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Comparative Effectiveness Research in the United States

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INTRODUCTION

The one hundred and eleventh Congress acted in early 2009 to expand the funding for Comparative Effectiveness Research in the midst of an economic crisis and a failing health care system (“CER”). On February 17, 2009, President Barack Obama signed the American Recovery and Reinvestment Act of 2009 (“ARRA”). The Act provided $1.1 billion for conducting comparative effectiveness research of drugs, medical treatments, surgical procedures and other treatments for various conditions.1 This funding was provided to the National Institutes of Health (“NIH”),2 the Agency for Health Care Research and Quality (“AHRQ”),3 and the Secretary of Human Health and Services (“HHS”).4 The goal of this funding is to “conduct, support, or synthesize research that compares the clinical outcomes, effectiveness, and appropriateness of items, services and procedures that are used to prevent, diagnose or treat diseases, disorders and other health conditions”.5 As the congressional debate on health care reform grew during the first year of Obama administration and the first session of the one hundred and eleventh Congress, so too has the specific debate regarding CER. Opponents claim that CER represents governmental intrusion into health decisions that should be made in private, between the patient and the physician, and that it will lead to government rationing of health care. Proponents claim that with the advent of new technologies, new drugs and various

2 “The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the primary Federal agency for conducting and supporting medical research”.
3 See Agency for Healthcare Research and Quality, available at www.ahrq.gov, [hereinafter “AHRQ”]. “The Agency for Healthcare Research and Quality’s (AHRQ) mission is to improve the quality, safety, efficiency, and effectiveness of health care for all Americans. Information from AHRQ’s research helps people make more informed decisions and improve the quality of health care services. AHRQ was formerly known as the Agency for Health Care Policy and Research”.
4 “The Department of Health and Human Services (HHS) is the United States government’s principal agency for protecting the health of all Americans and providing essential human services, especially for those who are least able to help themselves”; see also, American Recovery and Reinvestment Act of 2009 (ARRA), Pub. L. No. 111-5, 123 Stat. 115 (2009) [hereinafter “ARRA”].
other treatments for disease conditions, it is imperative that we know "what works best in medicine".⁶

Historically, the practice of medicine has been a mix of science and art.⁷ A significant portion of the clinical practice of medicine, which is embedded in the science component, has been based on the knowledge and experience of physicians derived from education and training.⁸ In order to reach an optimal mix of science and art, there should be a harnessing of available knowledge on treatment methods for particular disease condition. The harnessed knowledge and the findings must then be integrated into the everyday practice of medicine. More importantly, the integration process must emphasize the balance between the expected benefits verses the costs associated with treatments.⁹ A gap in integration deprives patients of the opportunity of receiving the most efficacious treatment. It also affects the value associated with treatment options, which is dictated by the cost of the treatment and the benefits derived from them. This lack in value of health care received, in turn, will affect the affordability of health care for society as a whole.¹⁰ Therefore, creating avenues that enable development, dissemination and incorporation of available knowledge on any disease condition will eventually provide high quality health care in a cost effective manner.¹¹

This note will discuss the potential importance of CER to the US health care system and what we must and must not learn from other countries, particularly the United Kingdom, that have implemented CER systems for allocating government funds to health care. Part I will provide an overview on comparative effectiveness research and the need for CER in the US health care system. Part II will explain United Kingdom's CER system, called "National Institute for Clinical Excellence, also called "NICE", and how this system applies to the anti-cancer EGFR blocker Cerituximab (brand name Erbitux) and anticancer tyrosine kinase inhibitor Sunitinib (brand name Sutent). Part III will briefly describe the history of CER in the US. Part IV will discuss the obstacles and policy implications that the US might face in implementing CER. Part V will propose several regulatory approaches for implementing CER in the US and finally part VI will provide recent developments in the regulatory spending on CER funded by the American Reinvestment and Recovery Act of 2009.

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⁶ Nallamothu BK, Bradley EH, & Krumholz HM, *Time to Treatment In Primary Percutaneous Coronary Intervention*, 357 New Eng.J. Med. 1631 (2007). "Early administration of reperfusion therapy improves survival in patients with ST-elevation myocardial infarction by reestablishing coronary blood flow within the occluded infarct-related artery. Primary percutaneous coronary intervention (PCI) is superior to fibrinolytic therapy when performed rapidly by expert teams, but its effectiveness may be limited by delays in delivery. Recent national efforts are drawing attention to the importance of door-to-balloon time as a key indicator of quality of care for patients with ST-elevation myocardial infarction who are treated with primary PCI".


⁸ See id.


¹⁰ See id. at 331.

I. WHAT IS COMPARATIVE EFFECTIVENESS RESEARCH (CER)?

Generally, a traditional clinical trial of any given drug compares the safety and efficacy of a drug with that of a placebo. They do not provide data that compares the efficiency of the drug with two or more existing treatment options. Comparative effectiveness research addresses this by comparing a specific treatment option with one or more other drug, medical device, surgery regimen or other treatment option available for a particular disease condition. The information is tailored specifically to patient group or a subgroup.

