patient dilemma: Two treatment options

**PHotons**
- FDA-approved
- Currently used to treat breast cancer
- Long-term data; side effects well-documented
- Widely available

**PRotons**
- FDA-approved
- Currently used to treat breast cancer
- Not as well studied, but thought to have less side effects
- Requires travel
Real world patient dilemma:
Two treatment options

Patient interested in proton beam therapy due to possibility of reduced side effects

- Radiation oncologist #1: You should receive Photon therapy
- Radiation oncologist #2: You are a good candidate for protons due to young age and potential dose to heart
- Radiation oncologist #3: ME

Which treatment is better for me and why??
Impact of **NO** patient engagement

- Physicians did not think that a study comparing the two treatments was necessary
  - Proton therapy research funded since **1961** by NCI
  - Little comparative data
Impact of **NO** patient engagement
A. PLANNING RESEARCH
1. Topic Solicitation
2. Prioritization
3. Framing the Question

B. DOING IT
4. Selection of Comparators and Outcomes
5. Creation of Conceptual Framework
6. Analysis Plan
7. Data Collection

C. DELIVERING SOLUTIONS
8. Reviewing & Interpreting Results
9. Translation
10. Dissemination

A. PLANNING RESEARCH
1. Topic Solicitation
2. Prioritization
3. Framing the Question

B. DOING IT
4. Selection of Comparators and Outcomes
5. Creation of Conceptual Framework
6. Analysis Plan
7. Data Collection

C. DELIVERING SOLUTIONS
8. Reviewing & Interpreting Results
9. Translation
10. Dissemination

Do patients agree with the comparators for this study?

Will any patient agree to go on a randomized study?

What are the questions that patients want answered?

Patient engagement

• Patient advisors
  – Individual interviews with current and former breast cancer patients

• Patient focus groups
  – Cancer center support groups

• Patient Advocacy Groups
  – Susan G. Komen, NCCS, Living Beyond Breast Cancer
Patient engagement

- Patient perspective
  - “I would motivated to participate in such a study”
  - Patient interviews, patient advocates, focus groups
59% of patients stated they would either “definitely” or “probably” participate in a RCT
Choosing comparators for a CER study

- Established efficacy?
- Treatments used in the real world?
- Practice patterns vary?
- Is there equipoise?
Choosing comparators for a CER study

Treatments that patients consider in the real-world?

Do patients care if there is a difference?

Patient perceived equipoise?

Patient advisors confirmed that patients are interested in both therapies

Patients, advocacy groups, payers

Patient advisors, focus groups
Breast Cancer Example

**Stratify**
- **Age** (<65 vs ≥65)
- **Cardiovascular risk** (0-2 vs > 2 risk factors)
- **Surgery** (mastectomy vs lumpectomy)
- **Laterality** (right versus left)

**Randomize**
- **Arm 1**: Photon Therapy*
- **Arm 2**: Proton Therapy*
PCOR Crossing Cutting Standards: Choosing Outcomes

Measure outcomes that people representing the population of interest care about

Identify outcomes that inform decision-making

Select outcomes based upon input directly from patient informants
When patients or people at risk of a condition are the best source of information regarding outcomes of interest, then the study should employ patient-reported outcome (PRO) measures.
Choice of outcome: Prior to engagement

A. Locoregional recurrence first
   - Log-rank $p>0.1$; NS

B. Any first recurrence
   - 10-year gain 1.3% (SE 3.3)
   - RR 1.05 (95% CI 0.76–1.48)
   - Log-rank $p>0.1$; NS

C. Breast cancer mortality
   - 20-year gain 2.2% (SE 3.6)
   - RR 1.18 (95% CI 0.89–1.55)
   - Log-rank $p>0.1$; NS

D. Locoregional recurrence first
   - Log-rank $p<0.00001$

E. Any first recurrence
   - 10-year gain 0.6% (SE 2.0)
   - RR 0.75 (95% CI 0.67–0.83)
   - Log-rank $p<0.00001$

F. Breast cancer mortality
   - 20-year gain 8.1% (SE 2.0)
   - RR 0.84 (95% CI 0.76–0.94)
   - Log-rank $p=0.01$
Patient Feedback

• Direct patient feedback
  – 10 conference calls with individual patient advisors
  – Focus groups with patient and patient advocates
    • Engage with patients who are outside of your patient advisory group
  – Multi-stakeholder meeting/conference call at NCI
    • Patients
    • Patient Advocates
    • Researchers
    • Payers

Engaging together
I would be more motivated to participate in a big study if I knew we would learn whether proton therapy could avoid causing problems with my heart. That would help me weigh whether the long-term benefits of radiation outweigh the long-term side effects.

