Pain Physician 2010; 13:E55-E79 • ISSN 2150-1149

Health Policy Review

Facts, Fallacies, and Politics of Comparative Effectiveness Research: Part 2 - Implications for Interventional Pain Management

Laxmaiah Manchikanti, MD[1], Frank J.E. Falco, MD[2], Mark V. Boswell, MD, PhD[3], and Joshua A. Hirsch, MD[4]

From: [1]Pain Management Center of Paducah, Paducah, KY; [2]Mid Atlantic Spine & Pain Specialists of Newark, Newark, DE; [3]Texas Tech University Health Science Center, Lubbock, TX; and; [4]Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Associate Clinical Professor of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY.
Dr. Falco is Medical Director of the Mid Atlantic Spine & Pain Specialists of Newark, DE and Clinical Assistant Professor, Temple University Medical School, Philadelphia, PA.
Dr. Boswell is Chairman of Department of Anesthesiology and Director of the International Pain Center, Texas Tech University Health Sciences Center, Lubbock, TX.
Dr. Hirsch is Chief of Minimally Invasive Spine Surgery, Depts. of Radiology and Neurosurgery, Massachusetts General Hospital and Associate Professor of Radiology, Harvard Medical School, Boston, MA.

Address correspondence:
Laxmaiah Manchikanti, M.D.
2831 Lone Oak Road
Paducah, Kentucky 42003
E-mail: drlm@thepainmd.com

Disclaimer: There was no external funding in preparation of this manuscript. Conflict of Interest: Dr. Hirsch is a consultant for Cardinal Healthcare. He is a minor shareholder in Medtronic and Cardinal Healthcare. He serves on the Steering Committee for KAVIAR trial (volunteer position), and on the Data and Safety Monitoring Board (DSMB): CEEP trial (volunteer position).

Manuscript received: 01/04/2010
Accepted for publication: 01/12/2010

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The United States leads the world in many measures of health care innovation. However, it has been criticized to lag behind many developed nations in important health outcomes including mortality rates and higher health care costs. The surveys have shown the United States to outspend all other Organisation for Economic Co-operation and Development (OECD) countries with spending on health goods and services per person of $7,290 – almost 2½ times the average of all OECD countries in 2007. Rising health care costs in the United States have been estimated to increase to 19.1% of gross domestic product (GDP) or $4.4 trillion by 2018.

CER is defined as the generation and synthesis of evidence that compares the benefits and harms of alternate methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The, comparative effectiveness research (CER) has been touted by supporters with high expectations to resolve most ill effects of health care in the United States providing high quality, less expensive, universal health care. The efforts of CER in the United States date back to the late 1970s and it was officially inaugurated with the enactment of the Medicare Modernization Act (MMA). It has been rejuvenated with the American Recovery and Reinvestment Act (ARRA) of 2009 with an allocation of $1.1 billion.

CER has been the basis of decision for health care in many other countries. Of all the available agencies, the National Institute for Health and Clinical Excellence (NICE) of the United Kingdom is the most advanced, stable, and has provided significant evidence, though based on rigid and proscriptive economic and clinical formulas.

While CER is taking a rapid surge in the United States, supporters and opponents are emerging expressing their views. Since interventional pain management is a new and evolving specialty, with ownership claimed by numerous organizations, at times it is felt as if it has many fathers and other times it becomes an orphan. Part 2 of this comprehensive review will provide facts, fallacies, and politics of CER along with discussion of potential outcomes, impact of CER on health care delivery, and implications for interventional pain management in the United States.

Key words: Comparative effectiveness research, evidence-based medicine, Institute of Medicine, National Institute for Health and Clinical Excellence, interventional pain management, interventional techniques, geographic variations, inappropriate care.

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Comparative effectiveness research (CER) is defined by the Institute of Medicine (IOM) (1) as, "The generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. In contrast, evidence-baed medicine (EBM) is defined (2) as, "The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."

EBM is essentially focused upon the use of the right (types and extent of) knowledge to guide the right and good intentions and actions of medical practice, which is fundamental to prudential clinic decision-making (3,4). In contrast, CER is to assist consumers, clinicians, purchasers, and policy-makers to make informed decisions that will improve health care at both the individual and population levels. Thus, EBM and CER share many similarities and goals. They are analogous to religion and politics – meaning different things to different people (5-15).

Interventional pain management is an evolving specialty. Interventional pain management encompasses the discipline of medicine devoted to the diagnosis and treatment of pain related disorders principally with the application of interventional techniques in managing sub acute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment as a specialty designated as -09 in 2002 (16). The mainstay of interventional pain management is interventional techniques. These are minimally invasive procedures including percutaneous precision needle placement, with placement of drugs in targeted areas or ablation of targeted nerves; and some surgical techniques such as laser or endoscopic diskectomy, intrathecal infusion pumps and spinal cord stimulators, for the diagnosis and management of chronic, persistent or intractable pain (17). Interventional pain physicians – rightfully so, are apprehensive about the impact of CER. This may be related to a new specialty, or it may be related to involvement of many organizations and specialties with claims of ownership to the specialty.

In Part 1, we have described multiple basic considerations of CER. Part 2 will explore the role of CER in general and its impact on interventional pain management.

1.0 Potential Outcomes of CER

Potential outcomes of CER include scientific knowledge, improved health, and financial impact (5,18). In terms of science, across the spectrum of CER, from structured analysis of prior studies, databases, and registries, to the conduct of large clinical effectiveness trials, the scientific objective is rigorous, reliable information about what treatments are best for what patients, and under what circumstances. However, this is closely linked with financial impact, thus economic consequences are less direct. Discussions to date suggest that most of the funds will be spent comparing one clinical procedure, device, or drug with another (18,19). The funds are less likely to be spent testing the comparative effectiveness of one way of paying for care versus another, of organizing care using a chronic disease model versus another organizational principle or of implementing aggressive disease management programs. Even then, countless studies could be conducted to assess the comparative effectiveness of clinical procedures, devices, or drugs. A nearly infinite number of studies could be conducted to determine how often a person with back pain should receive chiropractic treatment or an interventional technique, or surgical intervention. On a benign end, an infinite number of studies could also be conducted to determine how often a patient with hypertension should receive follow-up care, how often a diabetic patient should see an endocrinologist or internist, or what form of treatment will achieve the best outcome for a patient either with hypertension or diabetes. Further, an infinite number of studies may be conducted, but time may be limited for patients with cancer to determine what form of radiation and chemotherapy will achieve the best outcome.

The major outcomes of CER which include the scientific knowledge to improve health should have a direct positive impact on health care, unless the conduct or public release of such research is compromised by poor quality, conflicts of interest, or the inability of the researchers to appropriately determine the evidence, which quite often happens in U.S. health care. However, the economic consequences are less direct and more controversial. Theoretically, whatever the total costs of health care, CER should have a positive impact on cost-effectiveness - meaning that we would be spending health care dollars more wisely on the most effective care, as concluded by the detailed analysis done by the Congressional Budget Office (CBO) (20,21). Pharmaceutical manufacturers may benefit financially because CER will compare drugs to not only other drugs, but also to medical devices and procedures. This could expand the conditions for which their drugs might be used, and thus would enlarge their market. Some expensive drugs may be found to be no more effective than less expensive versions already generically available at far less cost,

and this could compromise sales of their most profitable drugs. Similarly, for medical device companies, profits could be reduced. Currently, the FDA's statute mandates less evidence of treatment benefit for medical devices than for drugs. However, a new requirement for rigorous testing of effectiveness would require extra time and money, and ultimately likely would show that at least some devices have indiscernible treatment benefits, which would curtail sales (5).

After reviewing comparative effectiveness efforts in the United States, and internationally, the American College of Physicians (ACP) (22,23) concluded that the United States spends insufficient funds to develop comparative effectiveness data; that no coordination or prioritization of current efforts exists in either the public or private sector to produce comparative effectiveness information; and that the absence of readily available comparative effectiveness information interferes with the ability of physicians and their patients to make effective, informed treatment choices that meet the unique needs and preferences of the patient and facilitate the ability of payors to optimize the value of their health care expenditures. In addition, the college recommended that both comparative clinical and cost data must be generated and published, in the strong belief that both factors are critical to making health care resource decisions for all stakeholders.

1.1 Cost-Effectiveness

The ACP (22) believes that cost-effectiveness information is a necessary complement to compare clinical effectiveness information for all health care stakeholders. This information will help patients and their physicians make treatment decisions that better reflect the needs and preferences of the patient and support the profession's commitment to adjust distribution of finite resources (23). Further, it will provide relevant information for health care payors and plans to help insure value from their expenditures. It will also serve as a stimulus for medical innovation and technological advances that take the relative value of new equipment or procedures into account. The college also states that cost information is already being used to make decisions about health care coverage, rate setting, tiering, and utilization management decisions, but not always in a transparent, explicit manner (22). Further, it has been described that not to consider costs is not practical at all in the present atmosphere. Without consideration of costs, there will be no societal support for explicit cost consideration in clinical decisions and medical policies; all explicit health plan efforts will be suspect; and there will be continued difficulty negotiating prices in relation to evidence of incremental benefit.