If one medical provider could diagnose and treat a condition for $2000 while another medical provider diagnoses and treats the same condition for $4000, there is evidently a value gap in the cost-benefit analysis. CER will explore the value benefits associated with each treatment compared to its respective relative treatment option. With the information on the relative benefit of treatments, health care providers can curtail cost associated with treatments. CER will also enable the provider to choose treatment options that are clinically effective as well as cost effective. On the payor-side, the insurance companies can design value based insurance designs which compare the value gained by the patient with the cost associated with it. On the patient side, CER will provide a summary of efficacy, safety, and post market surveillance of different drugs used to treat the same disease condition and will determine value associated with each option. Based on the information from CER, patients can evaluate their treatment options and compare the cost of treatment under different providers.

One of the well-known clinical effectiveness research studies is the Diabetes Prevention Program sponsored by the Diabetes Prevention Program Research Group under the supervision of National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and NIH. The program compared lifestyle intervention to Metformin therapy in the prevention of diabetes. The study showed that intensive lifestyle therapy was more effective than Metformin therapy. Lifestyle intervention reduced the incidence of diabetes by 58 percent compared to placebo while the Metformin therapy reduced the incidence of diabetes by 31 percent compared to placebo.

In the present US health care system there is little information regarding which of the two treatments works more effectively on specific patients or whether the cost associated


14 Id.

15 Id.


19 See id. at 403
with each treatment renders value. First, the fee-for-treatment system favors the medical providers. As a result, even if a treatment shows little benefit or value, providers and patients tend to opt expensive treatments as long as the payment exceeds costs. Second, the fee-for-treatment system results in medical providers making decisions based on their judgments, experience and other evidence associated with their practice of medicine. Less than half of the medical decisions made in the US are based on evidence of the effectiveness of the treatment.

The Problem

Why Do We Need CER In The United States

The US health care system is in the midst of a tumult. The US spends twice per capita for health care compared to many industrialized countries. In 2007, US spending on healthcare was estimated to be $2.3 trillion or $7600 per person. After continued growth in spending and a change in the presidential administrations, the issue of health care has again reached the national stage with great vigor. Concerns include an increase in health care costs, decrease in the value gained, an increase in number of the people without health insurance, rise in the baby boomer generation, rise in medical litigation and people paying more to maintain their medical insurance. It is estimated that as of 2007, twenty-five million insured people from ages 19–64 are underinsured. Moreover, 42 percent of American adults are underinsured or uninsured. Most Americans are not covered for all medical expenses or conditions. Medical insurance might not cover certain conditions or certain diseases. Even though families are insured, the high cost of out-of-pocket expenses causes financial burdens on working class American families.

According to the Bureau of Economic Analysis, in 2007, an average American family spent approximately $6600 on health care. This cost is expected to increase significantly in the future. In 2016, the average family is expected to spend $9200 on health care. This increase is due to a number of factors, including an aging population, a growing number of uninsured Americans, and rising health care costs. The high cost of health care places a significant burden on American families, and it is estimated that 43 million Americans are uninsured, leaving them without the financial protection they need to pay for medical care.

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spent about 16.7 percent of their disposable income for medical care costs compared to other costs such as food (14.4%), housing (13.1%), and clothing and shoes (3.6%).

Rising health care cost has adverse affect on people with chronic conditions. A study conducted by the Agency of Health Care Research and Quality based on Medical Expenditure Panel Survey (MEPS) showed a prevalence of self reported chronic conditions in people of old age, mid life and earlier old age. This increase signifies a substantial out-of-pocket expense. Additionally, most people are reported to have more than one chronic condition. Families with members who have chronic conditions are 2.6 times more likely to spend more than $1000 for their medical care costs. The burdens imposed by chronic conditions tend to prolong for many years. Additionally, uninsured chronically ill patients had the highest medical care spending but were five times less likely to see a physician in a year. This signifies that chronically ill patients utilize more resources but receive limited benefits when compared to the rest of the patient population.

It is estimated that at the present rate, health care spending will consistently outpace the gross domestic product (GDP) growth by 20 percent by 2015, which would equal the present share of the entire federal budget. By 2015, the baby boomers will qualify for the Medicare benefits. By 2030, the Americans over the age of 65 will comprise one fifth of the population, and will consume 50 percent of the health care spending. The cost of prescription drugs has been on the rise during the past decade. Many blockbuster drugs that treat a rare disease condition represent a significant amount of cost to the patients. For Example, a blockbuster drug called Cerezyme (an analogue of the human enzyme β-glucocerebrosidase), which treats a rare and fatal disease called Gaucher disease costs more than $300,000 per year. The total estimated sale of Cerezyme is $1.1 billion, whereas the population affected by the disease around the world is only 5000 patients. The private insurance companies

31 Kathryn Anne Paez, Lan Zhao & Wenke Hwang, Rising Out Of Pocket Spending For Chronic Conditions: A Ten Year Trend, 28 HEALTH AFFAIRs 15-25 (2009).
32 See id.
34 See id.
35 See Cathy Schoen, supra note 23, at 718; see also Orszag, supra note 20.
37 Robert J. Samuelson, Rx for Health Care Pain, NEWSWEEK, Dec.17.2007
38 See Cerezyme, CEREZYME.COM, available at http://www.cerezyme.com/home/default.asp (last visited Nov 30, 2009) [hereinafter “Cerezyme”. Cerezyme is manufactured by Genzyme. It is “an analogue of β-Glucocerebrosidase produced by recombinant DNA technology. β-Glucocerebrosidase (β-D-glucosyl-α-acylphosphingosine glucohydrolase) is a lysosomal glycoprotein enzyme, which catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Cerezyme (imiglucerase for injection) is indicated for long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly”.
40 See id.
would reimburse for the cost associated with Cerezyme treatment. However, the amount of reimbursement largely depends on the negotiated rate between the insurance company and the hospital.\textsuperscript{41}

In view of the impending health care crisis in the US, CER in the US must first involve consolidation of all studies, clinical trials, post market surveillance and the like carried out in a therapy area for a specific disease condition. Second, it must apply the result of the studies to determine the value afforded by various treatment options available in the market. Third, it must weed out treatment options that are not beneficial to the patient population as a whole. In order to do so, we can use tools such as mathematical modeling, artificial intelligence algorithms, in addition to the regulatory approval processes.

