Welcome!

Please be seated by 8:55 am ET

The teleconference will go live at 9:00 am ET

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Assessment of Prevention, Diagnosis, and Treatment Options

Advisory Panel Meeting

October 9, 2015

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Welcome, Introductions, Overview of the Agenda, and Meeting Objectives

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Program Director, PCORI, Clinical Effectiveness Research

Alvin L. Mushlin, MD, ScM

Chair, Panel on the Assessment of Options

The Nanette Laitman Distinguished Professor of Public Health, Professor of Medicine

Department of Healthcare Policy and Research, Weill Cornell Medical Center

Margaret F. Clayton, RN, PhD

Co-chair, Panel on the Assessment of Options

Associate Professor, College of Nursing and

Co-Director of the PhD Program, University of Utah

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Housekeeping

- Today's teleconference is open to the public and is being recorded
  - Members of the public are invited to listen to this teleconference
  - Meeting materials can be found on the PCORI website
  - Comments may be submitted via email to advisorypanels@pcori.org; no public comment period is scheduled
- For those in the room, please remember to speak loudly and clearly into a microphone
- Where possible, we encourage you to avoid technical language in your discussion

Panel Member Introductions

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Clinical Effectiveness Research Team


David Hickam, MD, MPH


Yen-Pin Chiang, PhD


Diane Bild, MD, MPH


Anne Trontell, MD, MPH


Stanley Ip, MD


Julie McCormack, MA


Danielle Whicher, PhD, MHS


Layla Lavasani, PhD, MHS


Kim Bailey, MS


Sarah Daugherty, PhD, MPH


Jana-Lynn Louis, MPH


Katie Hughes, MA


Jess Robb, MPH


Fatou Ceesay, MPH


Geeta Bhat, MPH


Sandi Nayreau


Jackie Dillard


Jillian Nowlin, MA

Not pictured: *Allison Ambrosio, MPH; Holly Ramsawh, PhD; Marina Broitman, PhD; Cary Scheiderer, PhD*

Agenda Overview

Time	Agenda Item
9:00 – 9:30 am	Overview of the Agenda and Meeting Objectives
9:30 – 11:00 am	Review Topic 1: Non-Surgical Treatment for Cervical Neck & Disc Pain
11:00 – 11:10 am	Break
11:15 – 1:00 pm	Review Topic 2: Community-Acquired Pneumonia
1:00 – 1:40 pm	Lunch
1:45 – 3:30 pm	Review Topic 3: PCSK9 Inhibitors
3:30 – 3:40 pm	Break
3:45 – 4:00 pm	Background and Status of Previous Topics
4:00 – 4:25 pm	Announcements and Next Steps
4:30 pm	Adjourn

Meeting Objective and Procedures

- Recommend specific questions for further consideration as priority research areas

- Procedures for Reviewing Topics
  - 3 CER topics will be reviewed
    - Topic expert will present 5- to 10-minute introduction of topic
    - Approximately 1 hour and 30 minutes of discussion per topic
    - Panelists will discuss 4 or more questions per topic

Topic 1:
Non-Surgical Treatment for Cervical Neck and Disc Pain

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Duke Evidence Synthesis Group's Tasks

- Create a prioritized research agenda based on
  - stakeholder inputs
  - feasibility of impacting practice within the next 3 to 5 years

General Approach

- Appraise recent systematic reviews to identify important evidence gaps
- Transform the evidence gaps into potential research questions
- Engage relevant stakeholders to identify additional gaps and prioritize the research questions
- Cross-check potential research questions with ongoing studies

Background

- Neck pain is a common, bothersome, and potentially debilitating problem. Most neck pain results from problems affecting the structures of the cervical spine, which include the 7 cervical vertebrae, the pads between them (intervertebral discs), and the other joints between the vertebrae
- The incidence of new neck pain has been estimated to be 146-179 per 1,000 person-years, and the incidence of diagnosed disc herniation with radiculopathy is 0.055 per 1,000 person years.
  - A large systematic review estimated the point prevalence of neck pain among adults worldwide to be 8%, and the one-year prevalence to be 37%.
  - The 12-month prevalence of activity-limiting neck pain for adults is 1.7% (limited ability to work); 2.4% (limited social activities); and 11.5% (limited activities overall).
  - Neck pain prevalence peaks in middle age and is higher among women than men.

