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Mark Gibson, Deputy Director
Center for Evidence-based Policy
2611 SW 3rd MQ280
Portland, Oregon 97201

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I. Project Overview

While preparing the 2001 Medicaid budget for the state of Oregon, officials were shocked to see that analysts predicted a 60% increase in drug spending over the two year budget cycle. They immediately realized that something significant had to be done both from the standpoint of efficient use of tax dollars, and from the fact that rapidly increasing costs in Medicaid were constantly threatening the ability of the state to maintain Medicaid coverage for very low income Oregonians.

The state adopted a number of strategies to address this problem, one of which was to employ a preferred drug list (PDL). Preferred drug lists seek to create price competition among manufacturers by the state selecting the lowest cost drug in the class as its preferred drug and then giving providers incentives to prescribe that drug first. To the extent that the state can then shift usage to the lowest cost drug, the difference in price paid for the medications becomes savings that can be used to maintain access to the program for low income residents or to support other needed health services that would otherwise be dropped due to cost pressures in the program.

However, simply requiring doctors to prescribe the lowest cost drug in a given class of medications could be counter productive. Prescription drugs have changed over the years and in some cases, there have been significant improvements in the quality and effectiveness of some medicines. If insisting on the lowest cost drug caused doctors to prescribe inferior medications then not only would health outcomes be adversely affected, but other costs in the system could increase because patients might remain sicker longer, or have to use other health services more often.

The challenge facing Oregon was to create a clinically sound and effective PDL, based on the best possible assessment of the comparative effectiveness, safety, and effect on sub-populations of drugs within classes of medications. To get this information, the state partnered with the Evidence-based Practice Center (EPC) at Oregon Health and Science University in Portland. As a first step, the state commissioned the EPC to produce full systematic reviews of the global medical literature of four classes of drugs.

As the first four classes (Statins, NSAIDs, PPIs, and Opioid Pain Relievers) were completed, the information found its way to Medicaid officials in Washington and Idaho. Recognizing that these reports were more comprehensive and rigorous than what they were currently using they suggested that they join Oregon in an informal collaboration to fund studies of additional classes.

Soon additional studies were commissioned and the states began using them in their drug purchasing programs. However, because of its comprehensive nature, the process of doing systematic reviews is relatively expensive (approximately $130,000 per drug

class). In addition, it became clear that in some classes, frequent updates of the reviews would be required to stay abreast of the research taking place in the field.

As a result, the three Northwest states sought a broader collaboration with other states. The Center for Evidence-based Policy (Center) at OHSU with incubation support for the project from the Milbank Memorial Fund began working with a number of other states who had expressed an interest in gaining access to this high quality information and a larger collaboration quickly took shape.

This collaboration became known as the Drug Effectiveness Review Project (DERP). What had started out as one state working to bring the best clinical knowledge available to its Medicaid drug purchasing had become a broadly representative group of 14 states and two other organizations who would eventually commission systematic reviews of 26 classes of drugs, and routine updates of the classes once their original studies were completed.

Drug Effectiveness Review Project (DERP)

The Drug Effectiveness Review Project consists of the following elements:

- A collaboration of 16 participating organizations each contributing an equal amount to the financing of the project. The collaboration is producing systematic reviews of the comparative effectiveness, safety, and effect on sub-populations of drugs within 26 classes of drugs[1]. The participating organizations guide the operation of the DERP through a self-governing process in which each organization is equally represented. 14 of the 16 participating organizations are state Medicaid programs[2]. The other two participating organizations are the California Health Care Foundation and the Canadian Coordinating Office for Health Technology Assessment.
- The Center for Evidence-based Policy (Center), School of Public Health and Preventive Medicine, Oregon Health and Science University supports the collaboration, by executing the intergovernmental agreements and contracts required to finance the collaboration and by staffing the governance group that directs the Project. In addition, the Center supports communication between the