The United Kingdom and Australia each operate review systems that adopt value associated with treatments, based on CER. In those countries, comparative effectiveness of treatments has proven to curtail the overall healthcare spending.\textsuperscript{42} The US has no such consolidated and comprehensive review system for medical treatments, drugs or medical devices.\textsuperscript{43} However, the US has the tools needed to integrate the scientific knowledge to the everyday practice of medicine. The system in the US that minimally resembles the review systems as adopted by the United Kingdom and Australia is the database of clinical trials maintained by the NIH. The clinical trial database, however, does not compare the results of distinct clinical trials of drugs or the relative treatment option in a specific therapy area to determine the clinical effectiveness or cost effectiveness.\textsuperscript{44}

According to the estimates created for the Commonwealth Fund Commission on a High Performance Health System, adoption of a CER regimen in the US could potentially provide a savings of $1.3 trillion in ten years.\textsuperscript{45} Moreover, the US does not have a nationalized medical recording system.\textsuperscript{46} In Denmark, a national information exchange repository contains patients' clinical information. This allows improved decision-making. Such a system in the US could provide savings of $88 billion in ten years.\textsuperscript{47} In sum, the American Reinvestment and Recovery Act aims to learn from the CER system of other countries and save costs associated with the US health care system.\textsuperscript{48}

II. COMPARATIVE EFFECTIVENESS RESEARCH IN THE UNITED KINGDOM

The United Kingdom operates a nationalized health care system.\textsuperscript{49} The government essentially determines the availability and effectiveness of treatment options through its Na-

\textsuperscript{41} See Cerezyme, supra note 40.
\textsuperscript{42} See Cathy Schoen, supra note 25, at 1753.
\textsuperscript{43} See Id.
\textsuperscript{44} See CLINICALTRIALS.GOV, http://clinicaltrials.gov/ (last visited Nov.12, 2009).
\textsuperscript{46} See Cathy Schoen supra note 23, at 1753.
\textsuperscript{47} Id.
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ational Institute of Clinical Excellence (NICE). The philosophy behind this approach is to increase the standard of care by introducing competition and patient choice. This philosophy has increased the quality of care in the UK where real improvements have been seen in deaths associated with patients suffering from cancer and cardiac problems.50

The role of NICE is to provide guidance in public health issues, clinical practice and new technologies. The objective of the agency is to evaluate the benefits associated with each treatment and determine the cost value of each treatment in relation to the benefits.51 To achieve this goal, NICE compares different treatments for a specific disease condition by the use of statistical methods and systematic review processes.52 The processes are transparent and it involves and encourages participation from the industry, academia and patient groups.53

In order to evaluate each proposed treatment under study, NICE calculates the cost per Quality Adjusted Life Year, also called QALY. The QALY computation is based on a mathematical model.54 The model takes input variable measurements based on the effectiveness of the drugs under comparison, the time gained by the treatment, the quality of life improvement rendered by the treatment, the disease progression and other time scales involved in the process. The rationale behind the cost per QALY evaluation is that a drug that extends the lifetime of a patient must not be one that makes the patient spend the extended lifetime in pain. For example, the cost per QALY analysis might analyze whether a month gained by a cancer treatment can be valued at $1000, $10,000 or $100,000.55 The assessment team combines the quantity of time a drug might provide to the life span of the patient with the quality of time.56 Based on the result, the researchers set a threshold point. At the threshold point, the cost associated with the treatment no longer adds value benefit to the patients.57 NICE does not support treatment options that have a QALY factor beyond the threshold point. Once the team determines the QALY factor, the result is returned to the appraisal committee. The appraisal committee consists of medical practitioners, researchers and lay people. This committee determines the guidelines for treatment based on the QALY factor. Generally, all recommendations with a cost per QALY value less than £30,000 are approved. Any recommendation that is higher than the limit of £30,000 is not approved. This type of decision-making is not free from debate.58 Critics argue that the quality of life cannot be determined on the basis of mathematical terms and such threshold values, particularly in life threatening diseases, demeans patient population. They claim that the process creates obstacles for patients who are willing to receive the drug, especially those who can afford the cost of the

50 See id. (“There have been massive improvements in waiting times for care and in general patient satisfaction with the NHS, as well as real improvements in outcomes (fewer deaths from cardiac causes and from cancer), but there has not been a clear correlation between the amount invested and hard health outcomes, and Britain’s Audit Office has raised doubts about the link between productivity and salary increments”).
52 See id.
53 See id.
54 See Cathy Schoen, supra note 23.
55 See id.
56 See Kerr, supra note 49.
57 See id.
58 See id.
On the other hand, the economists argue that such a system is the best available option in CER research and thereby provides an effective cost benefit analysis of medical treatments.  

