

**Galveston Association of Island Neighborhoods  
and Galveston Citizens Police Academy Alumni  
Association**

**Community Bioethics Dialogue: Patient-Centered  
Outcomes Research**

**Final Report, March 27, 2014**

*A Partnership among the Galveston Association of Island  
Neighborhoods, the Galveston Citizens Police Academy Alumni  
Association, and the Institute for the Medical Humanities, University  
of Texas Medical Branch, Galveston*

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# **Galveston Association of Island Neighborhoods and Galveston Citizens Police**

## **Academy Alumni Association**

### **Community Bioethics Dialogue: Patient-Centered Outcomes Research**

#### **Final Report, March 27, 2014**

#### **Introduction**

To carry out the project, an Academic Support Team from University of Texas Medical Branch-Galveston (UTMB) formed a partnership with the Galveston Association of Island Neighborhoods and the Galveston Citizens Police Academy Alumni Association. The ethical questions to be addressed were determined by the funding agency according to the initial grant proposal. The main ethical questions addressed were, in general:

- What ought to be the role of patient-centered outcomes research (PCOR) and comparative effectiveness research (CER) in guiding health policy in the U.S.?
- How should PCOR and CER function in connection with the physician-patient relationship?
- What role, if any, should commercial interests play in determining PCOR and CER policy?

#### **Our Process**

An advisory committee was formed by the two community organizations, that met with the Academic Support Team between May and October, 2013 to plan the dialogues. The advisory committee oversaw the recruitment of participants from the two organizations and

provided meeting facilities. Since the project was overseen by the Sealy Center on Aging at UTMB, it was agreed that all participants should be 65 years of age or older.

Prior to the start of the dialogues, the Academic Support Team compiled a list of articles from medical journals and the lay press related to ethical issues in PCOR and CER (Appendix 1). We all were provided with 1-page summaries of these readings. Those of us who requested were also provided with a) complete copies of the articles and b) audio recordings of discussions about the articles produced by the Academic Support Team.

The dialogues occurred for two hours each week for six weeks during January and February, 2014. Case studies formed one basis for discussion during each session (Appendix 2). We were also encouraged to do independent research and to discuss our deliberations with friends and family in between sessions. The Academic Support Team provided a trained facilitator and recorder, and other members of the Academic Support Team attended and took notes during sessions.

Before the final dialogue session, the Academic Support Team compiled a list of ethical values gleaned from notes taken during Sessions 1-5. The list was provided to us before Session 6 and we were asked to agree or disagree with each ethical value statement, and if we agreed, to rank the statement as having high, medium, or low priority. We discussed the list extensively during Session 6, and the results formed the basis for the first draft of this report. The draft was presented to us on March 27, 2014 and any further disagreements resolved at that time. This final report is the result.

## Major Ethical Conclusions

The statements in this section include ethical values which we unanimously agreed to include, and to which all or most of us assigned the highest priority.

*Physicians and patients.* Ultimately, the goal of PCOR and CER is to have a positive impact on the care of patients and the improvement of patients' health. We believe that for those goals to be achieved, certain things must be true about how physicians and other health professionals relate to patients. (We insist that even if discussion sometimes focuses on "physicians," health care is best provided by teams of professionals, and all members of the team ought to be given recognition and held to high ethical standards.)

- Recommendations resulting from PCOR and CER can best be implemented in an environment of patient-centered care, which in turn requires that health team members have adequate time to talk with patients and fully address patients' concerns.
- Patient-centered care requires an effective partnership between the patient and the health team, with the avoidance of extreme power differentials. This must be implemented with an awareness that some health decisions are very complex, and that some patients will need more help than others to navigate complex health decisions.
- "Team" can apply to both sides of the physician-patient relationship. Patients will often participate more effectively in their own health care if they are assisted by patient advocates such as selected family members
- Despite the importance of the cost of health care as a policy concern, cost considerations ought not unduly dominate the way the health team approaches the patient. In particular, the team should fully inform the patient of all realistic treatment options regardless of

their cost, and the patient's quality of life should always loom larger than cost considerations in the team's thinking.

- In a patient-centered care environment, patients also assume ethical responsibilities. Patients (and their advocates) should try to become informed about their treatments and participate actively in decisions, rather than blindly trusting physicians. When requested, physicians should be prepared to recommend their preferred solution and the reasons why.

*Policies to control health care costs.* Once the appropriate patient-centered care environment is established, we affirm the ethical appropriateness of certain policies aimed at cost control and moderation.