Management Options

- The goals of treatment for neck pain are generally to reduce pain and muscle spasm, to reestablish normal cervical alignment, and to improve functionality.
- Only a minority of people with neck pain seek health care; seeking care is likely determined by multiple factors, including perceived pain severity, speed of onset, presence of trauma at onset, previous experience, costs, and availability of care.
- Management options include:
  - Surgery
  - Pharmacotherapy
  - Nonpharmacologic, noninvasive management
  - Injections

Stakeholders

- North American Spine Society
- National Business Group on Health
- American Physical Therapy Association
- International Association for the Study of Pain

Central Themes from Stakeholders

- Nonspecific neck pain is not sufficiently useful as a clinical topic because many different etiologies contribute to neck pain. The recommendation was made to specify a more specific diagnosis or clinical characteristics (e.g., neck pain due to “whiplash” or hyperextension injury, or cervical disk injury/disease, or axial neck pain with directional preference, etc.).
- Proper diagnosis and classification is important, with the recognition that many different classification systems are currently in use.
- Axial neck pain with and without radiculopathy usually represent different clinical entities.
- Treatment options should be a function of specific etiology.

Central Themes from Stakeholders

- There is a paucity of comparative effectiveness research that evaluates some of the many therapeutic options in current practice. The suggestion was made that head-to-head RCTs would be useful.
- There was interest in the question of patient preferences for therapeutic options, but in the absence of adequate effectiveness data from RCTs, stakeholders felt that studying patient preferences directly might not be especially helpful.
- There is an interest in CER that includes persons of working age (as opposed to solely Medicare populations) and outcomes that would be of interest to large employers.
- Outcomes of interest include commonly used standardized questionnaires such as the Neck Disability Scale. Functional outcomes are of interest to stakeholders.

The Four CER Questions (Not in Ranked Order)

- **Research Question 1:** Does the presence of centralization vs. non-centralization or directional preference vs. no directional preference predict response to therapy for axial neck pain without radiculopathy?
- **Research Question 2:** Within specific patient populations of interest, what is the comparative effectiveness and safety of available nonsurgical treatments (prescription oral pharmacotherapy, over-the-counter oral pharmacotherapy, injections, or non-pharmacologic treatments) either alone or in combination for short-term symptomatic improvement of neck pain? Patient populations of interest include: (1) patients with axial neck pain with radiculopathy, and (2) patients with axial neck pain without radiculopathy. Outcomes of interest should include intervention's impact on pain, function, and work loss/return to work/degree and longevity of disability or impairment.
- **Research Question 3:** What is the comparative effectiveness of existing assessment instruments for persons with neck pain with or without radiculopathy for the purpose of prognosis or assessing the effectiveness of therapeutic interventions?
- **Research Question 4:** Are there patient characteristics, biopsychosocial and economic factors, physical examination, and imaging findings that predict which patients with new onset axial neck pain are at risk for developing chronic pain, opioid dependence, or other undesirable outcomes?

BREAK

11:00 am – 11:10 am

Topic 2:

Narrow-Spectrum Antibiotics vs. Broad-Spectrum Antibiotics for Community-Acquired Pneumonia in Adults

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JHU Evidence Synthesis Group's Tasks

- Create a prioritized research agenda based on
  - stakeholder inputs
  - feasibility of impacting practice within the next 3 to 5 years

General Approach

- Appraise recent systematic reviews to identify important evidence gaps
- Transform the evidence gaps into potential research questions
- Engage relevant stakeholders to identify additional gaps and prioritize the research questions
- Cross-check potential research questions with ongoing studies