### NICE Systematic Review Of Cetuximab

Cetuximab (brand name Erbitux) is a chimeric monoclonal antibody that inhibits intercellular signaling through the Epidermal Growth Factor (EGF) receptor. It is used to treat metastatic colorectal cancer, as well as head and neck cancer. Cetuximab blocks EGF receptors (EGFR), thereby inhibiting the proliferation of cells that depend on EGFR activation for growth and downstream signaling.

In June 2009, NICE recommended the use of Cetuximab in combination with chemotherapy as a first line of therapy for the treatment of metastatic colorectal cancer. The guidelines required that the patient meet two additional criteria. First, the patient must present as a potential candidate for curative surgery. Second, the cancer should have spread only to the liver and patient must have a normal, or wild-type, K-ras tumors. In addition, the guidelines specifically mentioned that the patient should continue the treatment for only 16 weeks. After 16 weeks, the patient is to be evaluated for liver metastasis. These guidelines are based on two randomized clinical trials submitted by the manufacturer: (1) CRYSTAL (Cetuximab combined with iRinotecan in first line therapy for metastatic colorectal cancer), which is a phase III multicentre randomized clinical trial that compared treatment with Cetux-

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59 See id.
60 Id.
62 See id.
63 See Robert M. James et al, K-ras Proto-Oncogene Exhibits Tumor Suppressor Activity As Its Absence Promotes Tumorigenesis in Murine Teratomas, 1 MOLECULAR CANCER RESEARCH 820-825 (Sept. 2003), available at http://mcr.aacrjournals.org/content/11/11/820.full.pdf+ (last visited Nov 30, 2009) (“Ras proteins transduce signals from membrane-bound receptors via multiple downstream effector pathways and thereby affect fundamental cellular processes, including proliferation, apoptosis, and differentiation. K-ras activating mutations play a key role in neoplastic progression and are particularly prevalent in colorectal, pancreatic and lung cancers”), FDA, Cetuximab (Erbitux) and Panitumumab (Vectibix), available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm172905.htm (last visited Nov 13, 2009).
65 See id.
66 See id. See also Robert M. James et al, K-ras Proto-Oncogene Exhibits Tumor Suppressor Activity As Its Absence Promotes Tumorigenesis in Murine Teratomas, 1 MOLECULAR CANCER RESEARCH 820-825 (September 2003), available at http://mcr.aacrjournals.org/content/11/11/820.full.pdf+ (last visited Nov 30, 2009) (“Ras proteins transduce signals from membrane-bound receptors via multiple downstream effector pathways and thereby affect fundamental cellular processes, including proliferation, apoptosis, and differentiation. K-ras activating mutations play a key role in neoplastic progression and are particularly prevalent in colorectal, pancreatic and lung cancers”).
imab in combination with Folfiri and treatment with Folfiri alone; and (2) OPUS (OxaliPlatin and cetUximab in first-line treatment of mCRC), a phase II randomized clinical trial, which compared Cetuximab in combination with Folfox and treatment with Folfox alone.

The appraisal committee considered the analysis of clinical effectiveness and cost effectiveness of Cetuximab. In order to assess the accuracy of testing on patients with the K-ras mutation gene, the committee reached out to clinical specialists. The committee was concerned about the statistically non-significant progression of the survival rate in the two trials. However, they based their assessment on the reassurance of clinical specialists that Cetuximab played a primary role in shrinking secondary liver metastases and that it enabled curative liver resection in people with K-ras wild-type metastatic colorectal cancer. In evaluating the cost-effectiveness, the QALY factor for Cetuximab in combination with FOLFOX as opposed to FOLFOX alone was between £26,700 as estimated by the manufacturer and £33,300 as estimated by the Decision Support Unit (DSU) of NICE. This was within the threshold limit established by NICE and the appraisal committee approved Cetuximab as a first line therapy for treating metastatic colorectal cancer.

NICE Systematic Review Of Sunitinib

The evaluation of Sunitinib (brand name Sutent) for the treatment of kidney cancer caused some trouble for NICE. Sunitinib, manufactured by Pfizer, is indicated for the treatment of gastrointestinal stromal cell carcinoma and advanced renal carcinoma. Sunitinib inhibits multiple tyrosine kinases that play a role in tumor growth and cancer metastasis. During the initial evaluation, NICE concluded that the price of Sunitinib outweighed its...
clinical effectiveness and, therefore, did not exhibit value. This decision resulted in patient outcry and physician disapproval of using NICE’s system used to evaluate drugs that treat small patient population affected by rare diseases. The media questioned NICE’s evaluation strategies, particularly the use of a mathematical model. They suggested that mathematical models are primarily designed to test the clinical effectiveness and cost effectiveness of drugs in large groups of patients. Following the negative response, NICE reevaluated its assessment strategies. The reassessment was in part due to the decision of Pfizer to provide Sunitinib free of cost for the first round of treatment. In spite of the heavy discount, the drug was still very expensive. However, NICE claimed that it was “a significant step-change in treating a disease for which there is currently so little to offer patients”. This led to the approval of Sunitinib.

