Reconvening Webinar: Prioritizing Comparative Effectiveness Research Questions for Treatment Options for Chronic Low Back Pain

January 7, 2016

pcori

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

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Participants

Alan Rosenberg	Alesia Sadosky	Dylan Nelson
Benjamin Hando	Christin Veasley	Robert Kane
Robert Dworkin	Ernie Merritt	Suchitra Iyer
Thomas Zimmerman	Nancy Ryan	Partap Khalsa
Alan Rosenberg	Sharon Radtke	James Witter
W. Michael Hooten	Myra Christopher	Lynn DeBar
John Knightly	Mary Deary-Weiss	Leah Hole-Marshall
Todd Wetzel	Jordan Ginsburg	
Debra Weiner	Mary Pak	
Nicki Bush-Sawyer	Jill Morrow-Gorton	

Today's agenda

1. Background (Hal Sox)
2. Specifying the study population: Inclusion and exclusion criteria.
3. Predicting response to treatment A (vs. Treatment B)
4. Design of the comparison of non-surgical interventions
5. Recruitment of study participants
6. Wrap-up

Timeline

Action	Date
CER Program Advisory Panel	April 17, 2015
Multi-stakeholder Workshop	June 9, 2015
SOC Vote	July 7, 2015
Met with NA Spine Society	September 1, 2015
Met with American Academy of Orthopedic Surgeons	September 21, 2015
Met with American Academy of Neurological Surgeons	September 23, 2015
Meeting with American Physical Therapy Association	December 18, 2015
Meeting with American Academy of Family Practice	December 21, 2015
Multi-stakeholder conference	January 7, 2016
Board of Governors	January-February 2016

Overview

- Chronic low back pain is defined as low back pain occurring on at least half of the days in a 6-month period.
- A large majority of chronic low back pain sufferers have non-specific low back pain, which is defined by the absence of neurological symptoms and signs (e.g., leg pain, numbness or weakness in a nerve root pattern).
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Overview (continued)

- The Cochrane Library describes systematic reviews of randomized trials of 28 interventions for non-specific low back pain. While the evidence is high quality for 10 interventions, the effect sizes are small.
- Few studies have examined combinations of interventions. The June 7th workgroup focused on combinations of potentially complementary treatments.

Overview (continued)

- 90% of lumbar vertebral fusion surgery is done for chronic non-specific low back pain.
- The annual rate of lumbar fusion surgery increased from 13.9/100,000 to 61.1/100,000 from 1988 to 2006.
- Systematic reviews in 2007 (Mirza and Deyo) and 2009 (Chou et al) found that lumbar fusion surgery had small effect sizes that were of questionable clinical significance.
- The June 7th workgroup recommended a trial comparing lumbar fusion surgery with non-surgical interventions.

Study Population, Study Outcomes, and Project Period

- **Population/Patient Problem:** Adults with chronic non-specific low back pain (no neurological symptoms or structural abnormalities other than disc degeneration) on at least 50% of days during the past six months despite self-care, physical therapy, muscle relaxants, NSAIDS, etc.
- **Interventions and Design:** As described in other slides
- **Outcome:** Primary endpoints are
  - NIH Low Back Pain Task Force (function, pain, sleep, mood, medication use, productivity, use of opioids
  - Care utilization [ER visits, surgery, hospital admissions]
  - Safety [major complications of treatment, infections].
  - PROMIS measures required; legacy measures (Oswestry, RMDQ) encouraged.
- **Time:** follow-up for primary end points for 2 years
- **Setting:** Community practice

Study Design: Question 1

- The work group's research question was:
  - "Combined intervention (cognitive and physical) vs. cognitive invention alone vs. physical intervention alone. All patients on medication."
    - The workgroup recommended excluding patients on chronic opioids. Others have disagreed.
- The randomized trial has 3 arms (let A and B be the two components of combination therapy):
  - Combination of A+B vs. A alone vs. B alone
- This design compares combination therapy vs. its component monotherapies
- Patients earlier in their course OR who don't want to risk surgery might enroll in this study.