- High health care costs represent a genuine ethical and policy problem for the U.S. Patients are harmed as health care becomes increasingly unaffordable and if taxes or insurance premiums rise inexorably. Simply ignoring costs is not an ethical option.
- Generally, PCOR and CER are helpful and should be promoted and funded.
- In seeking to control health care costs, the most ethical method is to selectively refuse to pay for measures that provide the lowest likelihood or amount of effectiveness, based on sound evidence. We should avoid any cost-containment scheme that denies treatment to any group based on presumed social worthiness.
- Policies based on the findings of PCOR and CER must take into account individual differences in how patients respond to treatments. "One size fits all" requirements are inappropriate. For example, we support robust appeals processes by which both patients

and health teams can challenge a denial of service by an insurer, when the clinical situation suggests that the patient could benefit from the treatment in question.

- A tiered system of coverage for non-urgent health problems is justified. Insurers may require patients to first try lower-cost treatment options that have a good chance of success, advancing to higher-cost modalities only if the less expensive ones fail.
- If an insurer (private or government) refuses to pay for a treatment, individuals who can afford it must be accorded the right to purchase the treatment with their own funds.
- If an insurer will pay for coverage for a lower-cost treatment, and the patient desires to purchase a higher-cost form of treatment for the same medical condition, the insurer should pay the equivalent of the lower cost, so that the patient only has to pay the difference (and not the full cost of the more expensive option) out of pocket.
- Recommendations arising from CER should be applied in the same way to public health policies as to individual treatment choices.
- We grappled with the question of what counts as adequate evidence of benefit to justify a policy decision that could allow or limit patients' access to treatment. We generally agreed that when there appeared to be sufficient evidence of level of benefit, policy choices ought to be made, even when conceivably, better quality evidence might be available some years in the future. The sticking point for some was assuring that there would be regular review of any resulting policy decisions when new evidence in fact became available.
- Policies designed to implement CER recommendations *should* take into account the relative costs of different tests or treatments. We specifically dissent from current Federal policies that discourage cost information from being considered.

*Influence of commercial interests.* We agreed that commercial interests, such as the private insurance, pharmaceutical, and medical device industries, present certain challenges for fair policies related to PCOR and CER.

- An organization free of commercial interests should become a “clearing house” by which the American public can be provided with evidence-based information about the effectiveness, safety, and costs of medical treatments.
- Transparency is essential. Standards for disclosing any commercial ties that might affect health decisions should be mandated and enforced for all parties—physicians, hospitals, insurers, government boards, etc.

### **More Problematic Ethical Conclusions**

For some of the other ethical issues we grappled with, it was harder to reach consensus.

*“Rationing.”* The word “rationing” engendered considerable debate. Opinions ranged from the view that the term “rationing” should not be used at all, to the view that rationing was already widespread within health care and that the real ethical question was a fair and open way to do it. We disagreed as to the extent to which merely reducing waste could limit the need for rationing, and whether sufficient funds could be diverted from other uses. There seemed to be less dissention if “rationing” was defined merely as the acknowledgement that resources are finite and are limited relative to the population’s desires for health services, and therefore that some limits need to be placed somewhere. However, no formulation allowed the group to reach a full consensus.

*Personal choice vs. limits.* Individual free choice is an important American value and we sought to find ways to maximize choice. In the end we confronted the fact that meaningful limits on costs are difficult to reconcile with maximal freedom of choice. Many, but not all of us, agreed that it became more ethical to limit the patient's choice of treatment when a high-cost treatment worsened the patient's quality of life while providing only a very slight extension of survival. Many, but not all of us, agreed with a proposal to restrict coverage for "minimally effective" treatments so long as the burden was spread fairly across the whole population and decisions were made by an open, democratic process. We generally agree that preserving the option for the individual patient to confer with the physician or health team and make a personal decision about a treatment, even if others judge the treatment to be high-cost and with low likelihood of meaningful benefit, is of ethical value, even if other ethical values have to take priority over it some of the time. We also generally agreed that "doing what's most patient-centered" does not necessarily mean "doing whatever the patient wants" as some patient choices are emotionally-based or ill-informed.

*A seat at the table for commercial interests.* We did not agree on the ideal role for commercial interests in deciding on policies that affect PCOR and CER funding and direction. Some argued that the only way for the insights provided by those who take an industry perspective to have effective influence over policy was to grant voting rights to those representatives. Others argued that they could still be effective sitting without a vote but able to participate in discussion, or simply giving testimony as requested without formally being a part of the policy board. We generally agreed however that no government policy board deciding on PCOR/CER should be made up of *a majority of* industry representatives with voting privileges.