There is no more contentious element of comparative effectiveness policy than the question of what to do with cost effectiveness (24). With quite reasonable apprehension, some stakeholders worry that cost-effectiveness could be used as a single criterion by which to make recommendations for the insurance coverage of medical services. Further, there are concerns that the cost-effectiveness methodology is rooted in an overly utilitarian ethic, that it poorly captures the value of interventions for severely disabled patients, and that it can catch important innovations at an early, more expensive stage and snuff them out before they have a chance to prove their worth (24).

Wilensky (25), formerly the Administrator of the Health Care Financing Administration from 1990 to 1992, adamantly opposes the ACP's recommendation that the new entity should prioritize, sponsor, and produce cost-effectiveness information in addition to comparative clinical effectiveness information. While she supports the use of cost-effectiveness information as an element in decision making by physicians, patients, and payors for developing smart strategies of reimbursement, she thinks it is vitally important to keep comparative clinical effectiveness analysis and cost-effectiveness analysis separate from each other. She also alludes to the fact that the use of cost-effectiveness information is more politically contentious and is becoming more controversial than comparative clinical effectiveness (26,27). In addition, she alludes to the fact that ACP partly understands the history of failed attempts to use cost-effectiveness information and substantially overestimates the likelihood that assigning these 2 functions to one national program would be successful and sustainable. Consequently, she recommends that because the clinical effectiveness is the most basic and costly step in learning how to spend smarter, it should proceed first and in as politically protected a manner as possible. She concludes that she is not arguing against the importance of cost-effectiveness information; rather, she is sharing concerns about the potential for misuse of this information.

Another editorial by Garber (28) claims that for the well-insured, obtaining health care in the United States is like dining in a sumptuous restaurant that has menus without prices. It has been described that many studies, particularly old ones, have not followed recommended analytic practice standards (22,29); however, adherence to accepted standards may resolve this issue (30). Cost-

effectiveness studies, like conventional analysis of clinical effectiveness, can become obsolete if they are not updated consistently and frequently. Further, cost-effectiveness, according to Garber (28), does not require placing a dollar value on human lives. There is confusion between cost-effectiveness analysis and cost-benefit analysis, which does require monetizing lives. Cost-effectiveness analysis is preferred for health care evaluations precisely because it does not impose this requirement; it simply estimates how much must be spent by using a particular intervention to gain a given health effect, telling us how to achieve the greatest health effect for the dollar.

With heated debates for and against health care costs being used in coverage decisions by the public and physicians, the deepest objections undoubtedly stem from anxiety about how policy makers, and payors, both private and public, apply cost-effectiveness information. Potentially it rewards care that produces large benefits in relation to cost and penalizes expensive care that improves health little. Not all products and services that are profitable today would be successful in a health system that rewarded value this way. However, even to those who wish to maintain the status quo, policies to promote cost-effective care may be more attractive than price controls, broad cuts in reimbursement and other cost-control strategies, as well as because these policies offer the prospect of improving health while reining in expenditures.

However, the inadequate methodology, conflicts of interest, inadequate representation on panels by clinicians, clinicians practicing a particular technique, etc. publication bias, political ramifications, and finally the financial implications, will decide coverage policies rather than actual cost-effectiveness. The recent mammography recommendation from the Agency for Healthcare Quality and Research (AHRQ) (31) has elicited significant controversy, with even Dr. Bernadine Healy (32), the former director of the NIH, speaking against the AHRQ recommendations. If it was not for health care reform and political horse trading, this recommendation might have been embraced by private and public payors and neither Congress, nor the public would have been able to do anything about it. The comparative effectiveness recommendations are in contrast to Agency for Healthcare Policy and Research (AHCPR) guidelines which led to its demise in 1995 (33-36). As Wilensky points out (27), whether Medicare will be granted the right to use cost-effectiveness information in setting reimbursement rates is unclear, even though the history in this regard is not promising. The first attempt happened when Wilensky was the Administrator of the Health Care Financial Administration (HCFA) from 1990 to 1992. The proposed rule was never released from the Office of the Secretary of HHS because of concern about potential future misuse of this authority. Even then, before the rule could have become final, it would have been necessary to specify and resolve with the various affected constituencies, make decisions about what costs to count, which discount rates to use, from whose perspective, and all of the other controversial issues. The Medicare Payment Advisory Commission (MedPAC) in its report to Congress in June 2007 (37) highlighted the need for increased comparative effectiveness information, and recommended the development of a national entity to compare the clinical effectiveness of treatment approaches. The MedPAC commissioners also showed substantial ambivalence about including such data during the public meeting where they reviewed this recommendation (38). Further, through its rule making process, Medicare has twice attempted to endorse the use of cost-effectiveness data in coverage decisions. On both occasions, strong, broadly based concern was expressed, including the fear that such use would be a forerunner to rationing of care leading to the abandonment of these efforts (39). This policy directly would have affected the traditional Medicare Parts A and B and private plan Medicare Part C, which must provide at least the basic traditional benefits and must abide by all Medicare national coverage decisions that expand coverage (40). However, the Medicare coverage benefit program (Part D) provides greater flexibility for private drug plans to use costs in formulating decisions.

Traditional state Medicaid programs are also restricted in applying cost or cost-effectiveness data to their formularies (41). Medicaid programs must cover all drugs approved by the U.S. Food and Drug Administration from every manufacturer that signs an agreement with the Secretary of Health and Human Services to pay rebates to the states for the drugs purchased; however, a preferred drug list can be established if specific regimen requirements are met. In addition, states do have the flexibility to employ costs and cost-effectiveness evidence in deciding whether to require prior authorization or other utilization management procedures, even though state Medicaid programs are directly influenced by cost factors and their budgets are severely impacted. Only one state has a program that formally assesses safety, efficacy, and cost-effectiveness to inform these decisions. Washington (42) and Oregon attempted to use cost-effectiveness to prioritize Medic-

aid benefits in the early 1990s, but subsequently minimized the influence of costs on the prioritizing process after substantial stakeholder criticism (39).

At present, commercial health plans and purchasers appear to be reluctant to use formal cost-effectiveness data, even though 90% use costs in some form when evaluating new interventions (43). In a survey of private U.S. health plans, only 40% indicated that they use formal cost-effectiveness assessments (43). However, 51% of private payors used either cost-effectiveness analysis or cost-benefit analysis (44). Also, Blue Cross Blue Shield Association's national Technology Evaluation Center generally excludes cost-effectiveness considerations in their analysis (45). However, despite all the perceived difficulties of using cost-effectiveness, private insurers use significant restrictions and in general covered procedures and drugs less than Medicare and Medicaid. Thus, patients and their advocates continue to be concerned that any use of cost data including formal cost-effective analysis or cost-benefit analysis will inappropriately limit access, be used primarily for cost-containment, and be a substantial step toward rationing of care (39,46,47). Supporters of cost-effectiveness argue that rationing is already occurring and health care resources are limited with inappropriate utilization patterns across the country. Finally, Garber and Tunis (12) describe that the deepest concern about CER is that it will be misused, which is why some legislatures seek to prohibit information on comparative effectiveness from influencing coverage policy and payment decisions. The partnership to improve patient care, a coalition of 36 industry, patient-advocacy, and clinician organizations, raised concerns that CER will not take adequate account of individual patient differences and may impede the development and adoption of improvements in medical care and "stymie progress in personalized medicine" (12,48).

2.0 Impact of CER

The CBO report states that to affect medical treatment and reduce health care spending, the results of comparative effectiveness analysis would ultimately have to change the behavior of doctors and patients (49). Further, for any large-scale changes to occur, CER would have to generate new findings for a substantial number of medical conditions, which may take many years. To have the maximum effect on behavior, these findings would then have to be incorporated into the incentives for providers and patients, a process of adjustment that might also take time.