Study Design: Question 2

- The workgroup's research question was:
  - "3-way combined intervention (cognitive + physical + lumbar fusion) vs. combined 2-way non-surgical intervention (cognitive and physical) alone vs. lumbar fusion alone"
- The randomized trial has 3 arms (let A and B be the two components of non-surgical combination therapy):
  - Combination of A + B + lumbar surgery
  - A + B alone
  - Lumbar surgery alone
- Patients who have already failed some non-surgical alternatives and are more troubled by disability/pain might prefer this study.

Potential interventions

- Physical intervention: spinal manipulative therapy, exercise, massage, physical therapy.
- Cognitive intervention: multidisciplinary biopsychosocial rehabilitation, behavioral therapy (operant, cognitive, or respondent)
- Lumbar fusion surgery

The future –

1. Pending approval by PCORI's Board of Governors, we plan to issue a funding announcement that will specify two randomized trials (but leave the study design to the applicant):
    - Comparison of combination therapies
    - Comparison of combination therapy with lumbar fusion surgery.
2. In approximately 12 months, we expect to announce an award. At that time the successful applicant will assemble a multi-stakeholder advisory committee and write the study protocol.
    - Today's discussion will provide advice to the study team.

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Inclusion and exclusion criteria

1. Specifying the study population: Inclusion and exclusion criteria.

- An inclusion criterion is a factor that a patient must have in order to be eligible for the study.
  - Everyone in the study has the inclusion criterion
- An exclusion criterion is a factor that disqualifies the patient from being in the study.
  - No one in the study has the exclusion criterion
- If these criteria are chosen wisely, the investigators should feel that, for this population, treatment assignment can reasonably be left to chance.

Exclusion criteria (factor disqualifies patient; would likely not be in equipoise)

	Surgery vs. non-surgical study	Combinations of non-surgical interventions study
Receiving disability comp		
radiculopathy		
Prior back surgery		
Back instability		
Spine tumor		
Back deformity		
Osteomyelitis of the spine		
Spine fracture		
Patient engaged in lawsuit		
Serious medical comorbidity		

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Inclusion criteria

Inclusion Criteria for Lumbar Fusion Surgery and for Non-Surgical Intervention

Suggestions:

- Need homogeneity of study group
  - If the patients are in equipoise, it is better for them to be heterogeneous.
- At a minimum, patients should have reliable subgroup classification with specifically designed surgical option.
- Older adults are receiving lumbar fusion, so studies should include older adult demographic

Inclusion criteria (patient must have the factor; researchers likely to be in equipoise)

Surgery vs. non-surgical study	Study of combinations of non-surgical interventions