*Personal responsibility for healthy lifestyle.* We remained quite divided over whether, or how, one's healthy or unhealthy lifestyle should play a role in what one pays for health insurance or what treatments one is entitled to.

*Incentives to use CER results.* In general we agreed that the reimbursement system should provide incentives for physicians to pay close attention to and use the results of CER in recommending treatments. However, it was also argued that the application of CER in this manner is part of being a good doctor, and thus no additional incentives should be needed.

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# **Appendix 1.**

## **List of Background Readings and Session Topics**

# Preliminary Schedule and Topic List: Community Bioethics Dialogue on PCOR/CER

## Week 1

### Case Studies: ALLHAT, Generic Drugs

**Topic: Ethics and cost containment: Is there an ethical mandate to contain health care costs?**

Brody, H. “Is There an Ethical Mandate to Contain Health Costs in the U.S.?”

### Topic: What is PCOR/CER?

Washington, A. Eugene, and Steven H. Lipstein. “The Patient-Centered Outcomes Research Institute — Promoting Better Information, Decisions, and Health.” *New England Journal of Medicine* 365, no. 15 (2011): e31. doi:10.1056/NEJMp1109407.

Coelho, Tony. “A Patient Advocate’s Perspective on Patient-Centered Comparative Effectiveness Research.” *Health Affairs* 29:1885-1890, 2010.

Wu, Albert W, Claire Snyder, Carolyn M Clancy, and Donald M Steinwachs. “Adding the Patient Perspective to Comparative Effectiveness Research.” *Health Affairs (Project Hope)* 29, no. 10 (October 2010): 1863–1871. doi:10.1377/hlthaff.2010.0660.

## Week 2

### Case Study: Vertebroplasty

**Topic: The potential impact of CER/PCOR on patient autonomy and the doctor-patient relationship (How can doctors continue to be patient-centered while applying population-based research? How can we make the research and its application more patient-centered? How would participants prefer to see PCOR results implemented in individual care/ doctor-patient decision-making? Should doctors and patients be tied down to what evidence shows works best?)**

Bensing, J. “Bridging the Gap. The Separate Worlds of Evidence-based Medicine and Patient-centered Medicine.” *Patient Education and Counseling* 39, no. 1 (January 2000): 17–25.

Buetow, Stephen, Linn Getz, and Peter Adams. “Individualized Population Care: Linking Personal Care to Population Care in General Practice.” *Journal of Evaluation in*

*Clinical*

*Practice* 14, no. 5 (October 2008): 761–766. doi:10.1111/j.1365-2753.2007.00938.x.

Chen, Pauline W. “A Tool to Strengthen the Doctor-patient Relationship.” *The Hastings Center Report* 39, no. 6 (November 1, 2009): 15–17.

Parker, Lisa S., and Howard Brody, “Comparative Effectiveness Research: A Threat to Patient Autonomy?” *Health Progress* 92 (5): 64-71, 2011.

Payne, Richard. “The Quality Mantra: Proceed Carefully.” *The Hastings Center Report* 39, no. 6 (November 1, 2009): 7-20.

Weeks, William Brinson, and William A Nelson. “Ethical Issues Arising from Variation in Health Services Utilization at the End of Life.” *Frontiers of Health Services Management* 27, no. 3 (2011): 17–26.

## Week 3

### Case Study: Rapid Approval of a Cancer Drug (Iressa)

**Topic: Pros: Using CER as a rationing criterion to reduce costs** (some of these articles are not necessarily “pro” but focus on how cost management might be implemented using CER). Many of these articles also address the reasons why cost might be problematic.

Brody, H. “Two Approaches to Rationing by Appeal to Evidence of Effectiveness”

Buyx, Alena, Daniel Friedrich, and Bettina Schöne-Seifert. “Rationing by Clinical Effectiveness.” *BMJ* 342:531-533, 2011.

Garber, Alan M, and Harold C Sox. “The Role of Costs in Comparative Effectiveness Research.” *Health Affairs (Project Hope)* 29, no. 10 (October 2010): 1805–1811.

Kreis, Julia, and Harald Schmidt. “Lessons from Abroad.” *The Hastings Center Report* 39, no. 6 (November 1, 2009): 20–22.