Health policy-makers and health care advisors foresee that there is a potential for savings on health care; however, predicting the impact CER could have on health care spending is difficult. In essence, research could show some of the denied treatments are effective: then there would be a public outcry. CER could also cause spending to increase on treatments already considered effective, but not used as extensively as recommended protocols indicate. Even then, new research on comparative effectiveness seems unlikely to increase the use of services that are already deemed effective. But, as shown in Fig. 1, it appears quite certain that it

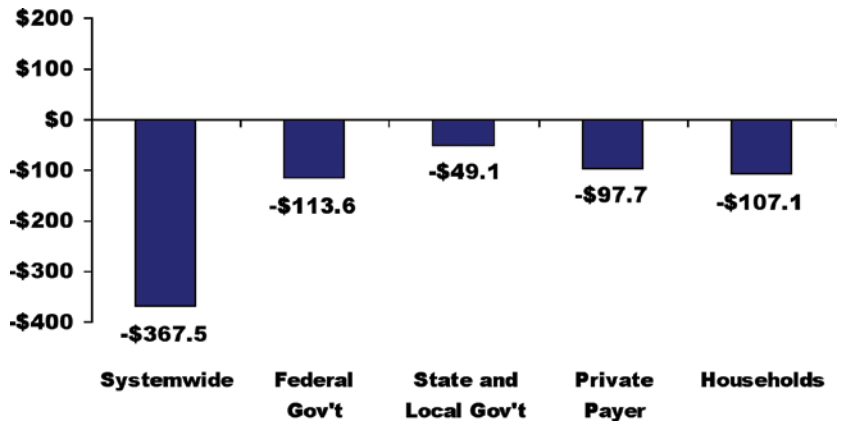

Fig. 1. *10-year impact of comparative effectiveness on spending.*
Source: Based on estimates by The Lewin Group for The Commonwealth Fund, 2007 (50).

will decrease the utilization and the cost (50). The ten year impact of CER has been shown to illustrate approximately $368 billion in systemwide savings.

To affect medical treatment and reduce health care spending, the results of comparative effectiveness analysis would ultimately have to change the behavior of doctors and patients. This essentially translates into using fewer services or less intensive and less expensive services than are currently projected. However, this may not occur without action by the public and private insurers to incorporate comparative effectiveness information into some combination of their coverage and payment policies. Those steps, which are foreseen, could be difficult and controversial.

The new health care language in essence may provide the support for private and public payors to implement cost-effective measures based on CER, no matter how deficient it may be.

Consequently, private insurers may not cover drugs, devices, or procedures that were found to be less cost-effective. Alternatively, insurers could require enrollees to pay some or all of the additional costs of more expensive treatments that were shown to be less effective or less cost-effective, also known as value-based insurance design.

For Medicare to reduce spending, the new law may be enough. If not, the Administration may provide regulations on this, circumventing the legislature. Alternatively, Congress may provide additional legislative authority to allow the program to consider relative benefits and costs in a more extensive way and to modify the financial incentives facing doctors and enrollees accordingly.

2.1 Initial National Priorities for CER

The IOM committee on CER prioritization selected its 100 topics after obtaining input from professional organizations and the public, as required by the American Recovery and Reinvestment Act (ARRA) (1,51). Given the public criticism the research initiative has received, the IOM report noted that, "Engaging consumers in CER . . . could help improve the public's trust in the U.S. research enterprise" (51). The committee began with 1,268 CER topics that were nominated by stakeholders and the public, and dwindled them down to 82; the other 18 topics were recommended by the committee to fill gaps in the portfolio. However, the criticism still continues as to the restoring of the public's trust in the U.S. research enterprise by the government, and the definition of stakeholders and information dissemination, and finally, the constitution of the IOM committee on CER.

The IOM committee placed particular emphasis on leading questions regarding the clinical effectiveness of care. Approximately 50 of the 100 recommended primary research areas compare some aspect of health care delivery systems (51). The IOM has explained that the research topics categorized in this group focus on comparing how or where services are provided, rather than which services are provided. The prominence of health care delivery systems in the portfolio primarily reflects the interest of the public . . . as well as the committee's belief that an early investment in CER should focus on learning how to make services more effective (1).

Approximately a third of the other primary research priorities address racial and ethnic disparities,

Table 1. *Final list of priority relevant to Musculoskeletal Disorders.*

MS-A	Establish a prospective registry to compare the effectiveness of treatment strategies for low back pain without neurological deficit or spinal deformity.
MS-B	Establish a prospective registry to compare the effectiveness of surgical and nonsurgical strategies for treating cervical spondylotic myelopathy (CSM) in patients with different characteristics to delineate predictors of improved outcomes.
MS-C	Compare the effectiveness of treatment strategies (e.g., artificial cervical discs, spinal fusion, pharmacologic treatment with physical therapy) for cervical disc and neck pain.
MS-D	Compare the effectiveness (e.g., pain relief, functional outcomes) of different surgical strategies for symptomatic cervical disc herniation in patients for whom appropriate nonsurgical care has failed.
MS-E	Compare the effectiveness of different treatment strategies in the prevention Of progression and disability from osteoarthritis.
	(MS-A–B), including identification of patient-specific biomarkers to help predict outcome and inform treatment strategies. (MS-C–D), focus on surgical and nonsurgical treatment strategies for cervical disc and neck pain (MS-E) topic in this research area addresses interventions to prevent disability and progression of osteoarthritis

Source: Committee on Comparative Effectiveness Research Prioritization, Institute of Medicine. *Initial National Priorities for Comparative Effectiveness Research*. National Academy of Sciences, Washington DC, 2009 (1).

and nearly a fifth address patients' functional limitations and disabilities. Other key priority areas are cardiovascular disease, geriatrics, psychiatric disorders, neurologic disorders, and pediatrics. The committee also recommended supporting CER related to patients' decision-making, unhealthy behavior such as smoking, and determining the most effective dissemination methods to ensure translation of CER results into best practices. Thus, cardiovascular and peripheral vascular disease ranks second as primary research areas, after health care delivery systems in terms of the number of recommended research projects (1).

The third most frequent primary research area is psychiatric disorders, with the committee recommending CER studies on the location of mental health care, provider training, various pharmacologic treatments, depression, premature death related to mental disorders, and suicide.

Finally, the priority list also includes 6 topics related to neurologic disorders. Three of the following use imaging for diagnosing such conditions: treatment of headaches, multiple sclerosis, and epilepsy; and the detection, treatment, and management of Alzheimer's disease and other dementias. Finally, cancer is the focus of 6 recommended primary CER topics, including screening technologies for colorectal and breast cancers and the use of imaging technologies for diagnosing, staging, and monitoring all cancers.

Even though the ARRA legitimized the accelerated pursuit of government-funded CER, it did not provide for funding after 2 years or call for the creation of an entity that would oversee such research. However, Congress is considering legislation to create a permanent CER structure and to authorize sustained federal funding.

The list of 100 top priority CER topics are divided into 4 quartiles. The first quartile includes establishment of a prospective registry to compare the effectiveness of treatment strategies for low back pain without neurological deficit or spinal deformity (Table 1).

2.2 The Impact of Well Established CERS Programs – An Interventional Perspective

The National Institute for Health and Clinical Excellence (NICE) is the best known example of an agency that assesses and is most praised by policy-makers and promoters of national health care and criticized by many sectors of public groups and physician groups in the United States. NICE has published appraisals of over 100 specific technologies, guidance on the use of over 200 medical procedures, and about 60 sets of treatment guidelines (52). If NICE approves a drug, device, or procedure, it must be covered by the National Health Service (NHS), but local health authorities make coverage decisions about treatments that NICE has not yet evaluated. With a staff of about 200 and an annual budget of over $60 million, NICE does not fund new clinical trials or other forms of primary data collection. Instead, it commissions systematic reviews of existing research on clinical effectiveness and combines those findings with models of cost-effectiveness. Clinical trials are funded by the British Ministry of Health, but data on total spending in the United Kingdom for research on comparative effectiveness are difficult to come by. NICE has been cited favorably by Senator Daschle (53). However, opponents of the British health care system and NICE criticize that NHS health care is rationed through long waiting lists and, in some cases, omission of various treatments. It has been stated that NICE at its heart is a center for health technology evaluation that issues formal guidance on the use of new and existing medicines based on rigid and proscriptive "economic" and clinical formulas (54). Even though NHS is obliged to adhere to NICE's pronouncements, criticism of NICE has been ceaseless, particularly from various patient organizations. Consequently, NICE is considered a controversial body. It has been alleged that it has tried repeatedly to stop breast cancer patients from receiving the breakthrough drug, Herceptin , and patients with Alzheimer's disease from receiving Aricept (54). They also refused life extending medicines such as those to treat renal cancers on the grounds of limited resources and the need to make decisions based not on genuine market economics, but on an artificial assessment of the benefit that may be gained by the patient and society as a whole.

The criteria by which NICE makes its decisions have been kept largely secret from the public (54). In 2001, NICE restricted state-insured sufferers of multiple sclerosis from receiving Beta Interferon, claiming that its relatively high price would jeopardize the efficacy of the NHS (54-56). In addition, patients with rheumatoid arthritis have been restricted by NICE in certain instances to receive a sequential range of medicines that have often been proved to be of significant benefit (54). The institute also decreed that people will be prevented from trying a second anti-TNF treatment if the first does not work for their condition (57). In 2008, patients with renal malignancy were allegedly denied treatments designed to prolong their lives, often by

months or even a few years (54). In 2009, NICE denied osteoporosis drug Protelos® and only a minority of patients received it as a last resort (58). The calculations used by NICE have been systematically disputed by clinical experts who are more concerned with patient welfare than with vote-seeking, but the institute has also come under fire for not involving doctors who are active on the frontline of medicine (59). The criticism is analogous to the criticism which was faced in the United States by AHRQ's panel on mammography recommendations (32).

