Many Thanks To Our Sponsors For Their Generous Support Of The October 2012 Articles on Comparative Effectiveness Research And Today’s Briefing
Communicating About Comparative Effectiveness Research: A Health Affairs Symposium On the Issues

Presentation of the Case Study

By Susan Dentzer
Editor-in-Chief

Health Affairs
Communicating About Comparative Effectiveness Research

- The U.S. is pursuing an agenda of increased comparative effectiveness research to identify high-value health care.

- There are many issues surrounding this research, including communication, the focus of this symposium.

- How will research findings be communicated in ways that are accurate and are useful to patients and their providers?
Hypothetical Case Study

- To surface the relevant issues, we devised a hypothetical case study about a fictional drug for migraine.

- Estimated 28-36 million Americans suffer in some form from migraine; direct costs estimated at slightly more than $11 billion annually.
Hypothetical Case Study

• Fictional drug, Hemikrane, FDA-approved
• Migraine preventive agent shown in two randomized, double-blind controlled clinical trials to reduce migraine frequency and severity

• Taken weekly; monthly cost (to payers) is $200
Hypothetical Case Study: The Research

• Hemikrane was compared to Cephalal, a different preventive migraine drug that had comparable outcomes

• Cephalal taken daily; monthly cost to payers = $150

• A major philanthropic organization with interest in migraine wanted to test hypothesis that patients would be more adherent to the once-weekly Hemikrane and therefore overall effectiveness would be improved

• Harvard, a regional insurance company, Hemikrane’s manufacturer and a pharmacy benefit management firm participated in studies
The Comparative Effectiveness Research Studies

• First: Observational study based on insurers’ data base of patients with migraine who made frequent visits to doctors or hospital emergency departments

• Patients on Hemikrane compared to patients on Cephalal and to patients receiving no preventive treatment

• In lieu of symptoms, study measured use of other medications for migraine symptom relief

• Patients on Hemikrane had lower use of these medications; fewer emergency department visits; lower overall episode costs; higher adherence (80 percent versus 50 percent for Cephalal)
The Comparative Effectiveness Research Studies

- Second: Observational study in which database from a pharmacy benefit management company was analyzed

- Corroborated findings of first study

- Data collected from employers also showed that patients on Hemikrane were out of work for fewer days each month than patients on Cephalal

- “Real-world” studies with “real world” results: How should they be communicated?

- Issues and Responses from stakeholders
The Hypothetical Case Study:

Responses from Stakeholders
The FDA’s Critical Role in Preventing Promotion of Flawed Comparative Effectiveness Research

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HealthAffairs
Hypothetical Scenario

- 2 observational research trials support comparative effectiveness of Hemikrane over Cephalal
  - Possibly related to dosing schedule
  - No difference in (underpowered) randomized trial
- Why can’t the company promote this information?
1. These Studies Are Flawed

• Not a new-user design

• Adequacy of control for confounding?

• Conclusions based in part on comparisons with patients taking no drug
  – Substantially different cohorts
2. Observational Research Is Difficult And Prone To Bias

- Investigator-driven choices in design and unmeasured confounders can influence results
- Easy to “conduct” dozens of observational studies until one finds the results one wants
3. Pattern Of Improper Industry Promotional Behavior

- Selective reporting of clinical data to favor its products
- Misleading educational and marketing practices
- >$12 billion dollars in government settlements related to improper promotion in last 10 years
4. FDA Has Legal Authority To Restrict Manufacturer Promotion

- FDCA: Cannot market a drug if “there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use”

- Substantial evidence = “adequate and well-controlled investigations”
  - Traditionally interpreted as 2 randomized trials, but ...
4 (cont’d).

- **Flexibilities**
  - “one adequate and well-controlled clinical investigation and confirmatory evidence”
  - “substantial clinical experience”
  - Distribution of peer-reviewed articles discussing uses not in label can be “historically controlled studies, pharmacokinetic and pharmacodynamic studies, and meta-analyses”
Conclusion

• There is a reasonable legal basis for restricting promotion of flawed observational research, and rational policy reasons for doing so

• Flexibility in law/regs for companies to bring high quality observational data to FDA supporting a change to label, which could then allow company to use the information in promotion
Clear Standards and FDA Guidance Could Enable Balanced Communication of CER Results

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New Communication Environment

**Mid-1980’s**
- FDA-Approved Label
- FDA
- Pharmaceutical Representatives
- Medical Journals and Texts
- Professional Associations and Peer Groups
- CME

**~2012**
- FDA-Approved Label
- FDA
- Pharmaceutical Representatives
- Medical Journals and Texts
- Online Resources / Social Media
- Professional Associations and Peer Groups
- Academic Detailers
- Government Research Agencies
- Physician and Hospital Networks

FDA Regulated
Not FDA Regulated (Ranges from no oversight to peer review/standards)
Industry Component FDA Regulated

CME: Continuing Medical Education
FDA: Food and Drug Administration
Industry Communication Is Governed by Strict FDA Regulations Which Permit:

