



UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

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 Maryland10-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



***Based on:** Mullins CD, Abdulhalim AM, Lavallee DC. Continuous Patient Engagement in Comparative Effectiveness Research. JAMA 2012; 307(15): 1587-8.

Benefits of patient engagement: Step 4

Patient interest in study comparators

- Are we addressing real-world decisions?
- Improved enrollment

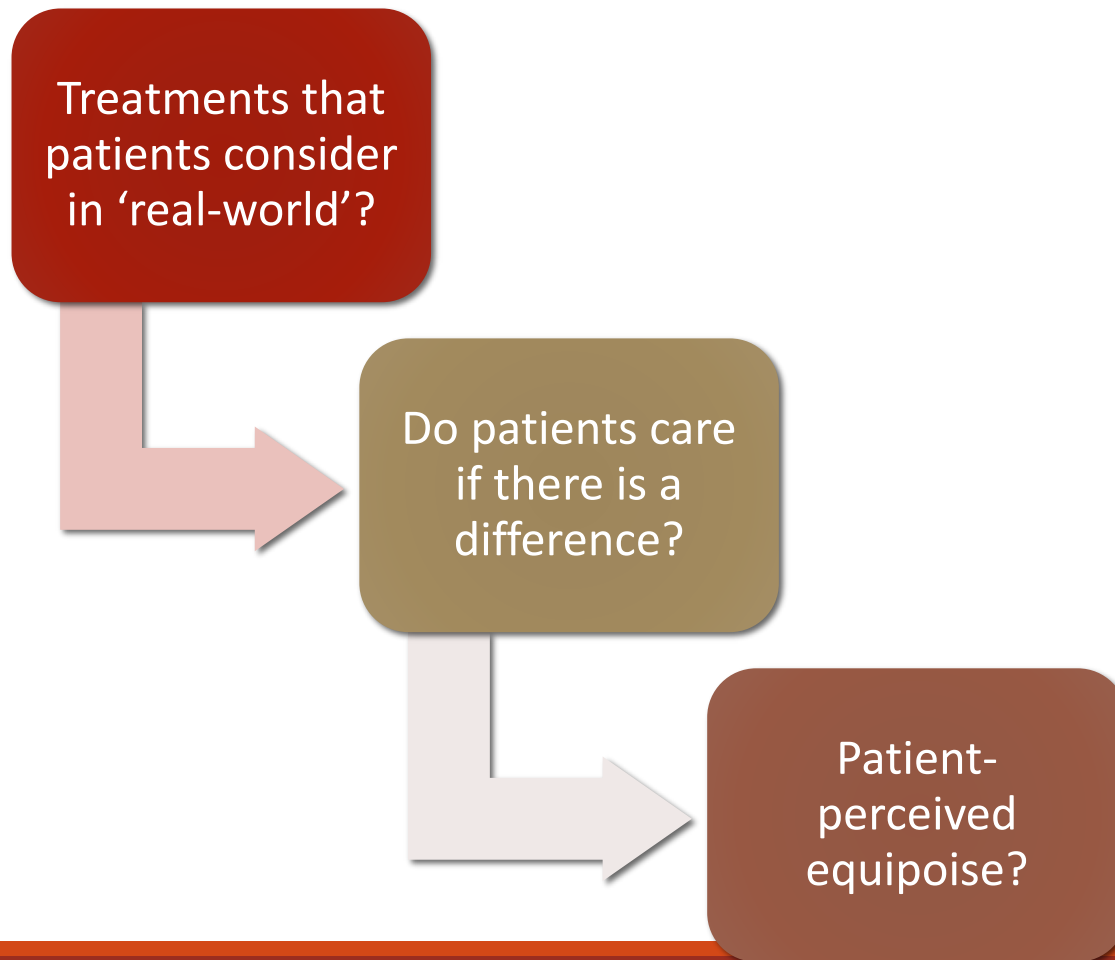
Patient interest in outcomes

- Answering questions that patients will care about → practice changing

Choosing comparators for a CER study

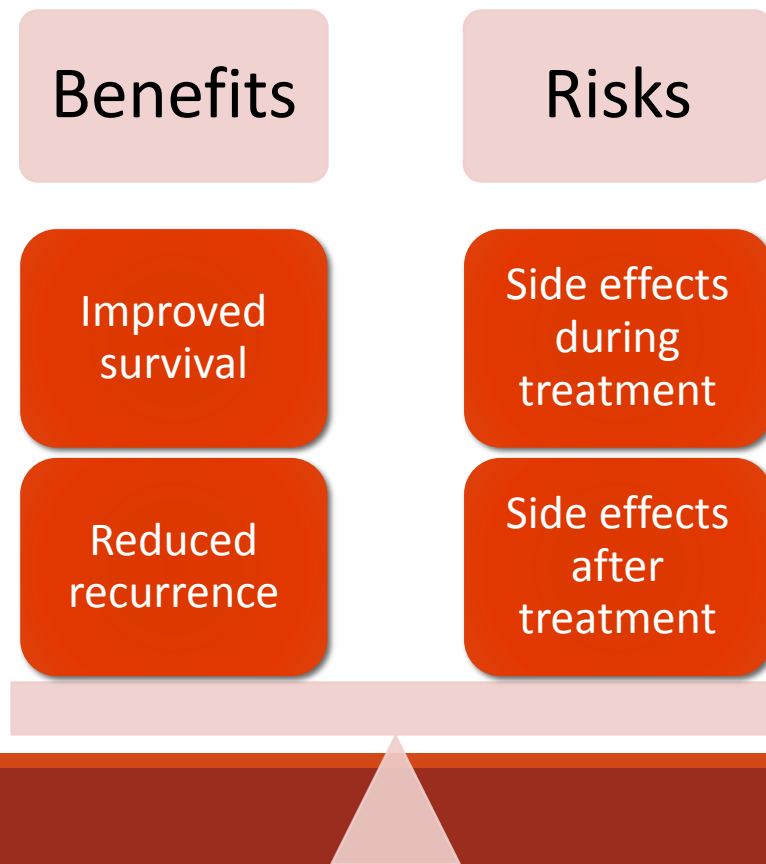


Choosing comparators for a CER study



Example: Breast Cancer

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



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
treatment breast
cancer

Not as well
studied, but
thought to have
less side effects

Requires travel

Real world patient dilemma: Two treatment options

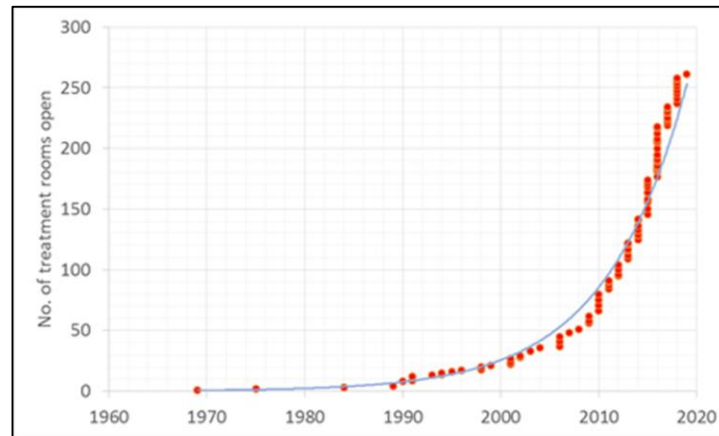
Patient interested in proton beam therapy due to possibility of reduced side effects

- 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

OPINIONATOR

It Costs More, but Is It Worth More?