Despite this, NICE has a broad mandate to set standards for the use of new technologies and procedures within the NHS and to produce guidelines for clinical, and now public, health. NICE has become the most influential technology assessment program in the world due to its reliance on cost-effectiveness as the fundamental basis of comparison between new technologies and their alternatives as well as its tested political durability. The key measure used by NICE to assess the comparative value of a technology is the additional cost per quality adjusted life year (QALY) gain. If appropriate data on quality of life are unavailable, cost-effectiveness is estimated using alternatives such as the cost for life year gained. NICE expects its advisory bodies to use estimates of cost effectiveness to inform, but not determine, their decisions. Nevertheless, NICE has arrived operationally at a band of approximately $30,600 to $45,900 per QALY as the threshold above which it would be increasingly likely to reject a technology on grounds of cost-ineffectiveness, however, the institute has approved the use of Etanercept and Infliximab, both with incremental cost effectiveness ratios of $47,430 per QALY, in the treatment of rheumatoid arthritis; but it has rejected some of the other treatments including anakinra which has an incremental ratio of $102,510 per QALY. It has been stated that NICE does not take the budget impact of a new technology into account. The approval by NICE of Herceptin has created a significant strain on NHS budgets.

Clement et al (60) described the impact of using effectiveness and cost-effectiveness to make drug coverage decisions in Britain, Australia, and Canada. In an attempt to control expenditures and to assess the value of new drugs, Britain, Australia, and Canada, along with many other countries, have established agencies to determine whether new pharmaceutical treatments should be listed in public formularies. As per earlier descriptions, this function is performed by NICE in England (52,61-64), Pharmaceutical Benefits Advisory Committee (PBAC) in Australia (65-67), and Common Drug Review (CDR) in Canada (68,69). Clement et al (60) provided listing recommendations for each drug by disease indication by descriptive analysis of retrospective data from 3 countries. The results showed that NICE recommended 87.4% (174/199) of submissions for listing compared with the listing rate of 49.6% (60/121) and 54.3% (153/282) for the CDR and PBAC respectively. Significant uncertainty around clinical effectiveness, typically resulting from inadequate study design or the use of inappropriate comparators and invalidated surrogate endpoints, was identified as a key issue in coverage decisions. They concluded that NICE, PBAC, and CDR face common issues with respect to the quality and strength of the experimental evidence in support of a clinically meaningful effect. However, comparative effectiveness and cost-effectiveness, along with other relevant factors, can be used by national agencies to support drug decision-making. The results of the evaluation process in different countries are influenced by the context, agency processes, ability to engage in price negotiation, and perhaps differences in social values. Clement et al (60) described that the study has limitations, including that the data set is based on publicly available data from NICE and PBAC. Although the public summary documents are thorough, there may be subtle issues that were not captured, particularly in the deliberation process. Another limitation is that there are surprisingly few common drugs across 3 systems, making comparisons across committees less conclusive (Fig. 2). The results also suggested that there were some differences in the way these jurisdictions use effectiveness and cost-effectiveness information in coverage decisions, requiring further research to establish the cause of these differences.

With regards to cost-effectiveness, this study, while it failed to provide direct evidence to inform the question of which of these agencies improve efficiency of care for their populations, other early work suggests that the system in Australia has reduced prices below those in comparable countries without compromising health outcomes (70). It also has been shown that establishment of the Veterans Affairs (VA) national formulary in the United States also has achieved significant cost savings while insuring access to a wide range of prescription drugs (71,72).

Clement et al (60) also concluded that existence of these 3 agencies confirms that it is feasible to es-

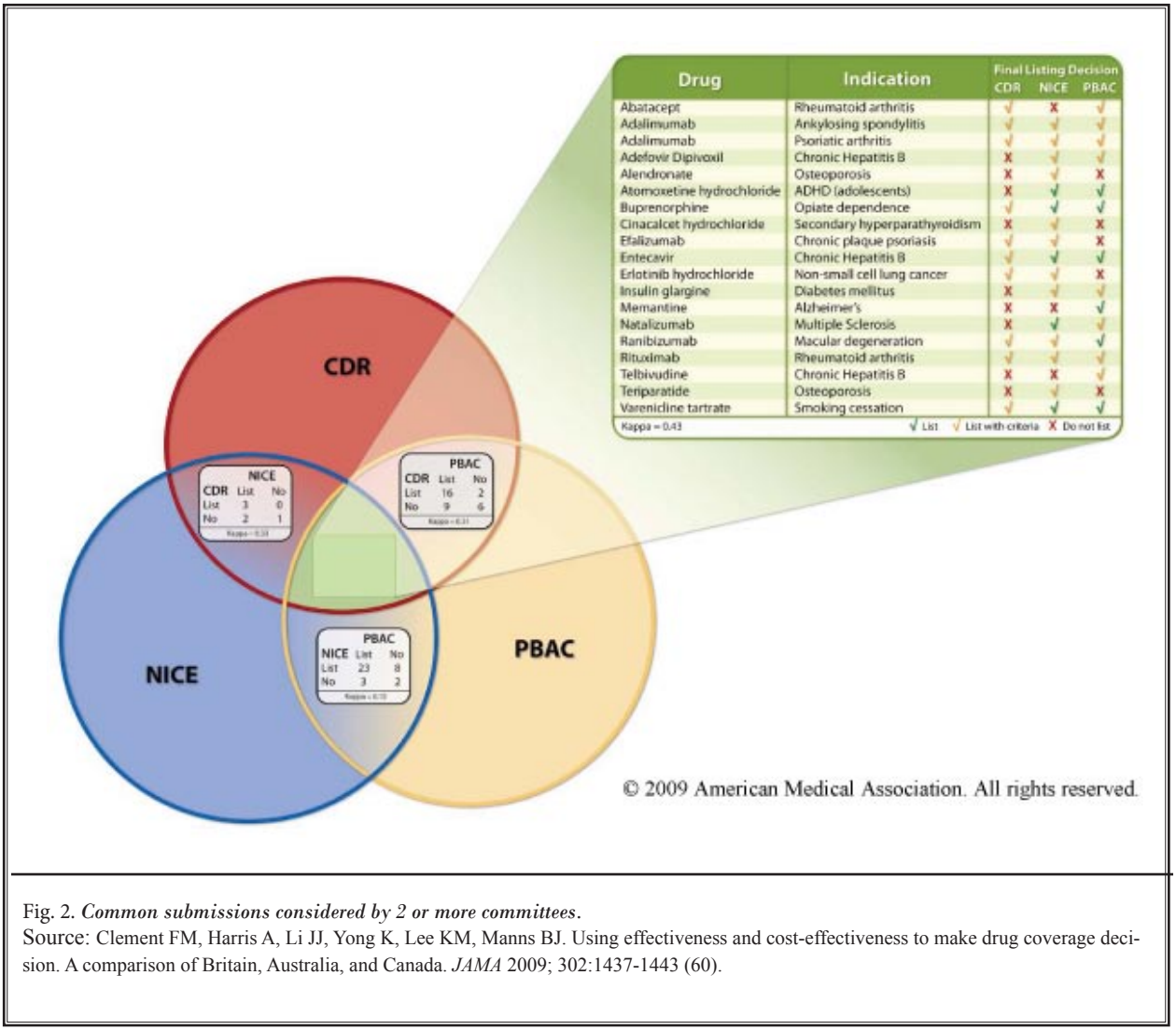

Fig. 2. ***Common submissions considered by 2 or more committees.***
Source: Clement FM, Harris A, Li JJ, Yong K, Lee KM, Manns BJ. Using effectiveness and cost-effectiveness to make drug coverage decision. A comparison of Britain, Australia, and Canada. *JAMA* 2009; 302:1437-1443 (60).

tablish an agency that considers comparative effectiveness in pharmaceutical reimbursement decisions. The differences that exist in the process of these agencies confirm that they can be adapted to local health care circumstances. They eliminate the primary concern in the United States that comparative effectiveness and cost-effectiveness would reduce the choice in therapeutic options (25,73). In addition, the use of cost-effectiveness in coverage decisions need not be an undue barrier to drug funding (65,74), even for expensive medications when there is robust evidence of effectiveness, at least in some patient subgroups, or where there are factors that appeal to the values of decision makers beyond the simple metric of cost and health gain (64). Table 2 lists a summary of the review process for pharmaceuticals by CDR, NICE, and PBAC (60,75).

Thus, due to multiple uncertainties and differences even in established programs, American physicians consider comparative effectiveness as problematic. Further, the application of CER is much more primitive with surgical techniques, interventional procedures, and multiple devices. Finally, the unlimited powers granted to the Department of Health and Human Services (DHHS) and their organizations controlled by the Administration rather than Congress remain a major issue.