Background

- Community-acquired pneumonia (CAP) is defined as an infection of the lung in persons who have not been hospitalized recently or exposed to other healthcare settings that markedly increase risk of contracting pneumonia.
- Typical symptoms of CAP include fever, cough, sputum production, and shortness of breath, with leukocytosis on laboratory testing and lung consolidation or infiltrate on chest imaging.
- In 2012, 1.1 million persons were diagnosed with CAP in the United States, resulting in 327,840 hospital admissions.
  - Characteristics of individuals at increased susceptibility to CAP include older age, comorbidities, immunosuppression, non-white race, and lower education and income.
  - In 2013, CAP was the 9th leading cause of death in the United States with a mortality rate of 16.9 per 100,000 contributing to 53,000 deaths.

Stakeholders

- American Academy of Family Physicians (AAFP)
- American Thoracic Society
- American College of Chest Physicians (ACCP)
- Infectious Diseases Society of America (IDSA)
- Centers for Disease Control and Prevention (CDC)

Central Themes from Stakeholders

- The definition of narrow- and broad-spectrum antibiotics varies; a study to answer this question would be challenging to conduct, and this study might be unlikely to change practice.
- Studies of outpatient, emergency department, hospitalized, and intensive care unit patients with CAP are needed, but outpatient is the top priority for these research questions.
- The duration of antibiotics to treat CAP may be as important as the choice of antibiotic, and these issues could potentially be combined in one comparative effectiveness trial.
- Patient-centered outcomes are needed in CAP studies.

Central Themes from Stakeholders

- There is general consensus that a comparative effectiveness study on diagnostics to identify causative pathogens for CAP could improve care.
- Antibiotic resistance is a concern, but studies designed to examine antibiotic resistance as an outcome would not be feasible.
- CAP treatments could be studied with innovative designs given the variety of treatment options available and prevalence of the condition.
- Additional areas of research:
  - Dose and duration of antibiotics
  - Pneumonia vaccination
  - Patient prognosis and the predisposition to mortality or long duration of illness

Revised CER Questions (Not in Ranked Order)

- **Research Question 1:** What is the comparative effectiveness and safety of different approaches for rapid, point-of-care diagnosis of the etiology of community-acquired pneumonia in adults (whether there is a bacterial contributing cause, the specific etiologic agent, and strain/antibiotic sensitivity)?

- **Research Question 2:** What is the comparative effectiveness and safety of different antibiotic regimens in the empiric treatment of community-acquired pneumonia in adults?
  - **Research Question 2a:** What is the comparative effectiveness of empiric narrow- versus broad-spectrum antibiotics for outpatients with community-acquired pneumonia?
  - **Research Question 2b:** What is the comparative effectiveness of different durations of antibiotic treatment for CAP (3 versus 5 versus 7 days) for outpatients with community-acquired pneumonia?

Other CER Questions

- Is the safety and effectiveness of narrow spectrum vs. broad spectrum antibiotic therapy different in distinct subpopulations of adults with community-acquired pneumonia (e.g., chronic conditions, immunosuppression, elderly, minorities, living in rural areas)?

- What is the comparative effectiveness of different approaches to de-escalate antibiotic therapy in the treatment of community-acquired pneumonia in adults?

- What are the implications of narrow spectrum vs. broad spectrum antibiotic therapy on antibiotic resistance?

LUNCH

1:00 pm – 1:40 pm

Topic 3:

PCSK9 Inhibitors

Cardiovascular Disease (CVD)

- Heart attack and stroke are the most serious
- Heart disease accounts for 610,000 deaths every year
- Risk factors: high cholesterol, hypertension, tobacco exposure, obesity, physical inactivity, diabetes
- High level of low-density lipoprotein cholesterol (LDL-c) is associated with an increased risk of CVD

Hypercholesterolemia

- 31.9 million adults: generally asymptomatic
  - First presentation may be heart attack or sudden death
- 68% get treatment
- Statins are the first-line treatment after dietary changes
  - Up to 5% of patients discontinue due to drug-related adverse events
  - 3% to 10% complain of non-specific muscular aches and pains, which does not necessarily mean statin intolerance, and usually does not require discontinuation