[1] Classes under review are: Proton Pump Inhibitors, Long-acting Opioids, Statins, Non-steroidal Anti-Inflammatory Drugs, Estrogens, Triptans, Skeletal Muscle Relaxants, Oral Hypoglycemics, Drugs to treat Urinary Incontinence, ACE Inhibitors, Beta Blockers, Calcium Channel Blockers, Angiotensin II Receptor Antagonists, 2nd Generation Antidepressants, Antiepileptic Drugs in Bipolar Mood Disorder and Neuropathic Pain, Newer Antihistamines, Atypical Antipsychotics, Inhaled Beta Agonists, Inhaled Corticosteroids, Drugs to treat ADHD and ADD, Drugs to treat Alzheimers, Anti-platelet Drugs, Thiazolidinedione, Newer Antemetics, Newer Sedative Hypnotics, Targeted Immune Modulators

[2] Alaska, Arkansas, California, Idaho, Kansas, Michigan, Minnesota, Missouri, Montana, North Carolina, Oregon, Washington, Wisconsin, Wyoming

participating organizations and the Evidence-based Practice Centers, provides technical assistance to participating organizations on the use of systematic reviews, ensures that timelines are met, and manages communication between pharmaceutical companies and the project.

- The Evidence-based Practice Centers (EPCs) perform the systematic reviews of medical evidence comparing the effectiveness of drugs within classes determined through the governance process of the Project. The EPCs are designated by the U.S. Agency for Healthcare Research and Quality as particularly well qualified to perform these evaluations of the medical literature.

The Project is based on the principle of "Globalizing Evidence and Localizing Decisions." The reports produced by the Project do not recommend a preferred drug nor do they consider the cost of the medications in question. They simple report on what the evidence shows about the comparative effectiveness, safety and effect on sub-populations of the medicines. This information is then taken by the states and incorporated into their local decision-making processes.

The Project's reports are created in a process that fully discloses each step taken, each source considered, and painstakingly describes the reasoning behind the analysis conducted. The process of producing the reports has numerous methods for soliciting comments and criticisms from the public, from advocacy groups, and the drug industry and this input is systematically used to improve the quality of the reports. Neither the researchers who produce the reports nor employees of the Center are allowed to have any economic interest in the drugs being investigated. The reports can be viewed at the Project's website at www.ohsu.edu/drugeffectiveness.

There are several ways in which the states use this information. In some cases they simply array it in formats readily useable by prescribers and distribute it as an educational service to practitioners serving Medicaid clients. In others it is used as a clinical check to analyses provided by commercial pharmacy benefit managers. In still others, the reports are the primary clinical information source for their PDL. However, all of the states using PDLs have processes for considering additional information including public testimony, review by local clinical experts, and incorporation of appropriate cost information.

Many of the states in the collaboration are experiencing significant savings in their drug expenditures. The clinical information provided by the DERP gives them clear indications of where they can aggressively bargain with drug companies for better prices and still maintain the quality of care provided in their Medicaid programs. Their savings vary according to the bargaining process they use, but virtually all that are using PDLs are experiencing savings as a result of higher utilization of equally effective lower cost drugs.

Many of the states are generating additional savings by coupling their PDL with a prior authorization process which requires doctors to give a clinical reason for not using the preferred drug before approval to purchase a higher cost drug is granted. This approach is so effective in moving usage to the preferred drug that manufacturers are willing to provide significant supplemental rebates to the states in order to ensure that their medications are included as first options in the PDL.

For example, one state reported that in a class where there was no evidence of any difference in effectiveness among the various medications available, their utilization of the preferred drug went from 33% of the drugs purchased in 2003 to 69% of the drugs purchased in the class in 2004. The savings were substantial because the monthly cost for the preferred drug was $77.61, and the average cost for the non-preferred drugs was $331.32 per month. This same state reports substantial supplemental rebates provided by providers wishing to ensure that their drugs are included in the PDL first option.

Moreover, using the best available clinical information can increase the quality of care in Medicaid and provide additional savings by ensuring that the best drug in a class is used. Here, the well known story of Vioxx provides a good example. In 2002, in the original report on Non-steroidal Anti-inflammatory drugs (NSAIDs), the EPC highlighted the potential cardiac risk associated with Vioxx. As a result, most states did not include Vioxx as a preferred drug. This not only saved the costs linked to purchasing Vioxx (typically one of the more expensive drugs in the class) but it also prevented the cardiac complications, suffering, disability and costs associated with the use of the drug before it was pulled from the market.