Table 2. *Summary of review process for pharmaceuticals by CDR, NICE, and PBAC.*

Agency	National Drug Coverage	Mandate of Agency	Agency Initiated	Public Information Available	Process	Possible Outcomes	Implementation
Common Drug Review (Canada)	No national drug insurance Drug insurance provided by provincial /federal and territorial drug plans with different policies, and copay for each Drugs administered outside a hospital, not covered by the public plan can be purchased out-of-pocket	Reduce duplication, and provide equal access to high level evidence and expert advice, thereby contributing to the quality and sustainability of Canadian public drug plans	2004	2004	Independent systematic review of published and unpublished clinical trials (75) Sponsor submits pharmacoeconomic information which is critically appraised by CDR Discussion by committee of 11 professional and 2 members of the public Since 2007, chemotherapy agents are not considered by the committee Requires 4.5 – 6 mos.	List List with criteria Do not list	No legal mandate Recommendation o public drug plans Recommendations are consistent with funding decisions >90% of the time
National Institute for Health and Clinical Excellence (England and Wales)	Drug coverage provided for all by the National Health Service If drug has been appraised by NICE, no differential coverage For drugs not appraised by NICE, coverage decisions are made at local levels and may differ across regions Drugs administered outside hospital, not covered by the NHS can be paid for out-of-pocket	Provide national guidance on promoting good health and preventing and treating ill health	1999	2001	Independent systematic review of clinical trials Independent Pharmacoeconomic assessment Discussion by 33 member committee from NHS, patients, academia and industry Process requires ~ 18 mos. New single technology assessment process initiated Sept 2006 for considering specific drugs (as opposed to classes); sponsor clinical and economic information is critiqued by NICE	List List with criteria Do not list	Legal mandate List or list with criteria requires local organizations to provide Do not list requires claw back
Pharmaceutic al Benefits Advisory committee (Australia)	National coverage for drugs approved by PBAC for all Australians Maximum copayment scheme for drugs Drugs administered outside a hospital, not covered by the public plan can be paid for out-of-pocket	Provide reliable, timely and affordable access to a wide range of medicines	1993	2005	Sponsor submits clinical and economic information Critique of sponsor Submission (both clinical and economic data), often including additional evidence, analysis and reinterpretation by consultants for the Australian Government Department of Health and Aging Discussion by committee of 15 members made up of doctors, health professionals, health economists, and 1 consumer representative. Requires <4 mos.	List List with criteria List at lower price Defer/refer to another committee Do not list	Recommendation to Minister who cannot list a drug on the Pharmaceutical Benefits Scheme without a positive recommendation from PBAC

Source: Clement FM et al. Using effectiveness and cost-effectiveness to make drug coverage decision. A comparison of Britain, Australia, and Canada. *JAMA* 2009; 302:1437-1443 (60).

3.0 Impact on Interventional Pain Management

The major impact on interventional pain management would be a lack of interventional pain management clinicians on the panels evaluating interventional techniques for comparative effectiveness as well as those also the panels making recommendations for coverage or lack thereof. It is a common practice in interventional pain management to perform systematic reviews and prepare guidelines by a host of physicians considered as peers and clinicians, even though these physicians are only methodologists, who are unaware of many of the clinical elements of interventional pain management. Consequently, the validity of any evaluation will be considered invalid or mostly focused on benefit for the guideline preparer.

3.1 Interventional Pain Management Under NICE

The role of comparative effectiveness studies in the United States has not been evaluated (76). However, multiple reviews have been performed in the United States based on principles of EBM. Consequently, the evidence upon which EBM rests is determined by the quality of systematic reviews and their synthesis of the evidence. Multiple evaluations and publications related to interventional pain management have been published by NICE (77-83). These evaluations essentially confirm the fear and uncertainty of American interventionalists. NICE (77), in conjunction with the National Collaborating Centre for Primary Care (NCC-PC) and Royal College of General Practitioners (RCGP) (78), developed guidelines for early management of persistent non-specific low back pain. However, these have been inappropriately applied for chronic persistent low back pain. In a document which is several hundred pages, only a few pages were allocated to invasive procedures. In the development group, there were 12 members of the primary group of which there was only one pain management and rehabilitation specialist (PW). Among the other 9 members, there were no pain specialists. In summary, of the 22 members of the guideline development group, only one was a pain specialist. Further, the guideline review panel had no pain specialists. All interventional techniques were utilized in Section 9.3 under the heading of injections. They conducted searches for any intramuscular, spinal, epidural, or nerve block injections. They identified only 2 systematic reviews and one RCT. The 2 systematic reviews included one diagnostic (84) and one therapeutic facet joint intervention (85) and the RCT was of Carette et al (86). They concluded that this was a well conducted systematic review with a low risk of bias; however, with no weight given to conclusions. Other systematic reviews were related to prolotherapy, a procedure not widely utilized or approved. They also included studies for intradiscal therapy. However, they failed to include many other systematic reviews (84,85,87-108) for various interventional techniques including the ones by Cochrane review and others (96,97).

The evidence statement provides that searches were carried out to identify any form of injection for the lower back; however, only data on facet joint, prolotherapy, and intradiscal injections were identified. It was very surprising that such a search criteria should fail to identify numerous treatments, including multiple guidelines and systematic reviews.

NICE, in its September 25, 2009, Conference on Quality and Productivity, presented various topics including their experience to date, technology evaluation, investing widely to save money, implementation, local perspectives, and a national perspective (109). There was significant focus on cutting costs. In fact, NICE provides a guidance document to cut costs in the downturn (110). NICE's role has been described as to support best practice through encouraging the use of cost-effectiveness interventions and discouraging the use of cost ineffective interventions. Further, the Centre for Health Technology Evaluation guidance programs described interventional procedures, technology appraisals, and evaluation pathways for medical technologies (diagnostic technologies). An interventional procedures program provides efficacy in 4 grades with normal or special arrangements for consent, audit, and clinical governance. A third category does not use evidence on safety and efficacy. The final category provides only for research purposes. Among the 342 individual recommendations in 166 technology appraisals, unrestricted decision was provided in 29% with optimized decision in 55%. Nine percent of the appraisals yielded a "not recommended," whereas 6% yielded "only in research." However, 80% of optimized recommendations were based on patient group and 27% were based on the price. Even though the evidence appears quite reasonable, it appears on many occasions to be inconsistent with suboptimal evaluation as shown above for low back pain and inappropriate application from one evaluation to another, such as from non-specific acute low back pain to chronic persistent specific low back pain. Among the interventional procedures, NICE has provided positive

evidence for spinal cord stimulation for chronic pain of neuropathic or ischemic origin (111).

3.2 CER in the United States

However, in the United States, there has not been much research on comparative effectiveness or its applications. Philosophically, a core concept of CER is to employ EBM to get better value in health spending. This has led to concerns of many organizations, the public in general, and interventional pain physicians. Even though President Obama has repeatedly told Americans that the plan will not tell which doctors to see or what treatments to get, and will not second guess decisions about their care, conflicting information has been provided by multiple other sources. The core concept of CER as illustrated over and over again by NICE is that less effective or cost ineffective treatments will be avoided.

3.3 Guidelines in Interventional Pain Management in the United States

Numerous divergent guidelines and interpretations with the same evidence yielding different results by different groups have been presented repeatedly. This has been more frequently illustrated by the authors who are consistently negative about interventional pain management. Chou (112) discussed discrepancies between reviews on interventional procedures of the spine. As focused in this manuscript, each one of them feels that they are the appropriate ones even though both reviews are associated with flaws. However, Chou (112) is accurate in that a number of conclusions differ between various other reviews and the 2 reviews (113,114). The differences actually become much more prevalent when positive and negative reviews are considered. It is difficult for clinicians to understand how and why these differences occur and also difficult to select the most appropriate review to guide their clinical decision-making, since most policy-makers attempt to utilize negative reviews, even though they are flawed, based on a philosophy of cost-effectiveness. Even though Levin's review (114) was associated with major flaws as documented by letters to the editor (115), Chou's conclusions (112) were even more negative. The differences are related as beneficial to insufficient evidence or insufficient evidence to not beneficial. Chou (112) claimed that Levin (114) failed to utilize quality assessment of systematic reviews. However, Chou accepted that the likelihood of publication bias was not assessed. While Chou noted the conflicts of interest being reported in both his articles (112,116), these conflicts were not clear to the audience.