These two case studies on NICE’s evaluation strategies elucidates three important factors about Comparative Effectiveness Research. First, CER is influenced by social, economical and political factors and requires cooperation between patients, physicians, payors, pharmaceutical and biotech industry and the government agency responsible for the approval of the drugs. Second, without hard assessment on the value obtained by drugs and the cost involved, the cost of health care will triple in the next few decades. Therefore, CER is a necessary mechanism. It is advancement in the right direction that might improve the quality of health care services and curtail the health care cost. Third, NICE’s guidelines are not etched in stone. The guidelines must be flexible, transparent, adaptable to necessity, patient and physician responses and other ethical concerns.

III. COMPARATIVE EFFECTIVENESS RESEARCH IN THE UNITED STATES

History

Comparative effectiveness research in the US has been in progress for the past two decades. During 1989, the Agency for HealthCare Policy and Research (AHCPR) established Medical Treatment Effectiveness Program (MEDTEP). The objective of MEDTEP was to fund research for determining effectiveness of treatments, develop guidelines and other databases. In 1992, the Congress directed AHCPR to include cost effectiveness and clinical effectiveness of treatment options in its MEDTEP program. The resulting criticism against the program led the Congress to decrease the budget of the agency by 20 percent; the MEDTEP program eventually ended.

79 See Susan Mayor, NICE recommends kidney cancer drug it previously rejected on cost grounds, BMJ.com, (Feb. 9, 2009), available at http://www.bmj.com/cgi/content/extract/338/feb09_2/f499 http://www.bmj.com/cgi/content/extract/338/feb09_2/f499 (last visited Nov. 13, 2009).
80 Id.
81 See id.
83 Id.
84 Agency of Health care Policy and Research, which was later called as Agency of Health care Research and Quality (AHRQ).
In 1999, the agency was renamed as Agency for Health Care Research and Quality. AHRQ has many centers that carry out health care research. In 1999, the Food and Drug Administration Modernization Act authorized AHRQ to conduct research on risks, benefits, cost effectiveness and optimal use of drugs, biologics and medical devices around the nation. The research was to be performed in conjunction with the FDA, academic institutions and health care industry. The Medicare Prescription Drug, Improvement and Modernization Act (MMA) of 2003 authorized $50 million for AHRQ to conduct research on clinical effectiveness and outcomes on pharmaceuticals, medical devices and health care services. Based on the allocation, the agency created programs such as DEcIDE and Evidence based Practice Center’s Program (EPCs) to effectively analyze the cost effectiveness of health care through technology assessments. Since 1985, the Technology assessment Center (TEC) of Blue Cross Blue Shield had evaluated the relative effectiveness of various treatment options on the basis of lifetime and quality of life. In 1999, AQHR funded TEC as an Evidence Practice Center. The Department of Defense (DOD) established Pharmaco Economic Center (PEC) in 1992 to improve the clinical, economic, and humanistic outcomes of drug therapy in support of the readiness and managed healthcare missions of the Military Health System.

In addition to AQHR, many non-profit agencies have been involved in CER. One among them is the Consumer Reports Best Buy Drug Projects, which evaluates the drug prices and effectiveness of drugs. It provides free report on its website. Similarly, ECRI, a non-profit organization provides health care and effectiveness assessments. Many for profit organization also develop clinical effectiveness information to support their decision-making..

87 See AHRQ, supra note 3.
89 See Mark Helfand, Incorporating Information About Cost -Effectiveness Into Evidence -Based Decision Making, 7 suppl. II MEDICAL CARE 33, 34-35-43 (July 2005). See also GRETCHE N A. JACOBSON, CONG. RESEARCH SERV., COMPARATIVE CLINICAL EFFECTIVENESS AND COST EFFECTIVENESS; BACKGROUND, HISTORY, AND OVERVIEW (October. 15, 2007).
IV. OBSTACLES AND POLICY IMPLICATIONS OF CER IN THE UNITED STATES

Role Of The FDA In Evaluation and Implementation Of CER

Laws regulating drug discovery, development and commercialization began with the Federal Food and Drug Act of 1906\(^{94}\), followed by the Federal Food, Drug and Cosmetic Act of 1938,\(^{95}\) and the Biologics Control Act of 1902.\(^{96}\) The laws have changed over time with the evolution of science, technology and medical practice. The recent Food and Drug Administration Amendment Act of 2007 (FDAAA)\(^{97}\) provides the Food and Drug Administration ("FDA") with significant power to regulate safety, post market study and surveillance of drugs, biologics and medical devices. In light of the need for comparative effectiveness research in the US, the FDA should be provided with the authority to set priorities, to compare various treatment options and to determine which treatment works best. The FDA has the scientific and technical expertise to engage in the process of CER.

During the next several decades, CER along with post market approval safety studies and risk evaluation and mitigation strategies codified in FDAAA\(^{98}\) may become the source for the most important advancements in laws regulating the discovery, development and commercialization of drugs, biologics, medical devices and advanced therapies. If carried out correctly, CER has the potential of becoming a repository of knowledge that summarizes and compares various discrete studies that aim to cure a specific disease.\(^99\) Thereby, it would enable the payor's, the patients, the policy makers and the practitioners to use the resources in the most efficient manner.