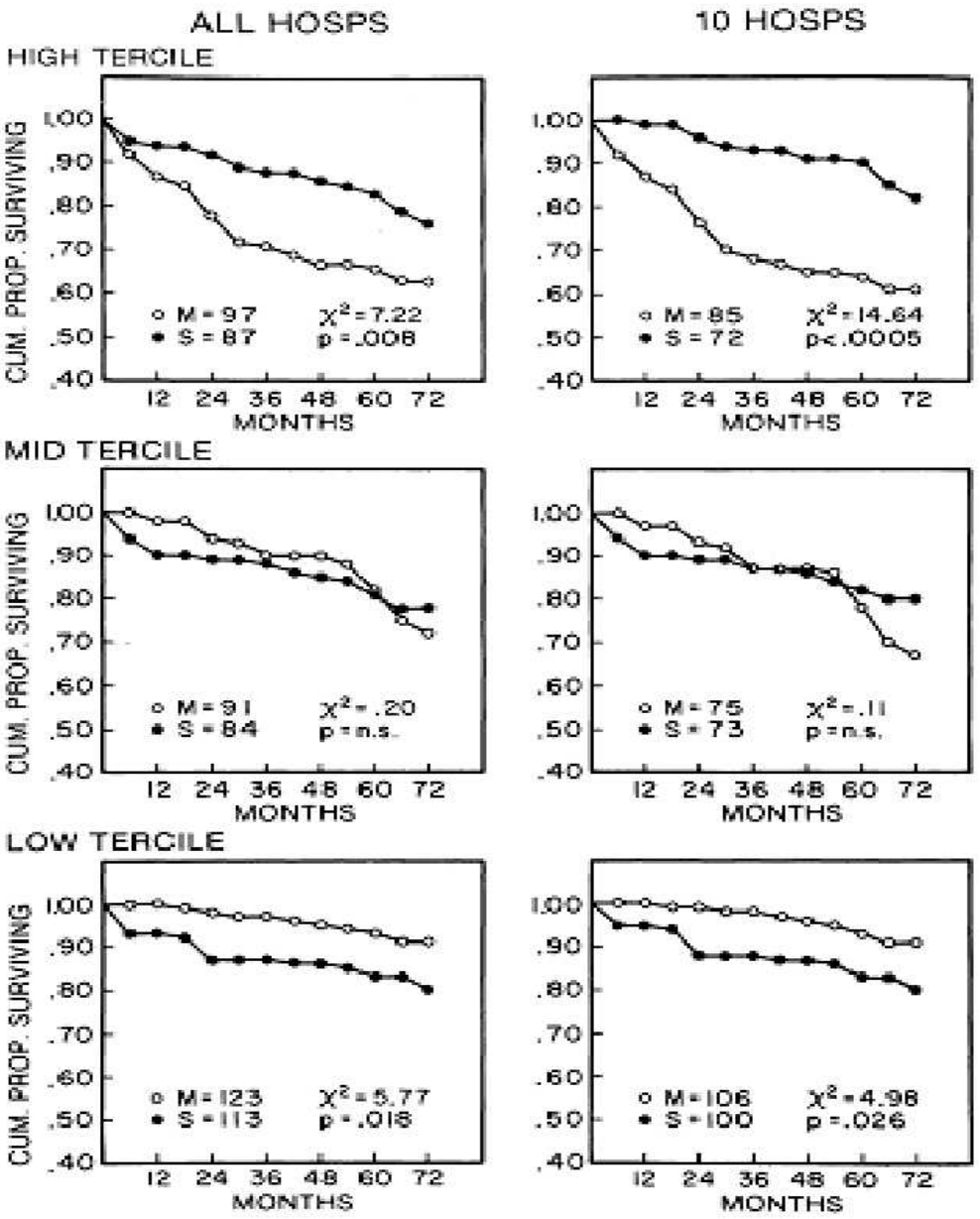
Treatment Response Heterogeneity: predicting the response to Treatment A (vs. Treatment B)

Treatment response heterogeneity

- Suppose a RCT shows that 60% got better on **A** and 50% got better on **B**.
  - Lacking any additional knowledge, you should always prefer **A**.
- Is it possible that some patients would have done better on **B** than **A**?
  - Can we identify them in advance?
    - Demographic predictors
    - Clinical predictors

Outcomes in the VA Coop Study

- 508 medical patients in the VA Coop Study of Bypass Surgery vs. Medical Management.
- Developed a 4-variable rule to predict 5-year mortality.
- Applied it to each patient randomized in 1972-74.
- Grouped patients into tertiles based on similar predicted 5-year risk of death
- Compared mortality in surgery vs. medical patients in each risk group



Detre et al. Circulation. 1981;63:1329.