By EZEKIEL J. EMANUEL and STEVEN D. PEARSON

JANUARY 2, 2012 10:18 PM

Future of cancer treatment or a pricey mistake?

Dan Mangan | @DanMangan
Sunday, 22 Sep 2013 | 9:00 AM ET

CNBC

Proton-beam centers sprout despite evidence drought

Medscape Medical News > Oncology

Uncertainty About Proton-Beam Radiotherapy Lingers

Roxanne Nelson

January 30, 2013

Blue Shield of California to curb coverage of pricey cancer therapy

Blue Shield says the high cost of some proton beam therapies for cancer treatment compared with conventional radiation isn't justified. The decision comes as hospitals build high-tech facilities.

August 28, 2013 | By Chad Terhune

Proton Beam Therapy Sparks Hospital Arms Race

MAY 31, 2013 3:22 AM ET

University of Maryland10-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



*Based on: Mullins CD, Abdulhalim AM, Lavallee DC. Continuous Patient Engagement in Comparative Effectiveness Research. JAMA 2012; 307(15): 1587-8.

University of Maryland10-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

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?



*Based on: Mullins CD, Abdulhalim AM, Lavallee DC. Continuous Patient Engagement in Comparative Effectiveness Research. JAMA 2012; 307(15): 1587-8.