The DERP continues to evolve as more is learned about using systematic reviews to compare drugs. It has prompted significant discussions about the quality of evidence available on the effectiveness and safety of many drugs. The systematic approach has provided a clear view of the lack of information available on many subpopulations and has highlighted the need for either the industry or the public sector to fill in these gaps in much needed information.

The quality of the research provided by the DERP has generated significant interest in its products in groups outside of Medicaid. Presently, DERP reports are the foundation for the Consumer's Union Best Buy Drugs web site. This initiative takes the highly technical DERP documents and combines the findings with cost information then presents the information in language understandable to the public at large. This enables consumers to work with their physicians to ensure that they are receiving the best value for their prescription drug dollar. A similar approach has been undertaken by AARP, and its summaries of our reports are also posted on its web site providing consumers with access to this vital information.

The DERP is poised to provide constantly improving comparative information on drugs for the foreseeable future. It promises to be a continuing resource for public programs and private purchasers for years to come. More detailed information on the research process, the methods of communication with the pharmaceutical industry, specific elements of the program is attached.

II. Systematic Reviews of Research and Evidence

The research produced by the project is the most rigorous and defensible clinical information for making drug purchasing decisions available today. The research consists of Systematic Reviews of the global medical literature. Well done systematic reviews are considered the gold standard for evaluating the whole of what research has to say on a given topic. The reports generated by the DERP compare the effectiveness, safety, and effect on subpopulations of drugs within therapeutic classes.

The reports generated by the DERP are also fully transparent. They fully disclose their methodology, sources, analysis, and conclusions. The final reports are posted in the public domain on the World Wide Web at www.ohsu.edu/drugeffectiveness.

The credibility of systematic reviews results from their painstaking research process. The following are the key elements of the systematic review process conducted by Evidence-based Practice Centers used in the collaborative effort:

- Formulating key questions;
- Finding evidence;
- Selecting and evaluating evidence;
- Synthesizing and presenting evidence;
- Conducting peer review;
- Revising draft documents into final systematic reviews; and
- Maintaining and updating reviews.

Each step of this process is important to producing the highest possible quality reports and in providing decision makers with relevant, reliable information as they address coverage, reimbursement and other decisions concerning pharmaceutical products. A greater understanding of the research process will demonstrate why policy makers can trust the information in a well done systematic review.

Formulating Key Questions

The most important and sometimes the most difficult steps in starting the systematic review process are to establish the questions that the review of research literature is to answer. Clearly, top quality research that answers an irrelevant question is useless to policy makers and wasteful of resources.

It is important to spend the time needed to engage fully in the process of identifying key questions. This step cannot be left to one party. Policymakers need advice on exactly how to

phrase questions clearly, and in ways suitable for an evidence-based process, so that they can obtain the information they need for policy formulation. Researchers need this dialogue to ensure that the work they are doing is relevant to the policies being developed.

In the Drug Effectiveness Review Project, the Center convenes a dialogue between the participating organizations and the researchers assigned to the class of drugs under review. This dialogue carefully specifies the populations to be addressed, the interventions to be studied, and the health or other outcomes (both positive and negative) to be evaluated.

The DERP usually starts with the following general template and then adds details to the template until it defines the scope of the research:

1. What is the comparative efficacy of different (name drug class) in improving (name the outcome desired) for (name type of patients by symptoms, disease etc.)?

2. What are the comparative incidence and nature of complications (serious or life threatening, or those that may adversely affect compliance of different (name the drug class) for patients being treated for (name the type of patients by symptoms, disease, etc.)?

3. Are there subgroups of patients based on demographics (age, racial/ethnic groups, and gender), other medications or co-morbidities (obesity for example) for which one or more medications or preparations are more effective or associated with fewer adverse effects?

Participating organizations have time to gather input from parties that will be affected by the policies in question, including among others, patients, pharmacists, and physicians. This feedback helps ensure that the concerns of patients and practitioners are thoroughly considered. In addition, draft key questions are posted to the project's web site and comments on the questions are solicited from the public, advocacy organizations, and the industry. Specifying clear and appropriate key questions *in advance* helps ensure that evaluations of the evidence are not biased and that the evidence is interpreted without regard for pre-existing opinions.