A prime example is Occupational Medicine Practice Guidelines (117,118), which have been extensively re-evaluated and reassessed (119-121). The American College of Occupational and Environmental Medicine (ACOEM) guidelines on chronic pain and low back pain have been concluded to lack applicability in modern patient care due to the lack of expertise by the developing organization -- ACOEM; lack of utilization of appropriate and current EBM principles; and lack of significant involvement of experts in these techniques resulting in a lack of clinical relevance. Thus, Manchikanti et al (119) concluded that this may result in reduced medical quality of care; may severely hinder access to appropriate, medically needed and essential medical care; and finally, they may increase costs for injured workers, third party payors, and the government by transferring the injured worker into a non-productive disability system. Manchikanti et al (120) also appraised these guidelines utilizing Appraisal of Guidelines for Research and Evaluation (AGREE) (122), American Medical Association (AMA) (123), IOM (124), and other criteria, and concluded that both the low back pain and chronic pain chapters of ACOEM guidelines may not be ideal for clinical use based on the assessment by the AGREE instrument, AMA attributes, and criterion established by Shaneyfelt et al (113). Contrary to ACOEM's conclusions of insufficient evidence for most interventional techniques, the reassessment results illustrated moderate to strong evidence for most diagnostic and therapeutic interventional techniques. Deficiencies of ACOEM guidelines are too extensive to be described in this manuscript. These have been clearly described in the reassessment of evidence synthesis manuscript (119-121). Chou et al (125) published evidence-based clinical practice guidelines from the American Pain Society (APS) describing interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain. These guidelines were published in May 2009 and submitted in October 2008 by a multidisciplinary panel of 23 experts to formulate low back pain recommendations convened in 2004. It appears that the research was performed at Oregon Evidence-Based Practice Center – an organization sponsored by AHRQ. Further, it shows that the activity was supported by the APS. But, no other disclaimers are provided as to the nature of the financial support from government as well as from APS to all or some authors. In 2007, they also recruited 2 or 3 ad-

ditional experts in the areas of interventional therapy or surgery to participate in the development of recommendations. Some of these authors withdrew their names; however, no such disclosure was provided. The final authorship appears to have included 2 interventional pain physicians of the 13.

The methodology included a systematic review that focused on evidence from randomized controlled trials (RCTs). Recommendations were graded using methods adapted from the United States Preventive Services Task Force (USPSTF) and the grading of recommendations, assessment, development, and evaluation working group (126). They reviewed a total of 161 randomized trials deemed relevant to the recommendations in the guidelines and developed a total of 8 recommendations. The recommendations on the use of interventional diagnostic tests and therapies, surgery, and interdisciplinary rehabilitation were presented which included shared decision making as an important component of a number of the recommendations. The literature search was through July 2008. The conclusions and recommendations were as follows:

1) Provocation discography is not recommended as a procedure for diagnosing discogenic low back pain, a strong recommendation, with moderate-quality evidence.
2) There was insufficient evidence to evaluate validity or utility of diagnostic selective nerve root block, intraarticular facet joint block, medial branch block, and sacroiliac joint block as diagnostic procedures for low back pain with or without radiculopathy.
3) Clinicians must consider intense interdisciplinary rehabilitation with a cognitive/behavioral emphasis with strong recommendation and high quality evidence.
4) In patients with persistent non-radicular low back pain, facet joint corticosteroid injection, prolotherapy, and intradiscal corticosteroid injection were not recommended with a strong recommendation with moderate-quality evidence.
5) There was insufficient evidence to adequately evaluate the benefits of local injections, botulinum toxin injection, epidural steroid injection, intradiscal electrothermal therapy (IDET), therapeutic medial branch blocks, radiofrequency denervation, sacroiliac joint steroid injection, or intrathecal therapy with opioids or other medications for non-radicular low back pain.
6) Clinicians should discuss risks and benefits of surgery as an option (a weak recommendation with moderate quality evidence).
7) There was insufficient evidence to adequately evaluate long-term benefits and harms of vertebral disc replacement.
8) In patients with persistent radicular pain due to a herniated lumbar disc, it was recommended that the clinician discuss risks and benefits of epidural steroid injection as an option, a weak recommendation, with moderate quality evidence.
9) In patients with persistent and disabling radiculopathy due to a herniated lumbar disc or persistent and disabling leg pain due to spinal stenosis, they recommended that clinicians discuss risks and benefits of surgery as an option with a strong recommendation with high quality evidence.

Multiple deficiencies in these guidelines include failure to utilize USPSTF guidance as shown in the methodology section, and over 12 months to get to the public, by which time numerous other manuscripts had been published without a mechanism to update the guidelines. Multiple studies which were excluded in other systematic reviews were the source of conclusions in these guidelines. Strikingly and conversely, well performed studies were excluded.

The recently published Official Disability Guidelines (ODG) also has taken the same path as ACOEM and APS guidelines (117,118,125,127). They have provided the following conclusions for interventional techniques:

Non-recommended therapies include the following:

- Percutaneous adhesiolysis
- Discography
- Medial branch blocks (dual or multiple diagnostic or therapeutic)
- Nucleoplasty
- Percutaneous discectomy
- Percutaneous electrical nerve stimulation
- Prolotherapy
- Pulsed radiofrequency treatment
- Thermal intradiscal procedures
- Vertebroplasty

Under study are as follows:

- Spinal endoscopic adhesiolysis
- Facet joint intraarticular injections or therapeutic blocks
- Facet joint radiofrequency neurotomy
- Kyphoplasty
- Oxygen-ozone therapy

Approved treatments are as follows:

- Epidural steroid injections, both diagnostic and therapeutic
- One diagnostic medial branch block for facet joint pain
- Spinal cord stimulation and intrathecal implantables only for selected patients.

In contrast, rigorously performed evidence-based guidelines for interventional techniques by ASIPP (128) with multiple supporting documentation to these guidelines (129-134), and 21 systematic reviews (88,89,135-153) also utilized strength of evidence as assessed by USPSTF criteria using 5 levels of evidence ranging from Level I to III with 3 subcategories in Level II and quality of individual articles, and quality of systematic reviews as described by Cochrane review and AHRQ criteria (154,155). With adherence to evidence-based principles and strict criteria applying methodology, clinical knowledge, and relevance, these guidelines' conclusions were quite different from ACOEM, ODG, and APS guidelines:

1) The evidence for accuracy of diagnostic facet joint nerve blocks was Level I or II-1 in the diagnosis of lumbar, thoracic, and cervical facet joint pain.
2) The evidence for lumbar and cervical provocation discography and sacroiliac joint injections was Level II-2, whereas it was Level II-3 for thoracic provocation discography.
3) The evidence for therapeutic interventions was Level I for caudal epidural steroid injections in managing disc herniation or radiculitis, and discogenic pain without disc herniation or radiculitis.
4) The evidence was Level II-1 or II-2 for therapeutic cervical, thoracic, and lumbar facet joint nerve blocks.
5) The evidence was Level II-1 or II-2 for caudal epidural injections in managing pain of post-lumbar surgery syndrome, and lumbar spinal stenosis.
6) The evidence was Level II-1 or II-2 for cervical interlaminar epidural injections in managing cervical pain.
7) The evidence was Level II-1 or II-2 for lumbar transforaminal epidural injections.
8) The evidence was Level II-1 or II-2 for percutaneous adhesiolysis in management of pain secondary to post-lumbar surgery syndrome.
9) The evidence was Level II-1 or II-2 for spinal cord stimulation for post-lumbar surgery syndrome.
10) The evidence for IDET, mechanical disc decompression with automated percutaneous lumbar discectomy (APLD), and percutaneous lumbar laser discectomy (PLDD) was Level II-2.

These different results illustrate that systematic reviews, meta-analysis, and CERs are labor intensive and require expertise in both the subject matter and review methodology. In addition, they must follow the rules of EBM, which suggest that a formal set of rules complement medical training and common sense so clinicians can interpret the results of clinical research effectively. Consequently, knowing the tools of either EBM or CER is important, but not sufficient for delivering the highest quality of patient care. Further, expertise in a single area is not enough and may lead to inaccurate conclusions, which leads to inappropriate application of the results. Non-practicing physicians are simply methodologists with basic knowledge about medicine. Consequently, a systematic review, a comparative effectiveness review, or guidelines must truly incorporate the definition which states that scientific strategies must be applied to limit bias by the systematic assembly, critical appraisal, and synthesis of relevant studies on a specific topic.

3.4 Systematic Reviews in Interventional Pain Management

Numerous systematic reviews have been published in interventional pain management in the U.S. and abroad. Similar to guidelines, the systematic reviews also arrive at different conclusions utilizing the same evidence due to methodological flaws, bias, land ack of clinical knowledge (84,85,88-108,135-153).