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

Clinical Investigation: Genitourinary Cancer

Prospective Preference Assessment of Patients' Willingness to Participate in a Randomized Controlled Trial of Intensity-Modulated Radiotherapy Versus Proton Therapy for Localized Prostate Cancer

Anand Shah, M.D., M.P.H.,^{*} Jason A. Efstathiou, M.D., D.Phil.,^{||} Jonathan J. Paly, B.S.,^{||} Scott D. Halpern, M.D., Ph.D., M.B.E.,^{†,‡,§,¶} Deborah W. Bruner, Ph.D., R.N.,^{**} John P. Christodouleas, M.D., M.P.H.,^{*} John J. Coen, M.D.,^{||} Curtiland Deville, Jr., M.D.,^{*} Neha Vapiwala, M.D.,^{*} William U. Shipley, M.D.,^{||} Anthony L. Zietman, M.D.,^{||} Stephen M. Hahn, M.D.,^{*} and Justin E. Bekelman, M.D.^{*,¶}

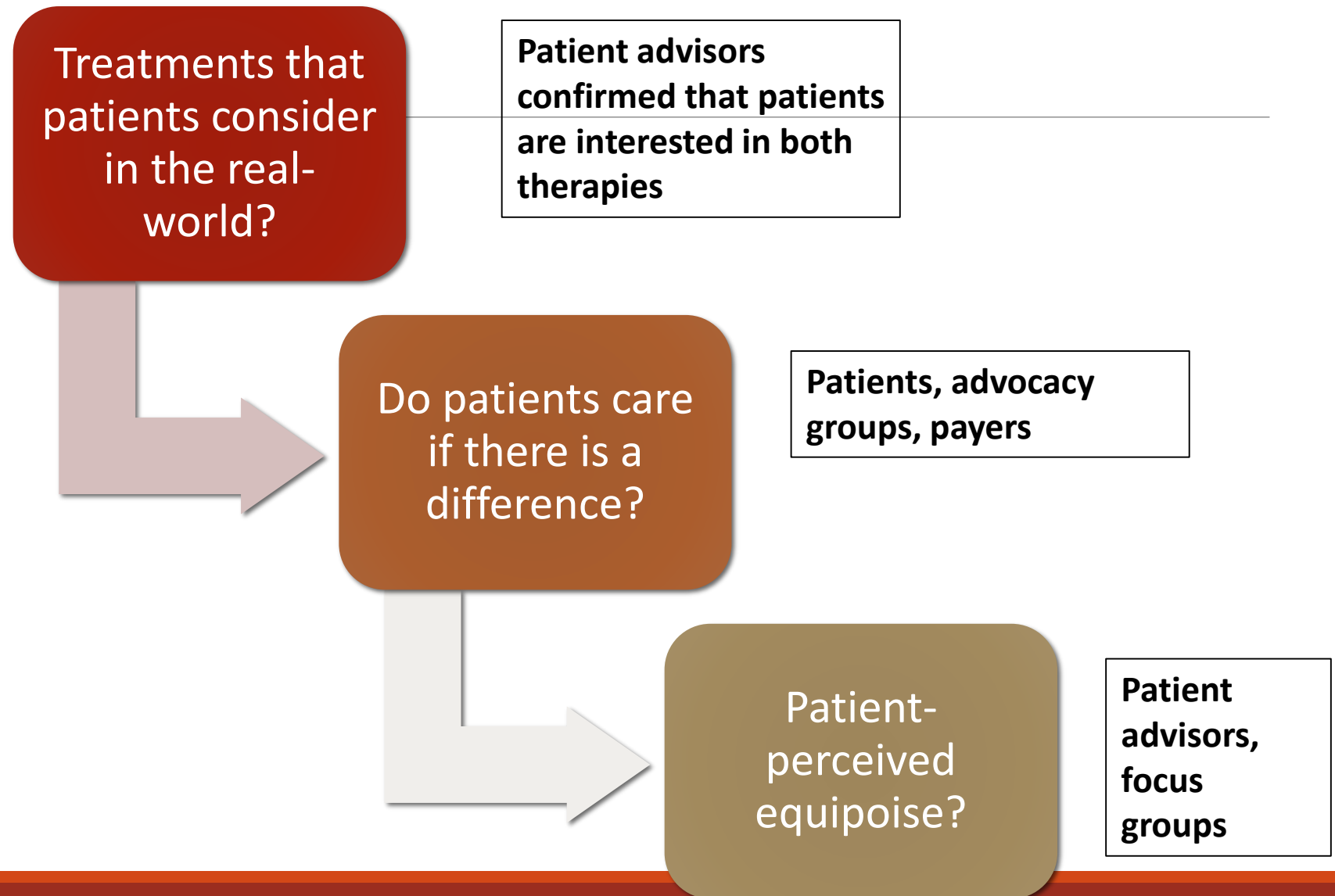
^{*}Department of Radiation Oncology, [†]Department of Medicine, [‡]Center for Clinical Epidemiology and Biostatistics, [§]Center for Bioethics, and [¶]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA; ^{||}Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; and ^{**}Winship Cancer Institute, Emory University, Atlanta, GA