Robinson, James C. “Comparative Effectiveness Research: From Clinical Information To Economic Incentives.” *Health Affairs* 29, no. 10 (October 1, 2010): 1788–1795.

### Topic: Cons: Using CER as a rationing criterion to reduce costs

Mikochik, Stephen L. “Rationing Human Life: Health Care Reform and People with Disabilities.” *Issues in Law & Medicine* 26, no. 3 (2011): 199–205.

### Topic: Cons: The involvement of private industry in the PCORI (conflict of interest)

Selker, Harry P., and Alastair J.J. Wood. "Industry Influence on Comparative-Effectiveness Research Funded Through Health Care Reform." *New England Journal of Medicine* 361, no. 27 (2009): 2595–2597. doi:10.1056/NEJMp0910747.

## Week 4

### Case Study: Proton Beam Radiation

**Topic: Inherent limitations of PCOR/CER methodology** (averages, unable to predict individual patient outcomes; limits of RCT method; defining "effective"; etc.)

Alexander, C. Caleb, and Randall S. Stafford. "Does Comparative Effectiveness Have a Comparative Edge?" *JAMA* 301:2488-2490, 2009.

Berlinger, Nancy, and Anne Lederman Flamm. "Define 'Effective': The Curious Case of Chronic Cancer." *The Hastings Center Report* 39, no. 6 (November 1, 2009): 7-20.

Susan Gilbert. "The Nesting-Egg Problem: Why Comparative Effectiveness Research is Trickier than It Looks." *Hastings Center Report* 39(6):11-14, 2009.

Saver, Richard S. "Health Care Reform's Wild Card: The Uncertain Effectiveness of Comparative Effectiveness Research." *University of Pennsylvania Law Review* 159:2147-2207, 2011.

Saver, Richard S. "The New Era of Comparative Effectiveness: Will Public Health End up Left Behind?" *The Journal of Law, Medicine & Ethics: a Journal of the American Society of Law, Medicine & Ethics* 39, no. 3 (2011): 437–449. doi:10.1111/j.1748-720X.2011.00613.x.

## Week 5

### Case Study: Advanced Cancer treatment (Erbitux)

**Topic: Conclusions: Ethical values that should guide policy decisions about the use of PCOR/CER** (these are articles that cover general ethical patient care)

"CER Ethics Controversy Spills over to Health Debate." *Clinical Trials Administrator*, October 1, 2009. Academic OneFile.  
<http://go.galegroup.com/ps/i.do?id=GALE%7CA214561483&v=2.1&u=txshracd2598&it=r&p=AONE&sw=w>.

Patrick S. Duggan, Gail Geller, Lisa A. Cooper, and Mary Catherine Beach. "The Moral Nature of Patient-Centeredness: Is It 'Just the Right Thing to Do?'" *Patient Education and Counseling* 62:271-276, 2006.

Potera, Carol. "Dignity-driven Decision Making Improves Advanced-illness Care." *The American Journal of Nursing* 112, no. 9 (September 2012): 16. doi:10.1097/01.NAJ.0000418910.72042.cf.

Vladeck, Bruce C, and Erin Westphal. "Dignity-driven Decision Making: a Compelling Strategy for Improving Care for People with Advanced Illness." *Health Affairs (Project Hope)* 31, no. 6 (June 2012): 1269–1276. doi:10.1377/hlthaff.2012.0173.

Wynia MK, Von Kohorn I., Mitchell, P. "Challenges at the Intersection of Team-based and Patient-centered Health Care: Insights from an IOM Working Group." *JAMA* 308, no. 13 (October 3, 2012): 1327–1328. doi:10.1001/jama.2012.12601.

## Week 6

**Topic:**

## **Appendix 2.**

### **Case Studies**

## Despite Scientific Data, Physicians Underuse Cheap, Effective Drugs

Physicians continue to prescribe expensive brand-name drugs for high blood pressure despite solid evidence that older, cheap generics actually work better, experts said.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was carried out between 1994 and 2002, and was funded by the National Heart, Lung and Blood Institute of the National Institutes of Health.

Experts claimed that ALLHAT is a good example of “patient-centered outcomes research” because it did not look only at whether a drug lowered blood pressure. The trial studied outcomes that matter most to patients—death, heart attack, stroke, and the development of other serious diseases of the heart and blood vessels. ALLHAT also qualified as comparative effectiveness research (CER) because it asked which of several alternative treatments did better in preventing these bad outcomes.