- Communicating about approved product indications/attributes that are on label or meet scientific requirements (e.g., trial data)
- Providing health care economic information, on label, to formulary committees and similar entities under certain circumstances
- Responding to unsolicited requests for off-label information with purely scientific information
- Providing scientific exchange under defined circumstances
Hemikrane Case

- Questions about the methods
  - Some best practices followed
  - Clear limitations; some are common
  - Space limitations, a partial culprit

- But, what if:
  - It all had been “perfect”?
    - Company still could not communicate!
  - Industry had not been involved at all?
    - Others could communicate & do now
## Proposed Solutions to Enable Rigorous, Balanced CER Communications

<table>
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<tr>
<th>Solution</th>
<th>Potential Approaches</th>
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| **Clear FDA Guidance for Industry to Meaningfully and Proactively Engage in CER Discourse** | - FDA develops and issues guidance describing circumstances under which industry can communicate CER information  
- Stakeholders could work together to define this standard (FDAMA Section 114, “competent and reliable” standard as a model?) |
| **Stakeholders Voluntarily Adopt “Good Communication Principles”** | - Stakeholders collaborate to develop “good communication principles” or similar criteria for dissemination of transparent, truthful, and scientifically sound CER  
  » Could be based on GRACE principles or other standards  
- Encourage voluntary adoption and application |

FDA: Food and Drug Administration  
CER: Comparative Effectiveness Research  
GRACE: Good Research for Comparative Effectiveness
Reviewing Hypothetical Migraine Studies Using Funding Criteria from PCORI

Rachael Fleurence, PhD
Scientist, Patient-Centered Outcomes Research Institute

Health Affairs
Washington, DC
October 11, 2012
Funding Research that Matters to Patients and Their Clinicians

The Patient-Centered Outcomes Research Institute (PCORI) is dedicated to producing and communicating research of high integrity that helps people make better informed health care decisions.
Observational Studies of Patients with Migraine

Considering Two Hypothetical Studies

What role can **rigorous observational comparative effectiveness research studies** play in guiding **clinical decision making**?

What **criteria** should be used in determining whether the **results** of such studies should be **communicated** to clinicians and patients?
Patient-Centered Comparative Effectiveness Research Should...

Be Relevant to Patients
Patient-Centered Comparative Effectiveness Research Should…

Have Potential to Impact Practice, Improve Outcomes
Patient-Centered Comparative Effectiveness Research Should...

Be Conducted Using Rigorous Analytic Methods
PCORI’s Final Assessment

Unlikely to Fund These Studies, Communicate Their Results

• Evidence of relevance to patients and clinical impact not clear
• Several methodological problems

Still, Finding Value in High-Quality Observational Studies

• Effectively complement findings from randomized trials
• Communicating their results to patients and clinicians is warranted
Patient Engagement

**Development of Research Questions**
- Determine questions that are useful to patients, caregivers, and consumers and would have real-world applicability

**Selection of Outcomes and Comparators**
- Identify outcomes of interest to patients, caregivers, and consumers

**Evaluation of Results**
- Evaluate findings against established criteria to determine whether research is conclusive enough to inform decision making

**Translation and Dissemination**
- Help patients, caregivers, and consumers understand findings

Develop Research Questions
Identify Outcomes & Comparators
Evaluate Results
Enhancing Patient Autonomy Through Peer Review To Replace The FDA’s Rigorous Approval Process

Arthur Caplan, PhD
Drs. William F. and Virginia Connolly Mitty Chair, Director, Division of Medical Ethics
NYU Langone Medical Center
Academic Detailing Can Play A Key Role In Assessing And Implementing Comparative Effectiveness Research Findings

Michael Fischer and Jerry Avorn
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Hemikrane Case Study

• **Strengths**
  – Large sample size
  – Patient-centered outcomes

• **Weaknesses**
  – Inappropriate control group
  – Lack of new user design
  – Inadequate adjustment for bias

see Selby et al.
Challenges In Disseminating CER

- Interpreting CER findings
- Credible sources of information
- Turning results into action

Academic detailing as a solution
Academic Detailing

- Educational outreach to clinicians
- Careful analysis of literature
- Unbiased summary of evidence
- Interactively presented
- Practical recommendations
Challenges In Disseminating CER

• Interpreting CER findings
  – Quality of CER may be uneven
  – Flaws not always obvious
  – Requires time and expertise
    • academic detailing programs
    • DERP, AHRQ EPC’s

• Credible sources of information

• Turning results into action
Challenges In Disseminating CER

• Interpreting CER findings

• Credible sources of information
  – Manufacturer messages problematic
    • >$10 billion fines and settlements
    • use of Hemikrane study
  – Payers may be too cost focused
  – Unbiased source needed

• Turning results into action
Challenges in disseminating CER

- Interpreting CER findings
- Credible sources of information
- Turning results into action
  - Data alone inadequate
  - Traditional CME has not improved care
  - Clinicians need specific tools
Challenges In Disseminating CER

• Interpreting CER findings
• Trusted sources of information
• Turning results into action
Academic Detailing As A Solution

• Interpreting CER findings
  – Expertise to review and evaluate

• Trusted sources of information
  – Non-commercial “honest broker”

• Turning results into action
  – Interactive outreach to improve care
Use Of Research By Payers And Clinicians: A Response

Robert W. Dubois, MD, PhD
Chief Science Officer
National Pharmaceutical Council

HealthAffairs
Key Points From the Article*

- CER needs to be evaluated critically, placed in a larger context, and communicated to clinicians
- Industry should not communicate CER
- Academic detailing can be a key communication vehicle

Fischer M. Academic Detailing Can Play a Key Role in Assessing and Implementing Comparative Effectiveness Research Findings. HealthAffairs 2012.
Is Academic Detailing Fully Unbiased?