**59% of patients
stated they
would either
“definitely” or
“probably”
participate in a
RCT**

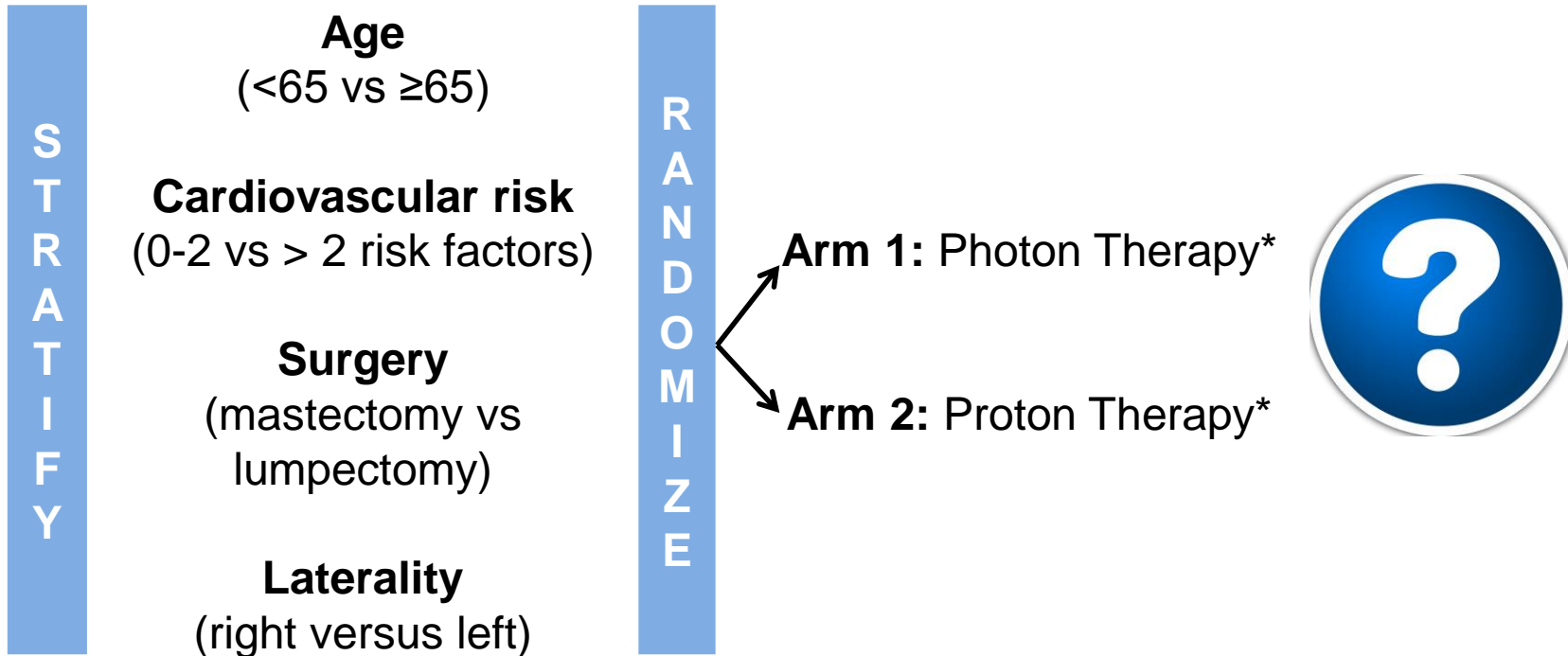
Choosing comparators for a CER study



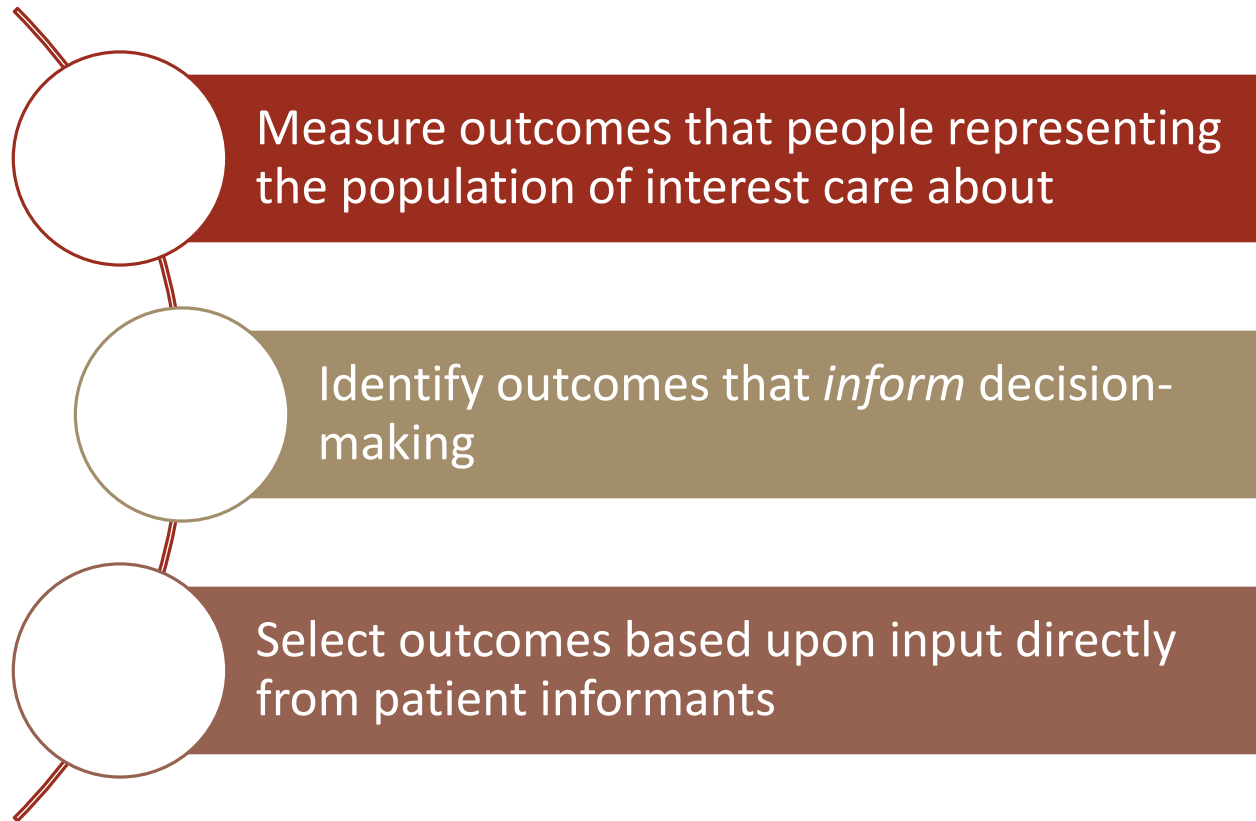