ALLHAT was a real advance, experts commented, because the first research studies of treating high blood pressure (hypertension) were carried out with older classes of drugs, diuretics and beta-blockers. These trials showed benefits of drug treatment in preventing later heart attack and strokes. Since then, newer classes of drugs were introduced also to treat hypertension. The classes of special interest in ALLHAT were angiotensin-converting-enzyme (ACE) inhibitors and calcium channel blockers. No one had studied whether these newer drugs were better than the older classes of drugs in preventing the bad outcomes associated with untreated hypertension.

The hypertension portion of the ALLHAT trial reported in 2002 involved 33,357 participants aged 55 or older who had hypertension and at least one other risk factor for developing heart disease. The participants were randomly assigned to receive one of three drugs: a generic diuretic (chlorthalidone); an ACE inhibitor (lisinopril); or a calcium channel blocker (amlodipine). They were then followed for 4 to 8 years.

The main outcome the study looked at was either death due to heart or blood vessel disease, or a heart attack. They found that this outcome occurred with equal frequency in people receiving any of the three drugs.

The study then looked at a number of other outcomes, such as stroke, heart disease without heart attack, and heart failure. They found that for these other (secondary) outcomes, the diuretic (chlorthalidone) was superior to either of the other two drugs for at least some of the outcomes.

The authors concluded that overall, the diuretic (chlorthalidone) was superior to the other two drugs, and they also noted that it was considerably cheaper. They concluded that diuretics should be preferred as first-line treatment for hypertension.

After the ALLHAT trial was published, a number of papers appeared in medical journals disputing some of its findings and arguing that some of its methods were flawed. Experts consulted for this article, however, noted that the majority of these critical articles were written by physicians who had a financial tie to companies making the more expensive anti-hypertensive drugs. The majority of authorities who were financially neutral appeared to endorse the ALLHAT findings.

### Reference

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting-enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288:2981-2997, 2002

## Case Study: Generic Drugs

The investigative reporting service ProPublica released (Nov. 18, 2013; <http://www.propublica.org/article/medicare-wastes-billions-on-name-brand-drugs>) their findings that just 913 physicians across the US are costing Medicare an extra \$300 million a year. How? By prescribing brand-name drugs instead of generics at a much higher rate. These same physicians also seem much more likely to have gotten payments from drug manufacturers, like fees for giving lectures favoring brand-name drugs.

Other data showed that the low-income portion of Medicare Part D, the prescription drug benefit, could save \$1.3 billion each year in just seven drug categories, if generic drugs were more widely used.

What does this have to do with comparative effectiveness research (CER)?

It's usually said that CER is a relatively new idea and needs to be expanded. But one form of what could be called CER has been going on routinely for many years without fanfare.

Whenever a brand-name drug goes off patent, meaning that generic drug companies can offer low-priced competition, the Food and Drug Administration requires scientific evidence of what's called bioequivalence before permitting the generic drugs into the market.

"Bioequivalence" means that the science has to show that the generic drug, when ingested into the average human body, acts essentially the same way the brand-name drug does.

You could call this a form of CER because if the science is accurate, it means that the generic drug will show *comparative effectiveness* to the brand-name product—it should be just as good at treating whatever disease the patient has.

This form of CER is not properly considered patient-centered outcomes research because it only looks at the chemistry of how the drug is handled in the human body. Generic drug makers are not looking at the outcomes for the patients. But the ProPublica article mentioned two major clinic chains, in Chicago and Las Vegas, that stress cutting costs by using generic drugs wherever possible. Those clinics have reported success rates in lowering cholesterol and controlling diabetes that meet or exceed national standards—suggesting that the effects on patients and their health is, overall, equally good with generics.

**Question:** Given these facts, what do you think ought to be the policy for Medicare Part D?

1. Brand-name drugs cost more, so they must be better. Medicare should not use any generic drugs at all if a brand-name drug is available. The elderly, and especially low-income elderly who need a subsidy to afford drugs, deserve the very best.
2. Medicare should recommend prescribing generic drugs whenever available. However, if a patient wished to have a brand-name drug instead, the simple request should be enough to get the doctor to prescribe it and for Medicare to pay—there should be no requirement first to try the generic and see whether or not it works as well.
3. Medicare should favor prescribing generic drugs whenever available. Some patients, for reasons we don't fully understand, don't respond well to generics. For those patients who have been tried on generics and have not responded well, physicians should be allowed to prescribe brand-name drugs.
4. Medicare should pay only for generic drugs whenever available. Any patient who wants a brand-name drug instead of a generic, for whatever reason, should pay for it out of pocket.