CER And Industry's Incentive To Innovate

Adoption of CER in the US poses many problems. First, there exists an argument that CER will undercut the incentive for the life science companies to innovate. The response to this argument is two-fold. First, if the US invests in and adopts a comprehensive CER for health care products such as drugs, biologics, medical devices and other advanced therapies, the regulatory agency responsible for its administration, might require manufacturers to provide information that compares the efficacy, safety and cost effectiveness of their product to those available in the market. Although the CER regime of this sort would press the health care industry to expand the scope and size of clinical trials and add the costs associated with conducting clinical and regulatory development, it will force each participant in the industry to evaluate its pricing and drug development strategies.\(^{100}\) The cost and complexity of complying with such a regime of CER could mean fewer new molecular entities will be discov-

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\(^{95}\) Federal Food, Drug and Cosmetic Act of 1938, 21 USC § 301.
\(^{96}\) Biologics Control Act, Pub. L. No. 57-244, 32 U.S. Stat 728 (July 1, 1902).
\(^{97}\) Food and Drug Administration Amendments Act, 21 USC § 301 [hereinafter "FDAAA").
\(^{98}\) Id.
\(^{100}\) Avalere Explores Impact of Comparative Effectiveness Research on Healthcare Innovation, AVALERE .NET (Nov. 17, 2009), http://www.avalerehealth.net/wm/show.php?c=1 (last visited on Nov. 31, 2009) [hereinafter "Avalere"].
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ered and developed as early stage pipeline candidates, fewer surviving to the late stage pipeline. In a CER regime of this sort, industry participants will have to live by the paradigm: “survival of the fittest”.101 On one hand, it will result in the availability of more capital investment to explore areas and technologies that have not yet been explored. The industry will have fewer incentives to discover and develop a “me too drug or device”. Instead, the industry will channel the available resources to explore new areas of sciences and narrowly defined markets that hold therapeutic and commercial potential102 such as personalized medicine and nanomedicine.103 On the other hand, the FDA, will have to engage in the approval process of drugs which otherwise would not be approved by FDA due to the lack of guidelines or the frame work that is required for the approval process.

We live in an era where gene matrixes and mRNA analysis are effectively used to decode the DNA of a disease-causing gene.104 Without effective CER regulations and implementation, such groundbreaking technologies will not be effectively used to provide cost effective medical options. Instead, they might end up as one of the many means of achieving an effective medical treatment.105 This is a double-edged sword for both the industry and the FDA. Participants of the industry would have to differentiate themselves from the others in their discovery, development and commercialization efforts, whilst the FDA must endeavor to approve drugs that hold promise in narrower therapeutic areas. The drugs that are approved under such regulations might hold greater promise for the cost effective and clinically effective treatment of diseases.106

Healthcare In The US

The US health care system is dissimilar to that of the UK. The US healthcare system reflects the American way of life. Therefore, there exist serious doubts whether adopting a threshold cost per QALY factor similar to that of UK is possible in the US. Adopting a regime that determines the availability of a drug or treatment based on mathematical models and systematic evaluation strategies might give rise to ethical concerns in the practice of medicine as well as drug discovery and development efforts.107 Moreover, it can also be argued that the US Constitution affords right for health care; any effort to limit an individual’s access to medicine violates his or her constitutional rights. These arguments require an in depth analysis of constitutional and ethical concerns associated with CER and, thus are beyond the scope of


102 Alvin Mushlin & Hassan Ghomrawi, Health Care Reform and the Need for Comparative Effectiveness Research, 362 New Eng. J. Med., e6(2) [hereinafter Mushlin & Hassan”].


104 See id.

105 See Mushlin & Ghomrawi, supra note 102, at e6(1).


this note. Considering the impact of health care spending on the US economy, the theme that emerges is the US must adopt a CER regime of some sort that effectively determines the value afforded by different medical options and restricts those options that provide lesser or no value benefit to the patients. For example, inexpensive diuretic medications are shown to prevent heart attacks more effectively in Prevent Heart Attack Trial (ALLHAT) than expensive angiotensin converting enzyme inhibitors, calcium channel blockers, and alpha-blockers.

User Redefined

In the context of CER, the concept of the “user” of products as discussed by the commentators seems to be an evolving concept. In 1963, the US District Court for the District of Columbia in Stottlemire v. Cawood and Parke Davis Company held that prescription drugs do not necessarily require that warnings be directed towards the general public. In 1969, the US Court of Appeals for the Eighth Circuit in Sterling Drug Inc. v. Yarrow held that “the manufacturer could be held liable for the injury resulting from the failure to give a warning reasonable under the circumstances.”

In both these cases the Court relied on the learned intermediary doctrine to determine that physicians comprise the target audience or end user for the purposes of determining the appropriateness of the respective labeling. In 1985, in MacDonald v. Ortho Pharmaceutical Corporation, the Massachusetts Supreme Judicial Court held that the manufacturer of birth control pills owe a direct duty to warn the patient about the risks involved with the drug. The Court defined the target audience for labeling information as the patients. In 1980, in Pharmaceutical Manufacturers v. Food and Drug Administration, the Court of Appeals for the Third Circuit held that under the provisions of Federal Food, Drug and Cosmetic Act of 1938, “the FDA was within its statutory authority to require patient package inserts where it found that without the insert, the estrogen labeling failed to reveal facts of consequences resulting from the use of the drug”.

These cases demonstrate the evolution of laws, which defines the “user” of the information provided by the drug manufacturers. The concept of CER prompts the question, who is the “intended user” of the CER information? The critics argue that the concept of CER is analogous to defining the “payor” as the intended user. They claim that since the information obtained through CER will help payors in their decision making process, CER effectively ignores the patient and physician classes and provides commercial empowerment to the payor class.