3.4.1 Cochrane Reviews

Staal et al (156) evaluated low back pain treatments with facet joint interventions, as well as epidural injections. They utilized 6 weeks of relief as short-term and longer than 6 weeks as long-term. They also had no inclusion criteria based on the validity of diagnosis for facet joint interventions. They included studies by Carette et al (86) and Lilius et al (157) in their analysis and qualified them as one high quality (86) and one low quality study (157), comparing the effects of facet joint injections with corticosteroids to placebo injections. They concluded that there was moderate evidence with 2 trials including 210 patients that facet joint injections with corticosteroids are not significantly different from placebo injections for short-term pain relief and improvement of disability. However, Datta et al (136) considered 5 randomized trials and 15 observational studies for inclusion and concluded that none

of them met inclusion criteria with appropriate diagnosis and duration of follow-up. Datta et al (136) utilized strict inclusion criteria of 80% pain relief with ability to perform previously painful movements with controlled diagnostic blocks and utilized at least 6 months of relief for short-term. Staal et al (156) also considered medial branch blocks for therapy. However, they utilized only one study by Manchikanti et al (158). Staal et al (156) concluded that there was no difference even though they failed to take into consideration the design of the study – non inferiority or equivalence trial versus efficacy trial, based on lack of placebos. Datta et al (136) utilizing stricter criteria as described above with utilization of 2 studies and appropriate analysis. Both the included studies (158,159) by Datta et al (136) utilized an active controlled design, which were referred to as non-inferiority or equivalence trials, lacking placebo. Even then they utilized active controlled design to compare therapy – the crux of comparative effectiveness. In contrast to Staal et al (156), Datta et al (136) provided Level II-1 evidence for medial branch blocks based on the USPSTF criteria (160). They also provided, based on Guyatt et al's (161) criteria, 1B - strong recommendation for the effectiveness of lumbar facet joint nerve blocks to provide both short-term (≤ 6 months of significant relief) and long-term relief (> 6 months of significant relief) in the treatment of chronic lumbar facet joint pain with 3-4 nerve blocks.

Similarly, in relation to epidural injections, they evaluated all types of epidural injections, namely caudal, lumbar interlaminar, and lumbar transforaminal as one category and also failed to separate for various conditions (herniation, stenosis, post laminectomy syndrome, or discogenic pain), reaching inappropriate conclusions. In contrast, ASIPP guidelines (128) and multiple systematic reviews (139,140,142) reached different conclusions with Level I evidence for short and long-term relief (≤ 6 months and > 6 months) in managing chronic low back and lower extremity pain secondary to lumbar disc herniation and/or radiculitis and discogenic pain without disc herniation or radiculitis; Level II-1 or II-2 for caudal epidural injections in managing low back pain of post surgery syndrome and spinal stenosis, with strong recommendation variable from 1A to 1C. In contrast, they also reached conclusions which were different for interlaminar epidural injections with Level II-2 for blind interlaminar epidural injections for short-term relief in managing chronic low back and lower extremity pain secondary to lumbar disc herniation and/or radiculitis. Further, they showed Level III evidence for blind lumbar interlaminar epidural injections in managing low back pain of spinal stenosis and discogenic origin without disc herniation or radiculitis with weak recommendation for long-term use. For lumbar transforaminal epidural injections, the level of evidence was II-1 for short-term relief and Level II-2 for long-term relief in managing chronic low back and lower extremity pain with 1C- strong recommendation.

3.4.2 American Pain Society Review

Chou et al (116) published non-surgical interventional therapies for low back pain with a search of the manuscripts through July 2008. Evidence selection included RCTs and systematic reviews. They utilized predetermined criteria with Cochrane criteria for both randomized trials and systematic reviews. They also have stated that they have utilized the USPSTF criteria for determination of overall strength of evidence (126).

For epidural steroid injections, they identified 40 randomized trials, with 33 trials being included in at least one of 9 systematic reviews. They also identified 7 additional trials. Twenty-one trials were placebo-controlled and they rated 9 placebo-controlled trials as high quality. The deficiencies of this review included the search period of July 2008 after which a number of manuscripts were published (159,162-166) with positive evidence, failure to separate 2 modalities (namely caudal and interlaminar), and inability to separate various conditions (disc herniation or radiculitis, discogenic pain without disc herniation, spinal stenosis, and post surgery syndrome). They utilized greater than 3 months as long-term relief. They identified 3 systematic reviews as high quality (167-169). All of them (167-169) used similar methodology which was as flawed as the present systematic review of Chou et al (116) and failed to meet inclusion criteria by others.

Chou et al (116) concluded fair evidence of moderate benefit compared with placebo injection for short-term pain relief in patients with radiculopathy. However, there was no evidence for long-term benefits.

In reference to facet joint injection and therapeutic medial branch blocks, they identified 8 randomized trials with 7 of them being included in at least one of 4 systematic reviews with one additional trial. There were only 2 trials evaluating facet joint injection, which were placebo control, by Carette et al (86) and Lilius et al (157). Unfortunately, they classified the Cochrane review by Staal et al (156) as high quality and 3 of them as lower quality (85,170,171). However, Cochrane review was deficient in multiple aspects. Surprisingly, it did not

meet the criteria for inclusion for epidural injections by Chou et al (116).The systematic review by Boswell et al (85) was classified as low quality and also as excluding Lilius et al (157) because he did not use diagnostic facet joint blocks on select patients, classified the trial by Carette et al (86) as favoring facet joint injection, classified an active-control trial as demonstrating efficacy of facet joint injection because both intervention groups improved compared with baseline (172), and included evidence from several small (n < 100), non-randomized studies. However, Boswell et al (85) utilized appropriate evidence synthesis and reached proper conclusions based on inclusion/exclusion criteria (173). Thus, Boswell et al's systematic review and other subsequent systematic reviews (85,128,132,136) are much more appropriate and up to date with non-biased evidence synthesis rather than Chou et al's (116) or even Cochrane's review (156).

They also concluded that there was no trial evaluating the efficacy of therapeutic medial branch blocks versus sham or placebo injection. They included 2 trials which evaluated short-term relief of medial branch blocks (174,175), one of them as higher quality (175), finding no difference between facet joint corticosteroid injection and medial branch block. However, these were excluded due to the high volumes utilized and short-term follow-up without outcome parameters by other systematic reviews (85,100,156,168). They also utilized a study by Mayer et al (176), which was considered as flawed, comparing facet joint injections in relation to segmental rigidity, which has no relevance in managing chronic facet joint pain. Further, it seems the authors believed they were medial branch blocks even though careful review of the text suggests that they were in fact intraarticular injections as they were described in the section about medial branch blocks. Chou et al (116) were accurate in concluding that intraarticular facet joint injections were ineffective. In contrast, Datta et al (136) concluded that evidence for diagnosis of lumbar facet joint pain with controlled local anesthetic blocks was Level I or II-1. The indicated level of evidence for therapeutic lumbar facet joint interventions was Level II- 1 or II-2 for lumbar facet joint nerve blocks, Level II-2 or II-3 evidence for radiofrequency neurotomy, and Level III (limited) evidence for intraarticular injections. Chou et al (116) conceded that they may have underestimated their effectiveness of facet joint injections and justified that the highest therapeutic quality study was negative. Thus, inclusion criteria is extremely important in evaluating effectiveness or lack thereof.

Chou et al (116) combined radiofrequency denervation, IDET and other related procedures into one category, specifically for presumed facet joint pain. They stated that trials of radiofrequency denervation are difficult to interpret. They considered one trial as optimal (177) utilizing controlled diagnostic blocks. They found multiple deficiencies with this study which was previously considered one of the best studies in the literature except for lack of long-term follow-up (136,178). Chou et al (116) misinterpreted Nath et al's data (177). Chou et al (116) reported the final scores in both groups were identical and there was no change in the low back pain; however, Nath et al (177) showed clear and distinct differences between both groups in all aspects. The active treatment group showed statistically significant improvement not only in back and leg pain, but also back and hip movement as well as sacroiliac joint pain. There was also significant improvement in quality of life variables, global perception of improvement, and generalized pain in the active treatment group. The results were superior despite the patients in the radiofrequency treatment group having significantly more generalized pain, low back pain, and referred pain to the leg when compared with the placebo group. Further, all hip movements were also worse in the radiofrequency treatment group.

They also looked at 3 other trials which met inclusion criteria but were thought to have suboptimal techniques and reported conflicting results (179-181). They included another lower quality trial (182) thought to have multiple deficiencies. Another sham-controlled study was considered as methodologically flawed as in other systematic reviews (183). However, all the studies were excluded (179-182) by Datta et al (136) utilizing stricter criteria.

They also utilized multiple systematic reviews – 2 of them as high quality (97,184) and 2 lower quality (85,170) - and found uncertain or inconsistent benefits associated with radiofrequency denervation for presumed facet joint pain, though none included the most recently published sham-controlled trials. The comprehensively performed systematic review by Boswell et al (85) was not given any weight because of presumed personal biases. They included the criticism of exclusion of a presumably higher quality trial (180) with more neutral findings because it used a single block to identify facet joint pain, leaving only a single, small (n = 31), higher quality randomized trial – which also did not appear to use controlled blocks to select patient-demonstrated benefits (181). The systematic

review was also criticized for utilizing observational studies and was alleged that the results of observational studies were poorly described. However, this criticism of the systematic review was based on bias without understanding the clinical aspects and inclusion criteria. Further, a recent systematic review (136) reached separate conclusions with exclusion of all the above mentioned studies. Datta et al (136) concluded that evidence for diagnosis of lumbar facet joint pain with controlled local anesthetic blocks is Level I or II-1. The indicated level of evidence for therapeutic lumbar facet joint interventions is Level II-1 or II-2 for lumbar facet joint nerve blocks, Level II-2 or II-3 evidence for radiofrequency neurotomy, and Level III (limited) evidence for intraarticular injections.