## Case Study: Insurance Coverage for Treatment of Spine Compression Fractures

You are a member of a members' advisory committee for OurCare, the managed care insurance plan in your community. The plan's management is seeking your advice about treatment for spinal compression fractures. These broken bones occur in osteoporosis, when the bones become brittle (which mostly affects women after menopause). One of the backbones (vertebra) basically gets squashed between the two bones above and below. This produces pain that could be severe and could go on for weeks or months, but is not dangerous as the bone stays in place and does not usually press on any nerves or other structures.

A recently popular treatment for spinal compression fracture is vertebroplasty. This procedure involves sticking a needle into the affected bone and injecting a special cement. The idea is that the cement will stabilize the bone and lead to much quicker healing and overall, less pain. The first few, limited research trials showed improved outcomes in patient receiving vertebroplasty.

In 2009, two scientific studies involving a total of 202 patients compared two procedures: patients with compression fractures received either the vertebroplasty procedure with acrylic cement, or else a sham procedure in which no cement was injected. This was a double-blind trial, meaning neither the patients nor the doctors assessing their outcomes knew which patient received which procedure. Double-blind trials are considered the "gold standard" of scientific evidence because they do the most to eliminate possible sources of bias. Both studies showed no difference, in the end, between the vertebroplasty group and the sham (placebo) group.

Given this evidence, OurCare's medical director advises that the insurance plan drop coverage for vertebroplasty for spinal compression fractures. The typical cost per patient is about \$1500 for the MRI scan needed to characterize the fracture plus \$2500 for the actual procedure. The plan, the director argues, should invest this money in medical treatments that actually work, and return to the standard practice of covering appropriate pain relievers for patient with compression fractures while the bones heal on their own, as they virtually always do.

Two other members of the advisory board, Sally and Glenn, now get into an argument. Sally has a good friend who had a painful compression fracture and had a vertebroplasty done. She thought the procedure was marvelous and had very prompt relief of her pain afterwards. The friend now swears by the procedure and advises it for everyone who needs it—especially since it is so simple, just inserting a needle in your back, no need for a big operation. Sally argues that if her friend had such a fantastic benefit, surely OurCare should go on paying for the procedure.

Glenn argues that the advisory board has a duty to follow the best scientific evidence, which shows that vertebroplasty is probably no better than a sham or placebo procedure. There is no reason for OurCare to waste money on placebos, when there are so many other health needs demanding attention, to say nothing of the goal of keeping premiums affordable for everyone.

Sally replies, "Well, you say that my friend got better because of a placebo effect and not because of some acrylic cement being injected—so who cares, if she got better? Isn't that what matters? She paid her premiums for her insurance, and then she had this terrible back pain and needed help. If it costs a few thousand dollars to give her the help she needed, why should she be deprived of that?"

How are you going to vote on this issue?

Adapted from: Susan Gilbert, “The Nesting-Egg Problem: Why Comparative Effectiveness Research is Trickier than It Looks,” *Hastings Center Report* 39(6):11-14, 2009.

Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 361:557-568, 2009.

Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 361: 569—579, 2009.

## Case Study: Rapid Approval of a Cancer Drug

Iressa (generic name: gefitinib) is one of a new class of drugs for cancer treatment. Its manufacturer, AstraZeneca, asked for approval from the U.S. Food and Drug Administration (FDA) to sell the drug for treatment of non-small-cell lung cancer, the most difficult to treat form of lung cancer. The drug was intended as a third-line drug to be used in the most advanced cases of the disease, after two previous types of chemotherapy have failed.

FDA rules allow a company to seek approval under a fast-track program if the drug is a novel drug and addresses a serious, unmet medical need. For normal FDA approval, a cancer drug might have to be tested on many hundreds of patients and shown to improve survival. For the fast-track review, it might only be necessary to show in a smaller number of patients that the drug slows tumor growth. If a drug is approved on this fast-track basis, a company may be required to run further studies after the drug is on the market to prove that it's really effective. If the drug does not do well in those follow-up studies, the FDA could then withdraw the market approval.

AstraZeneca originally sought fast-track approval in 2002 and sent the FDA the results of a study, that showed that in 139 advanced lung cancer patients, Iressa slowed tumor growth in only about 10 percent. Experts who had recommended this standard for fast-track approval had stated earlier that in order to win approval, ordinarily a drug had to show tumor slowing in 20-30 percent of patients.

