Comparative Effectiveness Research and its Impact on Managing Pharmaceuticals

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Subject Matter

• Place of CER in managing pharmaceuticals
  – Emphasis on managing Rx benefits
• Rx payer interest and involvement in CER
• Determinants of CER effectiveness
  – Research methods
  – Political and commercial considerations
  – Cultural responses
Lititz Pharmacopoeia: First formal CER for pharmaceuticals in US?

“Formulary of simple and yet efficacious remedies for use of the military hospital, belonging to the army of the Federated States of America: Especially adapted to our present poverty and straitened circumstances, caused by the ferocious inhumanity of the enemy, and the cruel war unexpectedly brought upon our fatherland.”
Time is right for focus on CER in managing Rx

- CER became applicable when Rx benefit payers began managing benefit tightly
- Increasing payer involvement in benefit allocation policy and clinical management programming over time has generated an intensified interest in and demand for CER
- Payers showing interest in participating in CER to get information they need
Application of CER in managing Rx benefits:  
*Decisions need to be made and will be made*

- Component of technology assessment
- Coverage of drug categories, drugs, drug indications, drug uses
- Coverage of companion diagnostics or services
- Development of clinical management programming
- Integration into pharmacy practice models and protocols
85% of employers believe CER research has at least moderate potential to improve health benefit decisions

- 5 - Very strong potential to improve health benefit decisions: 23%
- 4 - Strong potential: 29%
- 3 - Moderate potential: 33%
- 2 - Some potential: 5%
- 1 - No potential: 0%
- Don’t know: 9%

n = 75

Source: Comparative Effectiveness Research: Do Employers Care? What Will They Do? NPC, June 2011
Data (health status, benefits utilization/costs, health outcomes, productivity) is used regularly in benefit decisions

<table>
<thead>
<tr>
<th>Category</th>
<th>4 - 5 (Always)</th>
<th>3 (About half the time)</th>
<th>1 (Never) - 2</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical benefit plan design</td>
<td>95%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall strategy to manage health and costs</td>
<td>92%</td>
<td>3%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Pharmacy benefit plan design</td>
<td>91%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decisions regarding coverage/reimbursement of specific prescription drugs</td>
<td>72%</td>
<td>9%</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Wellness and disease management program offerings</td>
<td>69%</td>
<td>21%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Decisions regarding coverage/reimbursement of specific diagnostics</td>
<td>52%</td>
<td>23%</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>Decisions regarding coverage/reimbursement of specific biologic therapies</td>
<td>49%</td>
<td>24%</td>
<td>23%</td>
<td>4%</td>
</tr>
<tr>
<td>Decisions regarding coverage/reimbursement of specific surgical procedures</td>
<td>47%</td>
<td>32%</td>
<td>3%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Source: Comparative Effectiveness Research: Do Employers Care? What Will They Do? NPC, June 2011

October 18, 2011 • Atlanta, Georgia
Nine in ten employers believe all types of CER information will be at least moderately important in comparing alternative treatments.

- Clinical outcomes of alternative treatments (e.g., heart attacks avoided, episodes of worsening asthma): 95% very important, 5% moderately important, 0% not at all important.
- Information comparing utilization and cost of treatments (medical and pharmacy): 86% very important, 12% moderately important, 2% not at all important.
- Information about which treatments work best for specific populations (e.g., gender, age, ethnic groups): 81% very important, 19% moderately important, 0% not at all important.
- Comparative safety of alternative treatments (e.g., radiation therapy vs. surgery for prostate cancer): 80% very important, 20% moderately important, 0% not at all important.
- Impact of alternative treatments on employee absence, disability and ability to return to work: 70% very important, 24% moderately important, 6% not at all important.
- Information comparing impact of treatments on quality of life: 70% very important, 21% moderately important, 9% not at all important.
- Impact of alternative treatments on productivity at work: 62% very important, 29% moderately important, 9% not at all important.

Source: Comparative Effectiveness Research: Do Employers Care? What Will They Do? NPC, June 2011
Six in ten employers will expect vendors to use CER findings and one-third will play an active role to monitor and apply CER findings.

- Expect our vendors (health plans, PBM, EBCs) to use CER findings, but we will want to stay informed (3%)
- Play an active role to monitor, interpret and apply CER findings as needed to get the greatest value from our benefit policies and programs (4%)
- Rely completely on our vendors (health plans, PBM, EBCs) to monitor, interpret and apply CER findings (60%)
- Don’t know (33%)

n = 75

Source: Comparative Effectiveness Research: Do Employers Care? What Will They Do? NPC, June 2011
Of employers that will play an active role to monitor, interpret and apply findings, PCORI is the most reliable/trusted source of CER information in the future.