Choosing comparators for a CER study



Breast Cancer Example



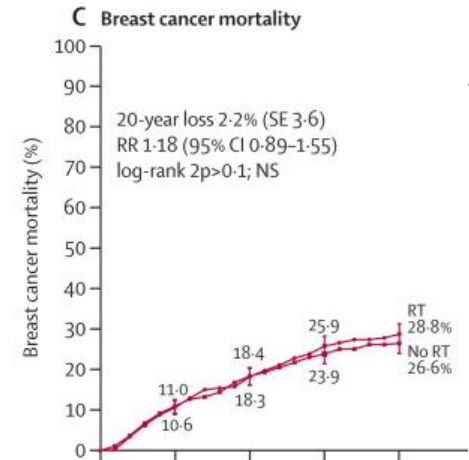
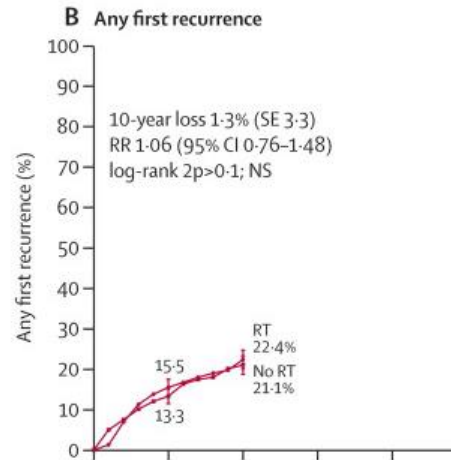
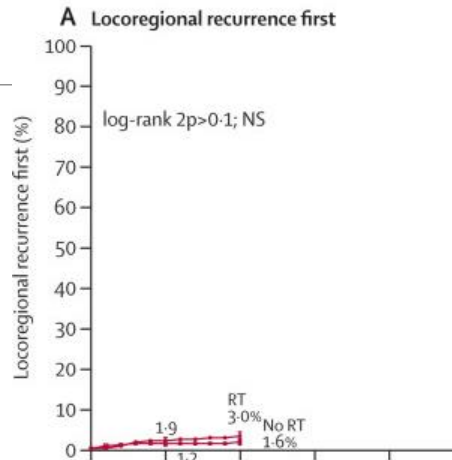