Ethical issues could be averted by drafting policies that involve academia, industry and practitioners in the assessment processes and by making the decision-making more transparent. The question whether CER violates individual’s constitutional rights is a subject for another article.


Id. at 99.


See Sterling Drug, Inc. v. Yarrow, 408 F.2d 978, 993 (8th Cir. 1969).

Id.


Id.
V. PROPOSED PLANS FOR IMPLEMENTATION OF CER IN THE UNITED STATES

This section proposes a three level plan for implementing CER in the US.

Physicians – The Implementors Of CER

Key to any successful legislation is the proper implementation at the most basic level. In CER, the basic implementors are the physicians. It is the physician who decides which drug to prescribe to the patient. In consultation, with the patients, they determine the cost associated with medical care. Any cost effectiveness analysis must directly address the physicians. One of the factors behind the success of the UK’s health care system is the strength of the primary care practice in the UK. The primary care physicians in the UK focus on the health of the patient as a whole rather than on one particular organ. They tend to use the help of specialty practice only when they really need it. In the US, the practice of medicine has a gross deficit of general practitioners of medicine. Meanwhile, specialty practitioners of medicine are increasing at a steady rate. The main reasons for this discrepancy are the expensive technologies that are being used and the pay-for-performance feature in the practice of medicine. Consequently, the specialty practice has the incentive to use expensive tests in lieu of the cost effective tests. Therefore, a regulation that curtails the cost of the procedure or bases the fees on the outcome of the procedure will not remedy the problem. This is because the amount charged for the procedures are completely at the will of the physicians and they control the volume at large. Therefore, one of the proposed solutions is limiting the pay-for-performance programs and turning the focus towards the practice of primary care medicine.

The United Kingdom’s Audit Office raised doubts about the link between the productivity and the salary increments of physicians in the UK when they found discrepancies behind the amount spent on health care reform and statistics on hard-health outcomes. Similarly, in the US, the pay of the physician correlates to the amount of expensive procedures prescribed and the volume at large. Such practices of medicine and payment methods affect the affordability of the society as a whole. The pay-for-performance system must be set such that it provides incentives for the physicians for providing higher quality care in a cost effective manner.

Expensive Health Care verses Quality Health Care

There must be a basic shift in the public notion regarding entitlement to expensive health care in the US. In general, the US economy cannot afford to make expensive procedures available to each patient into boundless future. It is imperative to find the balance between expensive health care for all and value based health care for all. This requires answers.

117 See Relman, supra note 115.
118 Id.
119 See Kerr, supra note 49.
120 See Avalere, supra, note 100.
to hard questions such as, is it cost effective and is it beneficial to have patients in the emergency room for simple diagnostic treatments that could be remedied at home? When does having a patient in a hospital bed provide value for the system in terms of cost of the bed, labor and other resources? Such regulation requires public involvement, education and public support. Physicians could be given the responsibility of explaining to the patients when they should be in a hospital bed and what other treatments could be practiced at home or at lower cost. This represents a need for shift in public's notion about health care in general and the need for more focus on general practice of medicine.121

**Prevention Better Than Cure**

Practice of medicine in the US is largely defensive in nature. The medical practitioners fear malpractice suits. Therefore, they are pressed to prescribe tests, which determine that the patient is not suffering from a specific disease condition, rather than prescribing tests that determine whether the patient is suffering from a said disease condition. This is one of the reasons why specialty practitioners thrive in the US, unlike in the UK.122 In spite of billions of dollars spent on health care each year, the patient population in the US is, on average, sicker than in many other countries. The US is ranked 54 -55 in the health care around the world.123

One of the methods of implementing CER is by practicing preventive medicine. About 7.8 percent of the US population suffers from diabetes. This amounts to approximately 23.6 million children and adults in the US. Every year an additional 1.6 million people under the age of 20 are diagnosed with type II diabetes.124 The cost associated with treating diabetes is $174 billion.125 However, type II diabetes, to an extent, is a preventable disease. Life style interventions such as proper diet, exercise and weight management can effectively prevent or control the disease in an efficient manner.

Similarly, vaccinations are an important source of preventive medicine for both children and adults. According to Center for Disease Control, pneumonia and influenza are fifth leading cause of death in the US, primarily for adults greater than 65 years of age. This figure has great impact on the health care cost in the US.126

Obesity is another therapy area that could be effectively prevented or controlled by life style interventions. The US spends more than $47 billion combating obesity each year.127 The factors needed for practicing preventive medicine are public education and strict regulations. Healthy diet for children, regulation on industry that markets sugar drinks, regulations on smoking, publishing caloric value of meals are few of the possible efforts that can enhance

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121 See Ann C. Bonham and Mildred Z. Solomon, Moving Comparative Effectiveness Research Into Practice: Implementation Science And The Role Of Academic Medicine, 29 HEALTH AFFAIRS, no. 10, 1901 (2010).

122 See Kerr, supra note 49.


125 Id.


COMPARATIVE EFFECTIVENESS RESEARCH

the practice of preventive medicine. The practice of preventive medicine must begin in medical schools. Aspiring medical practitioners must be able to provide the best treatments for the patients at a cost effective manner without the fear of litigation.