- Information directly from the Patient-Centered Outcomes Research Institute (PCORI) - 76%
- Health plan partners - 48%
- Employee benefit consultants - 44%
- Health care coalition meetings/presentations - 36%
- Health and benefits-oriented journals and magazines - 36%
- PBM partners - 16%
- Health and benefits-oriented e-news sources - 4%

Source: Comparative Effectiveness Research: Do Employers Care? What Will They Do? NPC, June 2011
Part of the Medco Research Institute, provides the interface between research, clients, and account executives

Gives clients additional insights into post market research

Promotes communication efficiency

Clients may join at no cost and receive:

- Access to MRI studies
- Invitation to attend lecture series (webinar) and events
- Monthly research offerings (email)
- Biannual research newsletter
- Client specific reporting
HMO Research Network Members

Source: http://www.hmoresearchnetwork.org/resources/tools/HMORN_Brochure.pdf
And thus…

• CER applies to payer interests and needs, and increasingly demands
• Payers willing to participate in data generation and application
• New government funding and structures to encourage and support CER

…but, will CER be effective in the management of pharmaceuticals?
CER Methods

• Considerations
  – Relevant *Effectiveness* data needs
  – Benefit plan context

• RCTs preferable but not always sufficient

• Field research methods often applicable and required, eg,
  – Quasi-experimental
  – Epidemiological
Medco-Mayo Warfarin Effectiveness Study

Primary comparison

- Historical control
  - July 2006 – June 2007
  - n=2688

- Intervention group
  - July 2007 – February 2009
  - n=896

Comparison of external controls

- External historical control
  - July 2006 – June 2007
  - n=2688

- External concurrent control
  - July 2007 – February 2009
  - n=2688

23 Benefit Plan Sponsors

56 Benefit Plan Sponsors

*6 month follow-up on all patients initiating warfarin in all groups

All cause

Adjusted for age, comorbid conditions, drugs, propensity score, indications, prior GI bleed or VTE, history of prior hospitalization

**Bleed or thromboembolism**

- **IG**
- **HC**

HR: 0.72 (CI: 0.53, 0.97)

p=0.029

Adjusted for age, comorbid conditions, drugs, propensity score, indications, prior GI bleed or VTE, history of prior hospitalization

Participant Distribution in MM-WES

Site Distribution in NIH/NHLBI sponsored “Clarification of Optimal Anticoagulation Through Genetics (COAG)”
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials
Gordon C S Smith, Jill P Pell
*BMJ* 2003;327:1459–61
Adding prudence

Never a slave to abstract principles or rules of conduct, never a moral preener espousing ‘ideals’ or doctrines, the prudent man knows that excellence really consists in finding and enacting the best thing to do here and now, always with a view to the good but always as seen in the light of the circumstances.”

Leon Kass, 2009
Pascal's Wager as heuristic for prudence

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>Eternal bliss</td>
<td>Status quo</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>Eternal misery</td>
<td>Status quo</td>
</tr>
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</table>

The best scenario from not believing is worst scenario from believing

Pascal
Applying the wager to genetic testing for warfarin at current level of certainty

<table>
<thead>
<tr>
<th>Test Relates to Outcomes</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Reduce bleed/clot</td>
<td>Status quo</td>
</tr>
<tr>
<td>No</td>
<td>Unnecessary bleed/clot</td>
<td>Status quo</td>
</tr>
</tbody>
</table>

The best scenario from not testing is worst scenario from testing.
Political and Commercial Considerations

- CER can produce political and commercial winners and losers; fear of losing trumps drive for winning
- Americans will not accept "no" (coverage)
- Science and Policy discordance
- Risk tolerance
FDA's Avastin decision is a breast cancer patient's worst nightmare
By: Sally C. Pipes | 12/26/10 9:05 PM
OpEd Contributor

On Dec. 16, the Food and Drug Administration made a decision that could cause thousands of breast cancer patients to lose their last hope. That day, FDA officials voted to revoke approval for Avastin for the treatment of late-stage breast cancer.

This move is a disgrace.

Medicare will keep covering Roche's Avastin
By Anna Yukhananov and Alina Selyukh
WASHINGTON | Thu Jun 30, 2011 7:31pm EDT

(Reuters) - Medicare will continue paying for Roche Holding's drug Avastin for breast cancer, regardless of what health regulators decide about the medicine's future, a spokesman said on Thursday.
Bevacizumab sterile compounds for wet AMD: Worth the risk?