PCOR Crossing Cutting Standards: Choosing Outcomes



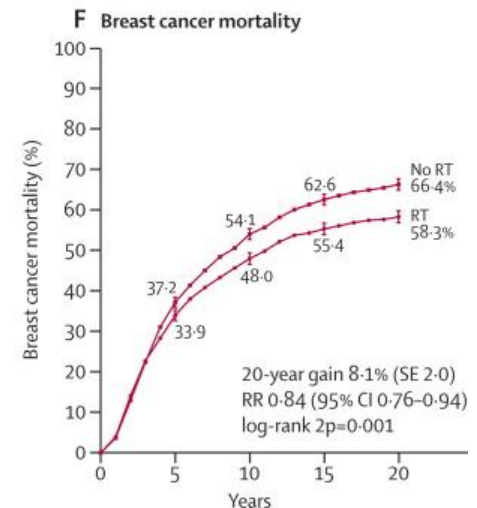
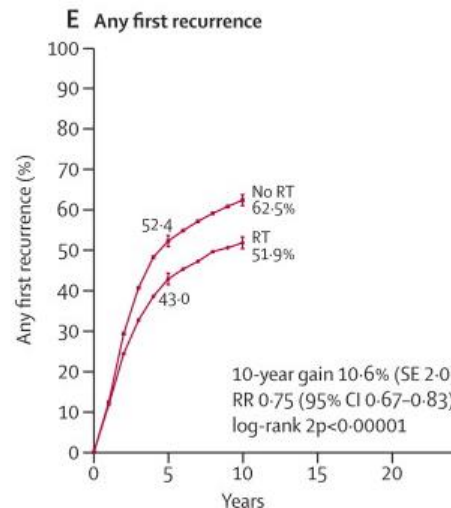
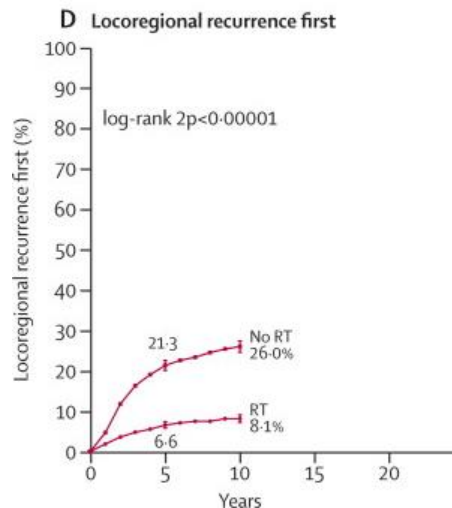
Patient-reported outcomes