I don’t only want to know about dying from heart problems from the radiation. I want to know about the heart problems that I would have to live with and the impact on my quality of life after cancer treatment.
Patient Viewpoints: Outcomes

I would be more motivated to participate in a big study if I knew we would learn whether proton therapy could avoid causing problems with my heart. That would help me weigh whether the long-term benefits of radiation outweigh the long-term side effects.

I don’t only want to know about dying from heart problems from the radiation. I want to know about the heart problems that I would have to live with and the impact on my quality of life after cancer treatment.

Patient identified outcome of interest:
Major cardiovascular events following Protons and Photons
I want to know whether a new therapy might reduce my cough or the feeling of the chest tightness after radiation.

I would want to know if proton therapy will improve the skin burn or my tiredness.

Would proton therapy allow me to get back to doing the things I enjoy sooner.

Patient identified outcome of interest:

- Treatment toxicity (patient-reported outcome)
  - Lung, chest, skin, fatigue
- Quality-of-life
Patient Viewpoints: Outcomes

Even if I knew that a bus wasn’t going to kill me if I were hit, I still want to look both ways before crossing the street.

Learning more about the chances of heart problems allows me to make more informed decisions. I might decide to stop smoking or alter some other behavior.

Patient identified outcome of interest:

To develop predictive models to examine the association of radiation dose distribution to heart and MCE and HRQOL outcomes.
Final study outcomes

Primary

• To assess the effectiveness of proton vs. photon therapy in reducing major cardiovascular events

Secondary

• To assess the non-inferiority of proton vs. photon therapy in reducing any recurrence
• To assess the effectiveness of proton vs. photon therapy in improving patient-reported body image and function, fatigue and other measures of HRQOL
• To develop predictive models to examine the association of radiation dose distribution to heart and MCE and HRQOL outcomes

Outcomes also discussed with payers, who agreed with study measures
Post-patient Engagement

Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer Receiving Comprehensive Nodal Radiation: A Radiotherapy Comparative Effectiveness (RADCOMP) Trial

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Funding Announcement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Justin Bekelman, MD</td>
<td>Pragmatic Clinical Studies and Large Simple Trials to Evaluate Patient-Centered Outcomes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organization</th>
<th>Project Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Pennsylvania</td>
<td>$111,830,530</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>State</th>
<th>Project Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennsylvania</td>
<td>60 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year Awarded</th>
<th>Project Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Awarded; In progress-Recruiting</td>
</tr>
</tbody>
</table>
Real world patient dilemma: Two treatment options

Patient Stories:

Twenty-nine year old patient diagnosed with locally-advanced breast cancer after palpating a mass in her left breast

- Surgery: Mastectomy and lymph node dissection
- Chemotherapy: 6 months of chemotherapy
  - Improve chances of cure but potential damage to heart
- Referred for radiation therapy to her chest wall and lymph nodes
Real world patient dilemma: Two treatment options

Patient interested in proton beam therapy due to possibility of reduced side effects

- Radiation oncologist #1: No role for protons
- Radiation oncologist #2: You are a good candidate for protons due to young age and potential dose to heart
- Radiation oncologist #3: ME

Which treatment is better for me and why??
Breast Cancer Example

**STRATIFY**

- **Age**
  
  (<65 vs ≥65)

- **Cardiovascular risk**
  
  (0-2 vs > 2 risk factors)

- **Surgery**
  
  (mastectomy vs lumpectomy)

- **Laterality**
  
  (right versus left)

**RANDOMIZE**

- **Arm 1:** Photon Therapy*
- **Arm 2:** Proton Therapy*
Patient Perspective

Cynthia Chauhan
Mayo Clinic
Patient Advisor, RADCOMP Study
Lori Abrams
Director, Diversity & Patient Engagement at Bristol-Myers Squibb, Princeton, New Jersey