2013 AHA/ACC Treatment Guidelines

- The American Heart Association/American College of Cardiology guidelines used absolute 10-year atherosclerotic CVD risk estimates to guide decisions about initiation and choice of statin therapy
- Prior guidelines focus on cholesterol levels; these focus on absolute risk of CVD, irrespective of baseline LDL-c
- Define high-, moderate-, and low-intensity statin therapy as a daily dose that lowers LDL-c by 50%, 30% to 49%, and <30%, respectively

Benefits of Statin Treatment

- Reduce risk of major vascular events by ~21% per mmol/L reduction in LDL-c, irrespective of baseline level or history of vascular disease
- In lower-risk individuals (<10% 5-yr predicted risk), absolute risk reduction of major vascular events of 11 per 1,000 over 5 yr per 1 mmol/L reduction

Statin Intolerance

- Definition varies from study to study
- Myopathy (muscle pain/weakness with high level of blood creatine kinase levels) ~0.1%
- Rhabodomyolysis (a severe form of myopathy with very high level of creatine kinase and release of myoglobin into the circulation, which can cause renal failure) ~0.002%
- High prevalence in patients of Asian descent
- May be dose related
- May be related to diabetes, chronic kidney disease, other medications, older age

Management Strategies

- Rule out conditions associated with statin-induced myopathy (e.g., renal insufficiency) and hepatic toxicity (e.g., alcoholic liver diseases)
- Try another statin
- Different dosing strategies
- Combination therapy (e.g., with ezetimibe)
- Strengthening dietary interventions
- Non-statin lipid lowering drugs

Non-Statin Lipid Lowering Drugs

- Colesevelam: bile acid sequestrant (BAS)
- Ezetimibe: intestinal cholesterol absorption inhibitor (ezetimibe)
- Fibrates: ↓TG, ↑HDL-c, mod↓LDL-c; mechanism not entirely clear
- Niacin: ↓TG, ↑HDL-c, ↓LDL-c
- Combination (e.g., niacin and BAS, ezetimibe + statin, ezetimibe + BAS, ezetimibe + fibrates)
- Alirocumab and Evolocumab: PCSK9 inhibitors

PCSK9

- Proprotein convertase subtilisin/kexin 9 is a protease that binds to low-density lipoprotein (LDL) receptors
- This binding reduces the activity of the LDL receptors, thereby decreasing LDL metabolism
  - which leads to increased LDL cholesterol levels

PCSK9 Inhibitors

- Monoclonal antibodies
- Bind to PCSK9 leading to increased activity of LDL receptors
  - Decreased LDL cholesterol levels
- Alirocumab and Evolocumab injectables are the two approved so far

Evidence Base

- Alirocumab
  - 5 placebo-controlled trials showed an average reduction in LDL-c from 36% to 59%, compared to placebo
- Evolocumab
  - 9 placebo-controlled trials showed an average reduction in LDL-c of ~60%, compared to placebo

FDA Approval

"approved for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol"

Cardiovascular and Adverse Event Outcomes

- One study of evolocumab with a median follow-up of 11 mo of 4,465 participants
  - Cardiovascular events at 1 year were reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group
  - Most adverse events occurred with similar frequency
  - Neurocognitive events were reported more frequently in the evolocumab group

Ongoing Studies

- Five studies
  - 4,428 to 27,564 participants
  - Cardiovascular events and safety outcomes
  - Most are projected to complete in 2018

Future Studies?

- Better characterize who would most benefit from the alternate treatments
  - Better define statin-intolerant
  - FH/genetic testing
  - Predict adherence
- Compare newer agents with other available non-statin treatments

BREAK

3:30 pm – 3:40 pm

Background and Status of Previous Topics

David Hickam, MD, MPH
Program Director, PCORI, Clinical Effectiveness Research

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Announcements and Next Steps

- Next in-person meeting will occur the week of January 25 to 29, 2016

Thank you for your participation

Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options

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