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



3131 pN+ women with Mast+AD



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



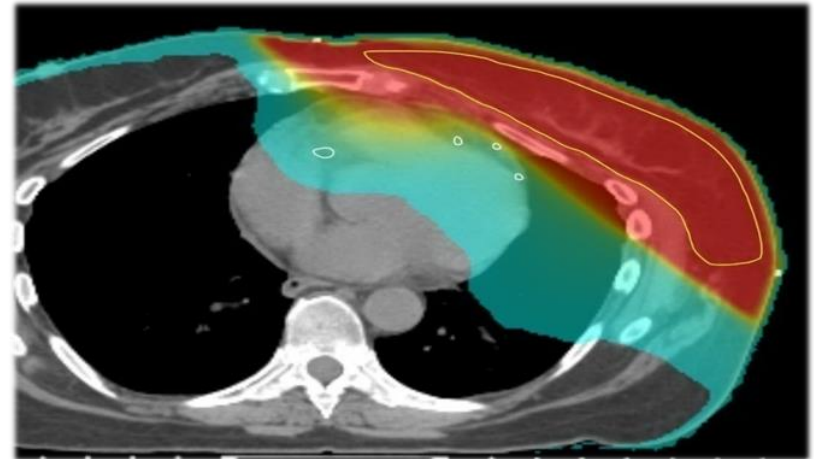
Engaging together

Patient Viewpoints: Outcomes

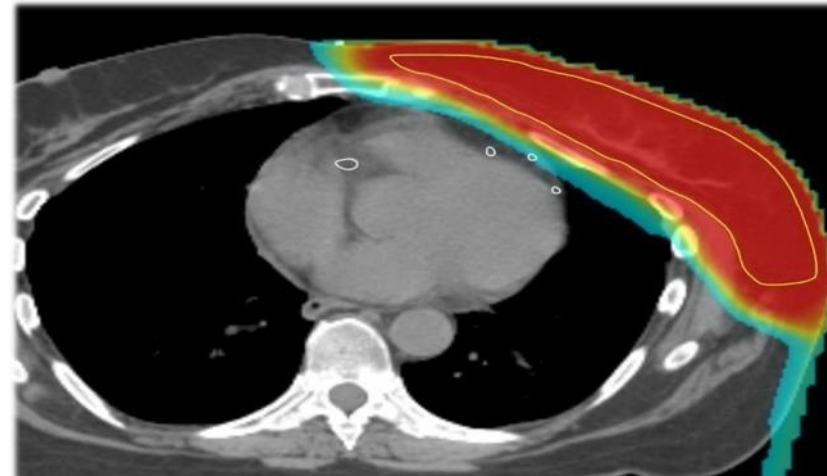
I would be more motivated to participate in a big study if I knew we would learn whether proton therapy could avoid causing problems with my heart. That would help me weigh whether the long-term benefits of radiation outweigh the long-term side effects

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

Photon Radiation Therapy



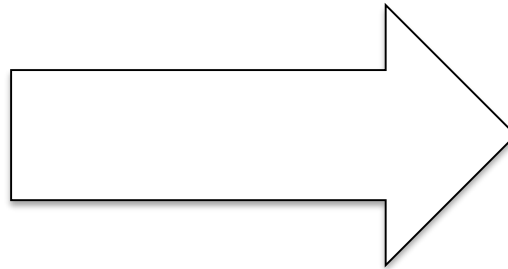
Proton Therapy



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:

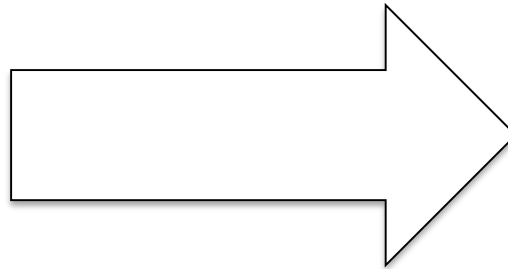
Major cardiovascular events
following Protons and Photons

Patient Viewpoints: Outcomes

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



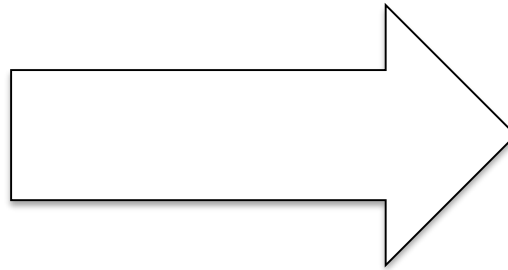
Patient identified outcome of interest:

- 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

Pre-patient engagement

OPINIONATOR

It Costs More, but Is It Worth More?

By EZEKIEL J. EMANUEL and STEVEN D. PEARSON

JANUARY 2, 2012 10:18 PM

Future of cancer treatment or a pricey mistake?