Apparently AstraZeneca was rather sure it would get quick approval of Iressa and so began a larger-scale study, called INTACT, which enrolled 2000 subjects and looked at survival as well as tumor shrinkage. The INTACT study had been completed as of September, 2002 and so the FDA had access to that information as it studied approval of Iressa. The INTACT study showed, unlike the earlier smaller study, that Iressa had no effect on tumor shrinkage. Worse, the drug also was shown not to improve survival.

The FDA scientific advisory committee considered the evidence about Iressa at a hearing on September 24, 2002. At that meeting, a number of cancer patients testified. Two patient organizations had identified these patients and paid their expenses to come to Washington to attend the hearing; both those organizations had received grants from AstraZeneca. Six patients testified how good a drug Iressa was in their experience and how they credited it with saving their lives. The scientific committee voted 11-3 to approve Iressa for marketing.

By December, 2004, there had been several new developments. First, Iressa had been found to cause a fatal pneumonia in about 2 percent of patients. Second, a further study had been done of Iressa's effectiveness which also showed it did not prolong survival. Third, there was now a new drug for non-small-cell lung cancer manufactured by another company, so Iressa was no longer the only chance for patients with that disease. The FDA advisory committee reviewed all this information, and could at that time have recommended that Iressa be taken off the market, but instead recommended that the drug be allowed to stay on the market.

When Iressa was in wider use, it reportedly cost about \$1800-2000 per month, and had to be taken indefinitely.

## Questions

1. Tumor size is not what is usually viewed as a "patient-centered outcome." Most people with cancer would be happy to learn that their tumors were shrinking, but only because

they thought that this had to mean that they'd either live longer, or else have fewer bad symptoms. If tumors shrink temporarily but the patient does not live any longer nor have any improvement in quality of life, most would be disappointed. Should the FDA be allowed to approve a drug based on this sort of non-patient-centered outcome?

2. The FDA committee's vote was heavily swayed by the testimony of actual patients taking Iressa. This testimony, apparently, was allowed to overcome scientific evidence showing no benefit from the drug. Isn't this the way it should be—if we believe in patient-centered outcomes, then we have to listen to patient's personal testimony and give that at least equal weight with large-scale scientific studies?
3. Some would say that the funding by the drug company was a biasing or distorting influence in the scientific hearing. Is this correct? Some would say that patients deserve to be heard and that all the drug company was doing was making it financially possible for these patients to travel to attend the hearing.
4. *Comparative* effectiveness research assumes that we have two drugs which each individually seems to be effective, and we want to know if one is more effective (or safer) than the other. Presumably Iressa could not undergo comparative effectiveness research because studies showed it not to be effective, period (at least in terms of survival). What role, if any, should comparative effectiveness research play in drugs for serious diseases like cancer?

Adapted from: Courtney Davis and John Abraham, "Desperately Seeking Cancer Drugs: Explaining the Emergence and Outcomes of Accelerated Pharmaceutical Regulation." *Sociology of Health and Illness* 33:731-747, 2011.

## Proton Beam vs. Standard Radiation Treatment for Prostate Cancer

*Background:* One treatment for prostate cancer that hasn't spread outside the prostate gland is radiation. This can be given in a standard way (intensity-modulated radiation therapy). Recently, with great fanfare, many hospitals have invested in proton-beam machines, that deliver radiation from a particle accelerator that costs about \$100-180 million to build. As a result, hospitals have to charge about twice as much for proton-beam therapy to recover their capital costs.

No controlled trials currently show that proton-beam radiation produces results that are any better than standard radiation. One type of trial that could address this question is a randomized clinical trial, where patients with prostate cancer are randomly assigned to standard or to proton-beam treatment. A different type of study could be done much more cheaply and quickly, by looking for existing patient outcomes in a large Medicare database called SEER. Advantages of a controlled randomized trial include being able to measure exactly what you want to, and being able to be sure that the difference in treatment caused any difference in outcomes, instead of those differences being due to some other variable that you don't know. Advantages of an observational study with an existing database, besides convenience, include very large numbers of patients and knowing that the treatments and outcomes are representative of what happens in the "real world" instead of the tightly controlled, artificial environment of a medical research study.

A large randomized controlled trial comparing proton-beam and standard radiation for prostate cancer is now underway but results are not expected for several years.