POTENTIAL SAVINGS TO MEDICARE PART B AND BENEFICIARIES IF AVASTIN REIMBURSEMENT RATES HAD BEEN USED FOR ALL WET AGE-RELATED MACULAR DEGENERATION TREATMENTS, CALENDAR YEARS 2008 AND 2009

<table>
<thead>
<tr>
<th></th>
<th>Medicare Part B</th>
<th>Copayment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Part B Payment for Avastin</td>
<td>$42.58</td>
<td>$11.22</td>
</tr>
<tr>
<td>Less: Average Part B Payment for Lucentis</td>
<td>$1,624.34</td>
<td>$406.09</td>
</tr>
<tr>
<td>Difference in Payment</td>
<td>($1,581.76)</td>
<td>($394.87)</td>
</tr>
<tr>
<td>Multiply by: Point Estimate of Lucentis Treatments</td>
<td>696,927</td>
<td>696,927</td>
</tr>
<tr>
<td>Potential Savings Using Avastin</td>
<td>$1,102,373,342</td>
<td>$275,195,564</td>
</tr>
</tbody>
</table>

Source: Office of Inspector General, A-01-10-00514, September 2011
Fig. 1: Estimated Number of Treatments Paid by Medicare Part B in CYs 2008 and 2009

- Avastin: 57%
- Lucentis: 43%

Fig. 2: Estimated Medicare Part B Expenditures in CYs 2008 and 2009

- Avastin: 3%
- Lucentis: 97%

Source: Office of Inspector General, A-01-10-00514, September 2011
FDA Alerts Health Care Professionals of Infection Risk from Repackaged Avastin Intravitreal Injections

The U.S. Food and Drug Administration (FDA) is alerting health care professionals that repackaged intravitreal injections of Avastin (bevacizumab) have caused a cluster of serious eye infections in the Miami, Florida area.

The Florida Department of Health (DOH) notified FDA of a cluster of Streptococcus endophthalmitis infections in three clinics following intravitreal injection of repackaged Avastin. Investigators traced the tainted injections to a single pharmacy located in Hollywood, Florida. The pharmacy repackaged the Avastin from sterile injectable 100 mg/4 mL, single-use, preservative-free vials into individual 1 mL single-use syringes.

The pharmacy then distributed the Avastin to multiple eye clinics for use in treating patients. To date, FDA is aware of at least twelve patients in at least three of these clinics who had eye infection. While all of these patients had visual deficits prior to their injections with Avastin, some of these patients lost all remaining vision in that eye due to the endophthalmitis.

The agency and Florida health officials continue to investigate the cause of the infection. While the investigation is not yet complete, the common link for the infections is the pharmacy that repackaged the Avastin and the single lot of Avastin used in the re-packaging.

Health care professionals should be aware that repackaging sterile drugs without proper aseptic technique can compromise product sterility, potentially putting the patient at risk for microbial infections. Health care professionals should ensure that drug products are obtained from appropriate, reliable sources and properly administered.

Avastin solution for intravenous infusion is approved for the treatment of various types of cancers. Some physicians also prescribe Avastin off-label for the treatment of wet age-related macular degeneration, although Avastin is not currently approved for this indication. Lucentis (ranibizumab injection) has been approved by the FDA for wet age-related macular degeneration.

Health care professionals and patients are encouraged to report any adverse events, side effects, or product quality problems related with the use of repackaged intravitreal injections of Avastin to the FDA’s MedWatch Safety Information and Adverse Event Reporting program:

- Complete and submit the report Online: www.fda.gov/MedWatch/report.htm
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the
“A hundred grand. There’s ‘not much to lose’? I guess I’m not in your income bracket. Since that strikes me as a whole lot.”

“...We’re talking about your wife’s life here...I have to assume that money is a secondary issue at best, if it’s an issue at all.”

“So, if I say it’s an issue, I’m an animal, right? But even if I fall in line and say, by all means, doctor, do anything you can...because I love my wife and money is no object. Why do you assume I’ve got a hundred grand?”

“...It’s really Mrs. Knacker’s decision, when she wants to call off further treatments...she sounded keen to try it.”

“...I realize she’ll try anything. But it is not my wife’s decision if she’s not the one who’s going to pay for it.”

Goldman was overtly discomfited by this kind of talk. He kept averting his gaze, working his face without concealing his disapproval, and edgily hitting his keyboard’s space bar. “I want to be very clear, Mr. Knacker. This drug is our last hope.”
“My insurance carrier figured out long before my accident through some cost—benefit outcome analysis…that I’d be going home in three days. It was predetermined by the intersection of some billing code and the code of my medical condition, with only marginal consideration given to my progress or lack thereof. Or maybe it was determined all along by the intersection of Venus retrograde in Scorpio. Whatever the faceless bureaucratic or mystical reason, this is my fate. I’m going home in three days.”
“She needed a better plan, one that didn’t include her playing beanbag toss with Evelyn in the Alzheimer’s Special Care Unit. One that didn’t cost John a fortune to keep alive and safe a woman who no longer recognized him and who, in the most important ways, he didn’t recognize either. She didn’t want to be here at that point, when the burdens, both emotional and financial grossly outweighed any benefit of sticking around.”
T.B. Harlem (1940)
Alice Neel (1900-1984)
1940, American.
Oil on canvas. 76.2 × 76.2 cm.
National Museum of Women in the Arts
The Sick Child (1907)
Edvard Munch (186-1944)
Oil on canvas support: 1187 x 1210 mm
Tate Modern, London, England