Searching for treatment response heterogeneity –

- A key to individualizing treatment
- A high PCORI priority
- To detect a clinical characteristic that predicts treatment response, patients in the study population must differ in the characteristic

Factors that predict response to treatment

	Predicts better response to surgery	Predicts better response to combinations of non-surgical interventions
Directional effect of movement on pain		
Patient is >65 years		
Patient is male		
No referral of symptoms below the knee (or any indication of nerve root involvement)		
Course of pain worsening		
No early use of advanced imaging and opiates in primary care (both are associated with higher levels of long term disability and utilization)		

- *Issue of heterogeneity of group—chronic non-specific low back pain is far too heterogeneous a group. Need proper subgroup designations. Such subgroups could include patients whose back pain is:*
  - *1) Improved by extension, worsened by flexion*
  - *2) Improved by flexion, worsened by extension*
  - *3)Improved by neither flexion nor extension*
  - *4)Worsened by both flexion and extension*

How do these factors predict response to treatment?

Factors that predict response to treatment

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Factors that predict response to treatment

	Predicts better response to surgery	Predicts better response to combinations of non-surgical interventions
Patient under emotional stress		
Short duration of symptoms		
SES		
Non-smoker		
Low fear avoidance beliefs/behaviors (as measured by FABQ)		
No anxiety or depression		
Workman's compensation		
Failed prior treatment		
Patient does manual labor		
Patient is physically fit		

Predictors of Response to Treatment

Other Feedback:

- *Preliminary research suggests that individuals can be stratified on whether or not they need CBT by using the StarT Back Screening tool* (see Hill et al., Arthritis Rheum, 2008 and Hill, Lancet, 2011)
- *No valid clinical features in literature that predict favorable response to lumbar fusion surgery*
- *Regarding physical nonsurgical interventions, sparsity of data examining treatment outcomes and specific subgroups*
- *Significant variability in literature concerning cognitive nonsurgical interventions—suspect key here is the use of specific assessment tool such as the lumbar spine questionnaire*
- *Consensus in literature: no more than 6 wks of modalities (including manipulation) will do much to shorten symptomatic interval and an active exercise program should be established ASAP – Please explain this comment. Do you mean that extending modalities beyond 6 weeks does not appear to add benefit:*

Design of a study comparing different combinations of non-surgical interventions

Option 1

- At the June multi-stakeholder meeting, we discussed a design that compared a combination of two interventions (one cognitively-based and the other physical) vs. each of the components alone.
  - A+B vs. A alone vs. B alone

Option 2

- An alternative design is to compare two or more combinations of physical and cognitive interventions (e.g., A+B vs. C+D vs E+F).

We want your opinion about these two ways of designing a trial of combination therapy.

Opinions on Two Proposed Ways of Designing a Trial of Combination Therapy

- *Option 1 (*A+B vs. A alone vs. B alone) *should be enough, but need basis for what constitutes adequate physical and cognitive intervention.*

- *Suggest Option 1. If a specific subgroup can be identified, specific PT protocols can be tailored to the clinical characteristics. This would provide a reasonable measure of efficacy of 'specific' PT.*

- *Should ensure that the interventions have evidence behind them (i.e. avoid passive modalities, etc.) and that they are defined operationally. CBT, PT, and exercise can mean different things to different people.*

Recruitment of study participants

Recruitment of study participants

- The “right” kind of patient for a study would be one that clinical experts believe would be equally likely to receive either study intervention in daily medical practice, reflecting uncertainty about which is best.
- Two types of studies:
  - Combinations of non-surgical options
  - Combination of non-surgical options vs. lumbar fusion surgery
- How do we recruit to these two studies?

Opinions on Recruitment of Study Participants

- *Pathways to care will vary, initial choice may reflect bias. Therefore, might be best to recruit from primary care practices (not neuro, chiro, or ortho).*

- *Priority is to recruit as homogeneous a population as possible. Intake step could be assessment by a healthcare provider for directional preference and subgroup classification. (we usually don't shoot for homogeneity.)*

- *Think we should limit this to folks who are seeking care, as opposed to active recruitment strategies such as flyers, etc.*

Wrap-up and thanks to all