Dan Mangan | @DanMangan
Sunday, 22 Sep 2013 | 9:00 AM ET



Proton-beam centers sprout despite evidence drought

Medscape Medical News > Oncology

Uncertainty About Proton-Beam Radiotherapy Lingers

Roxanne Nelson

January 30, 2013

Blue Shield of California to curb coverage of pricey cancer therapy

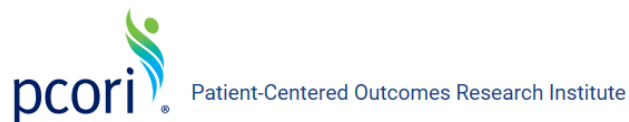
Blue Shield says the high cost of some proton beam therapies for cancer treatment compared with conventional radiation isn't justified. The decision comes as hospitals build high-tech facilities.

August 28, 2013 | By Chad Terhune

Proton Beam Therapy Sparks Hospital Arms Race

MAY 31, 2013 3:22 AM ET

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



Principal Investigator
Justin Bekelman, MD

Organization
University of Pennsylvania

State
Pennsylvania

Year Awarded
2015

Primary Condition/Disease
Cancer

Funding Announcement
Pragmatic Clinical Studies and Large Simple Trials to Evaluate Patient-Centered Outcomes

Project Budget
\$11,830,530

Project Period
60 months

Project Status
Awarded; In progress-Recruiting

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

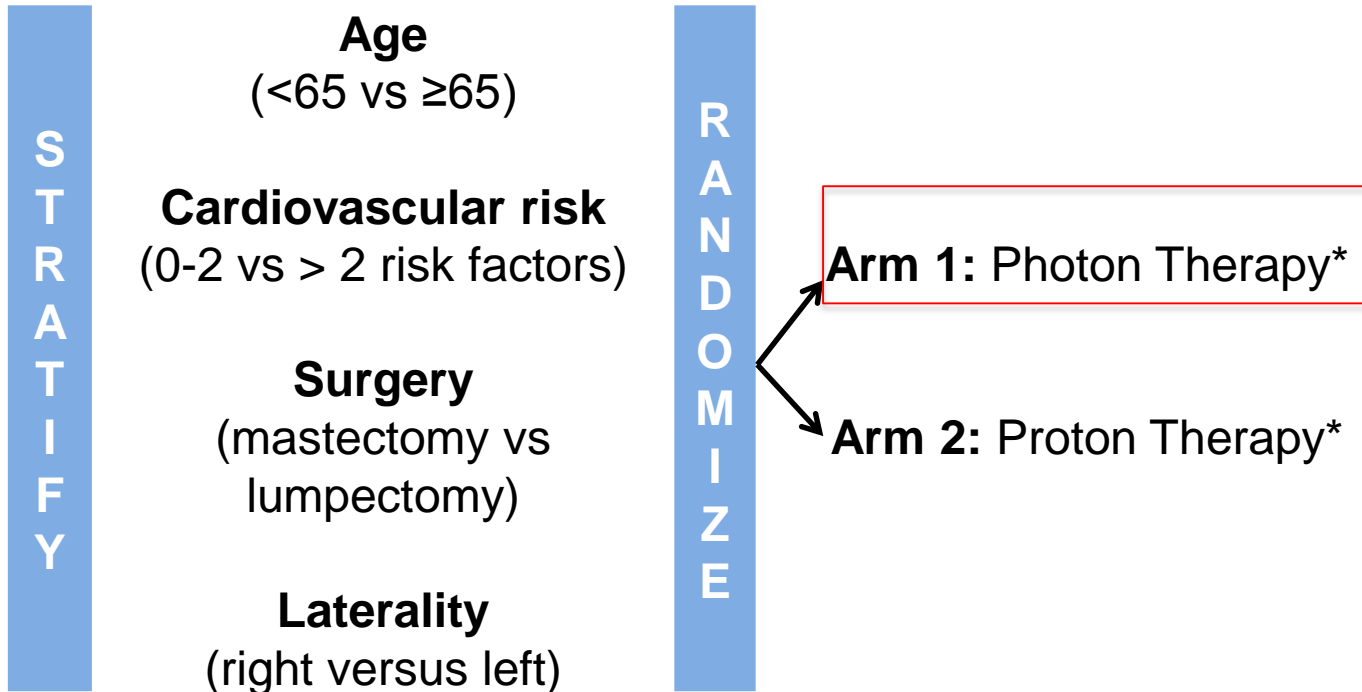
Real world patient dilemma: Two treatment options

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



Patient Perspective



Cynthia Chauhan

Mayo Clinic

Patient Advisor, RADCOMP Study



Lori Abrams

Director, Diversity & Patient
Engagement at Bristol-Myers Squibb,
Princeton, New Jersey