Methods of implementing CER are not simple. It requires a delicate balance between the American ways of life; incentive to innovate in pharmaceutical industry and effective regulatory or statutory guidelines that provide cost effective and clinically effective treatment options that are affordable to the entire society.

VI. RECENT DEVELOPMENTS

In June 2009, Institute of Medicine ("IOM") and the Federal Council for Coordinating Comparative Effectiveness Research issued reports on priority topics and future research engagements for the purpose of implementation of CER. The Federal Coordinating Council’s report to the President and the Congress identified prioritization criteria for conducting CER. Among the reported criterion are identifications of subgroups and priority populations which include: women, minorities, individuals with disabilities, children, people with multiple conditions and elderly population. The report stressed that the aforementioned priority groups should be studied in an effort to reduce the economic burden they exert on the US health care system, and to adequately represent such health conditions in the various research mechanisms. The report also set a long-term operation of CER, which involves continuous analysis of the CER instrument, determining the gaps that exist in the CER instrument and setting priorities accordingly. Additionally, the Patient Health Patient Protection and Affordable Care Act of 2010 provided funding for CER through 2019. This act sets priorities and established research agendas to the stakeholders of CER.

Tracking The Federal Spending on CER

Based on publicly available information concerning disbursement of American Reinvestment and Recovery Act funds for CER, as of August 4, 2010, $700 million has been provided to AHRQ and $400 million has been provided to Office of Secretary of Health and Human services. Out of the $700 million allocated to AHRQ, $400 million has been provided to NIH. As of August 4, 2010, 82.8 percent of $1.1 billion from ARRA has been accounted for. Out of the 82.8 percent, just less than 46.4 percent has been used for activi-

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128 Ari Hoffman et al., How Best To Engage Patients, Doctors, And Other Stakeholders In Designing Comparative Effectiveness Studies, 29 HEALTH AFFAIRS, 29, no. 10, 1834 (2010).
129 Id.
130 Id.
131 COMM. ON COMPARATIVE EFFECTIVENESS RESEARCH PRIORITIZATION, INST. OF MED. INITIAL NATIONAL PRIORITIES FOR COMPARATIVE EFFECTIVENESS RESEARCH. (National Academies Press; 2009).
135 Id.; see also NIH Research Portfolio Online Reporting Tools (RePORT): RePORT expenditures and results (RePORTER) NAT'L INSTIT. OF HEALTH; available at http://projectreporter.nih.gov.ezproxy.hofstra.edu/reporter.cfm.
136 Id.
Evidence development and synthesis involves collection of evidences through various methods and development of models to synthesize collected evidences on a given therapeutic area. The entity involved in granting the funding for evidence development and synthesis is the NIH. Infrastructure development involves developing methods to analyze data obtained through routine observational studies in patients and aims to study the cost, safety and effectiveness of treatments. The granting entity for development of methods and infrastructure is the Office of Secretary, Health and Human Services. Dissemination of evidence to different stakeholders of CER involves developing various methods for affording availability of CER data to payors, physicians, patients and policy makers. The entity involved in granting the funding for dissemination of evidence is the Office of Secretary, Health and Human Services. Stakeholder engagement involves development of citizen's forum for obtaining public input, development of horizon scanning systems to identify areas for future research and medical interventions. The entity involved in granting the funding for dissemination of evidence is the AHRQ.

NIH has funded 165 grants totaling $200 million for conducting CER research. The funds were awarded from the $400 million that was allocated for NIH under American Reinvestment and Recovery Act. Out of $200 million, 21 percent of the funding focused on oncology and hematology, 19 percent cardiovascular and peripheral vascular diseases and 15 percent to psychiatric diseases. Of the top 10 grants by dollar value, one grant was awarded to pharmaceutical company and the rest of the grants were awarded to academic institutions.

Further improvement in CER should focus on identification of experimental and quasi-experimental data for different therapeutic areas of interest, developing strategies to include understudied populations such as the disabled, rare conditions, development of a national clearing house to evaluate data collected via CER, dissemination of the available evidence to the stakeholders and encouraging use of the research data collected through CER systems.

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See Benner, supra note 134.
Comparative Effectiveness Research

Information gathered by the various federal grants awarded by NIH and AHRQ for CER research must be captured and made available in real-time. Absent a mechanism to capture and analyze the data, it would be difficult to analyze and compare the effect of information obtained from various CER grants on our national priorities. Such comparison will elucidate the strength and limitations of the database, its usefulness to the public and the CER as a whole. As of writing of this article, there is insufficient information to perform a comparative review between the information gathered under the federal grants for the purpose of CER and the national priorities. This is primarily due to the lack of infrastructure in reporting and recording of the information gathered by CER grants.

Conclusion

Implementing CER in the US needs support along the social, political and economic fronts. It will need collaboration from industry, public, physicians and legislators. In spite of the discrepancies surrounding regulations of CER, the need for CER and the rationale cannot be rebutted. It is time to overhaul the drug discovery and commercialization laws once again through effective CER regulations. The goal of attaining cost effective and value based health care system is not going to be realized immediately. It is an investment for the future in the right direction. The fruits of our labors by establishing and implementing CER regulations will be felt in future decades and by next generation of Americans. Curtailing cost of the health care system today, although rigorous, will be a positive step for our future generations.

149 Id.
150 Id.