Chou et al (116) reported positive results that spinal cord stimulation was more effective than either repeat surgery (185) or continued conventional medical management (186) for failed back surgery syndrome with persistent radiculopathy. However, Chou et al (116) showed only fair evidence for spinal cord stimulation in contrast to determination by NICE (52), ASIPP guidelines (128), and recent systematic review (145).

While Chou et al (116) admitted to several potential limitations, these are few and far between and have not been popularized. Not only did they include only RCTs, but they also provided substantial criticism to other systematic reviews, which included observational studies. The limitations of this review include the inclusion of manuscripts through July 2008 and publication of the manuscript in April 2009, which essentially invalidates the systematic review as multiple manuscripts have been published since then. While the authors touted as utilizing the USPSTF criteria, Cochrane review criteria, and other appropriate criteria, they have not provided clear data how they arrived at these numbers and it raises numerous questions. The previous guidelines were also sponsored by the American Academy of Pain Medicine (AAPM). The relationship of AAPM with this guideline development has not been divulged. Multiple authors who have withdrawn from this guideline synthesis have not been mentioned or disclosed. Lack of clinical expertise will add substantial issues to raise questions of credibility. Of the 4 authors of this manuscript (considering that at least 2 pain specialists withdrew their support to these guidelines), only 2 of them appear to be pain specialists. In addition, they reviewed multiple technologies which are irrelevant to interventional pain management and not even practiced in the United States.

Not surprisingly, Chou et al (125) provided a highly favorable opinion for interdisciplinary rehabilitation for low back pain and opioid therapy based on the philosophy of supporting organizations. Further, even though there is no evidence at all for surgery, they provided positive evidence so that surgical interventions can be carried out which reflects the inclusion of the surgeons as a majority in the guideline preparation (125,187).

3.4.3 American Academy of Neurology Assessment of Epidural Steroids

Armon et al (188) with 3 other neurologists (none of them interventional pain physicians) published the Assessment of Use of Epidural Steroid Injections to Treat Radicular Lumbosacral Pain as a report to the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

The manuscript was published in 2007 with data on expenses of low back pain in the United States in 1998 (188). The abstract reports that there is insufficient evidence to recommend the use of epidural steroid injections to treat radicular cervical pain (Level U), even though the focus of review was the use of epidural steroid injections to treat radicular lumbosacral pain, and the studies included in the synthesis related solely to that focus. In a letter to the editor, Manchikanti et al (189) showed that Armon et al (188) included only 4 studies considered to have met the predetermined inclusion criteria, although previous studies have included larger numbers of randomized trials in systematic evaluation including the Cochrane review and European Guidelines (87,90,168). Armon et al (188) also utilized a methodology which has not been standardized or published in evaluating the quality of individual articles. Further, other reviewers have utilized AHRQ and Cochrane review criteria (154,155). Finally, the recent systematic reviews based on mainly randomized trials have shown significantly better evidence (139-142) than Armon et al (188). Further, even Chou et al (116) has considered Armon et al's review (188) as of low quality.

3.4.4 ASIPPs Systematic Reviews

In the preparation of comprehensive spinal guidelines, 21 systematic reviews (88,89,135-153) have been performed evaluating interventional techniques. The conclusions of these systematic reviews for diagnostic and therapeutic interventional techniques have been summarized under the guidelines.

These systematic reviews have been performed with extensive search criteria of the literature, up-to-

date inclusion of all the studies, inclusion of observational studies when needed, assessment of the quality of individual articles utilizing Cochrane review criteria, and AHRQ criteria (154,155) with evidence ratings based on USPSTF criteria (126) and recommendations based on Guyatt et al's (161) criteria when appropriate.

3.4.5 Old Systematic Reviews of Interventional Pain Management

Numerous systematic reviews have been performed in the past prior to 2008. These have been discussed in detail in multiple other manuscripts (84,85,90-108).

4.0 Ideal Comparative Effectiveness

An ideal CER program in the United States will fulfill its purpose and mission with comparison of various treatments without bias or conflicts of interest, and assist citizens of the United States. However, in the present atmosphere philosophical differences, public outcry on both sides, issues on left and right, and political horse-trading, that would likely not be the case. However, policy-makers should follow, and the public should yield to, the appropriate recommendations. To do so will result in powerful political figures and their beliefs for the country.

To avoid unintended consequences of comparative effectiveness, the following should be implemented:

1. The Administration and Congress should reject the statutory creation of a board, council, or institute that would centralize government control without accountability to the public through Congress. This essentially will prevent additional enormous power to be vested in the Administration without Congressional oversight. One party in power may believe this is the best to do. The party in power at the present time may believe this is the best to do; however, once the power changes hands, they will regret it.

Every action taken in public should be accountable, especially when one-sixth of the U.S. economy is being controlled and at risk. Irrational, unchecked, biased, financially motivated decisions by a council, board, or institute will cause irreparable damage to the United States, not only to the U.S. health care system, but the entire economy.

This entity should be charged with systematically developing both comparative clinical- and cost-effectiveness evidence for competing clinical management strategies.

2. CER and HTAs should be undertaken utilizing the principles of EBM without inherent bias and with the involvement of all stakeholders.

CER should be conducted not only by the government, but also by the private sector, specifically providers. While the government can contribute to research efforts and promote the widespread availability of the best information, it must not exercise monopoly over the conduct of research itself or the distribution of information.

The definition of comparative effectiveness study and methodology must be clearly defined. The components of the panels performing the comparative effectiveness analysis should include at least 50% practicing clinicians of that particular specialty, but not academicians with removed connections, epidemiologists, methodologists, etc. However, the remaining 50% can be epidemiologists and methodologists, either physicians or non-physicians.

3. CER should be patient-centered and supportive of quality and value, not focused simply on cost-containment.

While cost effectiveness and cost benefit analysis is extremely important in determining what is covered and what is not covered, the analysis and the research must be performed appropriately without bias and financial conflicts of interest.

It is acknowledged there is general sensitivity toward the use of cost-effectiveness information (22), limited understanding among the general public, specific concerns regarding methodology, and the potential for inappropriately restricting access to necessary health care. Therefore, it is crucial that appropriate methodology is developed to produce high-quality cost-effectiveness information, which is adaptable, transparent, and reproducible.

Further, the cost-effectiveness should not be the primary criteria in approving or disapproving health services.

Finally, the CER must move beyond closed door systematic reviews, randomized trials with placebo control, utilization of methodologically flawed procedures, and ever changing parameters, to fully transparent and accountable methodologies which address the validity and general applicability of findings with consideration of all types of evidence, including observational evidence, equivalence or non-inferiority trial evidence, and the evidence obtained from practical clinical trials (PCTs).

5.0 Conclusion

As it is clear from these discussions, the British experience, and experience from other international examples, a comparative effectiveness strategy that relies on government with unlimited powers would be counterproductive to the U.S. health care and economy. Further, it would undermine the incentives for medical innovations and lead to the imposition of cost constraints that would worsen patients' medical conditions and damage the quality of their lives. The deepest concern about CER is that it will be misused, which is why some legislators seek to prohibit information on comparative effectiveness from influencing coverage policy and payment decisions. However, this can never be done. By the same token, these decisions will not be improved by discouraging the use of the most relevant and valid information about what works and for whom it works. Consequently, CER is not a panacea, but it is a key to individualized care and innovation and may not be a threat if appropriately conducted.

Given the explosion of health care expenses, patients being declined by private insurers, escalating unemployment, and increasing public payments, the time is right for patients, physicians, insurers, and health care policy-makers to explicitly and transparently factor the comparative effectiveness, comparative cost, and cost-effectiveness of both new and existing health care interventions into their decisions (22). Consequently, in the United States, keeping all politics aside, should establish a trusted, independent, adequately funded national entity. This entity should be accountable; it should develop and disseminate evidence on comparative effectiveness and costs; cost-effectiveness in health care; and educate the public about the urgency of modifying our cultural bias toward ignoring effectiveness in health care.

Interventional pain management is an evolving specialty. We are at a crossroads. Unlike the ACP or other major societies, we do not have a long history and tradition of initiating and performing outstanding CER, leading to strong evidence-based guidelines and dramatic improvement in clinical outcomes. However, these efforts have been initiated. Numerous studies in interventional pain management have been published recently, and well performed systematic reviews and evidence-based clinical guidelines have been developed. However, we are in the cross hairs of numerous critics, internal and external, with or without understanding of interventional pain management, resulting in widespread opinions and variations in practice. Some interventional pain physicians fail to adhere to guidelines, or promote cost-effective interventional pain management. Expensive technologies must be stopped in the absence of any evidence of better patient or public health. As Lauer (13) has quoted, we cannot say, "Let me tell you how I like to _____." Thus, we have to develop and practice evidence-based interventional pain management.

Acknowledgments

The authors wish to thank the editorial board of Pain Physician for review and criticism in improving the manuscript; Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript.

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