• Critique, synthesis, and context require assumptions and judgment (bias is not just from corporate sponsorship)

• Multiple National/State activities with different approaches and no agreed upon standards

• Would a comparison of 2 parallel efforts produce similar documents?
All Communication Should Address

• Study and evidentiary limitations
• Multiple outcomes/factors including quality of life, patient preferences, and productivity improvement
• Variation in individual treatment response
• And, how about CME, Payer, and Specialty Academy recommendations?
A Way Forward

1. Create communication standards
   – multi-stakeholder involvement similar to viewpoints in current *HealthAffairs* issue

2. Communication standards should apply to everyone

3. Following these standards, all stakeholders should participate in the CER dialogue
PCORI Should Focus On High-impact Research Questions That Can Be Answered Quickly

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The Dartmouth Institute for Health Policy and Clinical Practice
TERMINATION.—No amounts shall be available for expenditure from the PCORTF after September 30, 2019, and any amounts in such Trust Fund after such date shall be transferred to the general fund of the Treasury.”

Source: Section 6301 of the Affordable Care Act of 2011.
“Not later than 8 years after the date of enactment of this section, the adequacy and use of the funding for the Institute and the activities conducted under section 937 of the Public Health Service Act, including a determination as to whether, based on the utilization of research findings by public and private payers, funding sources for the Patient-Centered Outcomes Research Trust Fund under section 9511 of the Internal Revenue Code of 1986 are appropriate and whether such sources of funding should be continued or adjusted.”

Source: Section 6301 of the Affordable Care Act of 2011.
Section 6301 of the statute decrees that the institute “...shall identify national priorities for research, taking into account factors of
* disease incidence, prevalence, and burden in the United States (with emphasis on chronic conditions)
* gaps in evidence in terms of clinical outcomes
* practice variations
* the potential for new evidence to improve patient health, well-being, and the quality of care
* the effect on national expenditures associated with a health care treatment, strategy, or health conditions
* patient needs, outcomes, and preferences.”
An IOM Research Question

Compare the effectiveness of primary prevention methods, such as exercise and balance training, versus clinical treatments in preventing falls in older adults at varying degrees of risk.

Source: Initial National Priorities for Comparative Effectiveness Research, Institute of Medicine, 2009.
An IOM Research Question

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An IOM Research Question

Compare the effectiveness of primary prevention methods, such as exercise and balance training, versus clinical treatments in preventing falls in older adults at varying degrees of risk.

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Page 729 of Section 6301 of the statute states that the institute “shall establish and update a research project agenda for research to address the priorities identified under subparagraph (A), taking into consideration the types of research that might address each priority and the relative value (determined based on the cost of conducting research compared to the potential usefulness of the information produced by research) associated with the different types of research, and such other factors as the Institute determines appropriate.”

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Source: Section 6301 of the Affordable Care Act of 2011.
The Affordable Care Act

1. Comparative assessment of prevention, diagnosis and treatment options

2. Improving healthcare systems

3. Communication and dissemination: the stated goal is to promote informed decisions taken with clinicians.

4. Addressing disparities

5. Accelerating patient-centered and methodological research

Source: Section 6301 of the Affordable Care Act of 2011.
Five Reasons That Many Comparative Effectiveness Studies Fail To Change Patient Care And Clinical Practice

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Study Objectives

1. To develop a framework for assessing barriers and enablers to the translation of CER evidence into clinical practice

2. To identify key translation barriers and enablers using a case study methodology

3. To develop policy options to enhance CER translation
Root Causes Of Incomplete Translation Of CER Evidence Into Practice

1. Misalignment of financial incentives with CER evidence
   - Creates barriers at each phase of translation: design, interpretation, formalization, adoption

2. Ambiguity of CER results
   - Difficulty operationalizing “superiority”
   - Difficulty interpreting “flawed” randomized studies and observational analyses

3. Cognitive biases in decision making
   - Confirmation bias
Root Causes Of Incomplete Translation Of CER Evidence Into Practice

– Pro-intervention bias
– Pro-technology bias

4. Failure of CER design to address the needs of end-users
  – Tendency to focus on “downstream” decision-making

5. Limited use of decision support by patients and clinicians
  – Technical and workflow challenges
Policies To Facilitate Translation Of Research Into Practice

• Develop consensus objectives and standards for interpreting results prior to initiating each study

• Promote a broader professionalism in the development of guidelines and quality measures

• Promote the adoption of payment and coverage policies that provide strong incentives for efficiency
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