*The study:* A group published a comparative-effectiveness observational study comparing standard radiation with proton-beam therapy in 2012, based on an observational review of SEER data reflecting patient experience during 2000-2008. They were able to compare information about 6666 men treated with standard radiation and 684 men who received the proton-beam treatment. They found information about what happened to these men for about 45 months after their radiation treatment.

The outcomes the study looked at were common side effects of radiation treatment (bowel problems, hip fracture, urinary incontinence, and erectile dysfunction). They used whether the patient started a new course of prostate cancer treatment more than 9 months after completing radiation as a signal for possible recurrence of the cancer. (Since most men with localized prostate cancer survive more than 5 years after initial treatment, they were not able to use life or death as a study measure.)

The study results showed no difference between standard radiation therapy and proton-beam therapy in hip fracture, incontinence, erectile dysfunction, or need for further cancer treatment; the proton-beam group did have more bowel problems.

*Question:* Taking the results of this study, which course of action would you favor?

1. A randomized, controlled study is the only really reliable way to find out about the comparative effectiveness of these two treatments. We should go on using both treatments and continue paying for the proton-beam therapy for patients who want it and have it recommended by their physicians. If in the future, a randomized, controlled trial shows no difference, we can then re-evaluate this policy.
2. The observational study reported above raises questions about whether proton-beam therapy offers any advantages over standard therapy despite being twice as expensive. Since there is as yet no proof at all that proton-beam therapy works better, we should

regard proton-beam treatment as experimental only at this time, and *not* routinely pay for it with Medicare or insurance dollars. If after more research is done, there turn out to be clear advantages to proton-beam treatment, we can then re-evaluate this policy.

Sheets NC, Goldin GH, Meyer AM, et al. "Intensity-Modulated Radiation Therapy, Proton Therapy, and Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer." *JAMA* 307:1611-1620, 2012.

## Case Study: Advanced Cancer

Oncologist Dr. Tito Fojo and bioethicist Christine Grady wrote:

The all too common practice of administering a new, marginally beneficial drug to a patient with advanced cancer should be strongly discouraged. In cases where there are no further treatment options, emphasis should be first on quality of life and then cost. Although we recognize that oncologists are faced every day with dying patients who still want to pursue further therapy, we must avoid the temptation to tell a patient that a new drug ... is available if there is little evidence that it will work better than established drugs... that could be offered at a miniscule fraction of the cost and with possibly less toxicity.

To illustrate “marginally beneficial,” they report a large trial of the drug cetuximab (Erbix) for non-small-cell lung cancer. When added to two other standard drugs, cetuximab extended overall survival by an average of 1.2 months. Patients receiving cetuximab had more fevers, rashes, diarrhea, and reactions to the drug infusions. The cost of a full course of treatment with cetuximab at the time was about \$80,000.

Fojo and Grady went on to distinguish several things we could mean when we say that a cancer treatment is “effective”:

- The treatment could extend overall survival. As the cetuximab example shows, many drugs are approved that show only very small improvements in overall survival, so we could argue about how much survival on average is needed for a drug to be considered more “effective” than other drugs.
- A treatment could extend progression-free survival, the length of time a patient lives before the cancer starts to grow again. Most people would presume that if a drug extends progression-free survival, it must also extend overall survival, but a number of drugs have been disappointing in this regard.
- A treatment could allow a patient to live with an acceptable quality of life. As with cetuximab, some drugs that extend survival only slightly do so at a serious cost in terms of side effects and reducing quality of life for many patients.

### Questions:

1. In the current system, for those patients who have insurance and can get access to an oncologist for cancer treatment, the patient and oncologist together decide on what counts as a true benefit, what treatments should or should not be used, and so on. Often this amounts to the oncologist deciding, as many patients simply defer to the oncologist. Is there any reason to change this present practice?
2. An increasing number of cancer patients search on-line to find information about the drugs their oncologist recommends. What would count as an adequate on-line review of a drug like cetuximab, so that patients could make ideally informed choices?
3. Do you agree with Fojo and Grady that the cost of drugs ought to be considered as part of the judgment about whether they should be used?
4. Fojo and Grady’s recommendation, that oncologists might simply not mention to patients with advanced cancer that some newer, expensive drugs exist if there’s no good evidence that they extend survival more than existing drugs, might be viewed as inappropriately robbing patients of “hope” or their “last chance.” How do you assess these objections?

Fojo T, Grady C. How Much Is Life Worth: Cetuximab, Non–Small Cell Lung Cancer, and the \$440 Billion Question. *J Natl Cancer Inst* (2009) 101 (15): 1044-1048.