When the dialogue is completed, the key questions:

- Specify the clinical conditions (diagnoses, diseases) to be included in the review;
- Define the populations, interventions, and outcomes (expected benefits, potential risks or harms) of interest for the review.

Finding Evidence

In an electronically connected world, finding all the information needed to make good decisions sounds easy. Although finding some information is easier than ever, the diversity of sources for information pertinent to the types of decisions under consideration by states and other purchasers, requires knowledgeable and skilled personnel as well as access to a wide array of computer-based and hard copy sources of research literature. Using all available information sources ensures that the greatest possible amount of relevant information is obtained and analyzed.

The Evidence-based Practice Centers (EPCs) specialize in using multiple search techniques. These technologies are focused on major databases of the world's medical literature and other resources such as systematic reviews and clinical trials found in the Cochrane Collaboration Library. In addition, the Centers can accept published or unpublished information from all reasonable sources, if the party submitting the information allows the information to be made public so that it can be openly compared to other information acquired by more traditional methods.

After searching these data bases, the bibliographies of relevant studies are also searched for any citations that have otherwise been missed.

Finally, all U.S. and Canadian drug manufacturers are provided the key questions and are asked to provide a dossier containing any evidence they believe is useful in answering the questions posed.

Selecting Evidence

Sometimes the known or expected volume of information is overwhelming. Moreover, Separating information expected to be useful from potentially irrelevant or misleading data is a special challenge, even when key questions have been well specified. Thus, an important step is to specify, in advance, the sources of "admissible" evidence related to the key questions. This is referred to as "stating the eligibility criteria" for material that will be included or excluded from consideration in the review process. The evidence-based process calls for EPCs to take the following factors into account in describing evidence to be selected and retained:

- Which databases or other sources and information to include;
- What factors relating to language, year of publication, and similar details should be considered;
- What types of publications to include; and
- What types of research studies to include.

When considering the types of research that will be accepted, although randomized controlled trials (RCTs) involving head-to-head comparisons of drugs may be the optimal

design for this process, they are not the only evidence that may be valuable to or necessary for decision makers. RCTs with placebo controls, for example, may be important as well. Moreover, large, well designed studies other than RCTs are often critical sources of data on populations not typically included in RCTs, on longer-term outcomes, and on potential adverse events.

Once the eligibility criteria have been identified, the process of searching for relevant evidence begins by reviewing titles and abstracts of research studies, or entire articles reporting on such investigations, against the eligibility criteria already stipulated, and deciding which items to use and which to set aside. If an article or study is excluded from consideration, the reason for doing so is recorded as part of the final documentation.

Once the acceptable sources of information have been identified, the information in them is abstracted into detailed "evidence tables" that provide crucial information on study purpose and design, populations, diagnoses or conditions, interventions, outcomes, and other data.

Synthesizing and Presenting Evidence

Synthesis of evidence is the process of analyzing and combining all good information gleaned from the review of research studies and findings relevant to the key questions formulated at the outset. Analysts typically rely heavily on information from evidence tables for this task. This step, and the overall presentation of evidence, can be done in qualitative terms, through text discussion of the evidence, and in quantitative terms, through statistical combination of information in a technique known as meta-analysis.

A critical element of the evaluation of the evidence involves two related steps: grading the quality of individual studies and rating the strength of the overall body of evidence. These are formal steps for which well-recognized methods exist. For a systematic review to be defensible it is imperative that both of these judgments be made in a clear and consistent manner.

Review of the quality of individual studies relies on study design *and* conduct. Study design alone is insufficient. The best-designed study can provide poor evidence if the conduct of the study does not rigorously follow good research practice. The quality of a study is often summarized as providing good, fair, or poor evidence, and reviewers must clearly state how the review uses each category of evidence. For example, does the review consider (but down-weigh) poorly designed or conducted studies or exclude them altogether. This may be particularly important when quantitative syntheses are performed. Another consideration is that study quality may not, by itself, be sufficient. A very good study that has only limited applicability to a key question may not be as helpful as a fair study that is directly related to the question at hand. Often, systematic reviews will focus particular attention on a limited number of high-quality, critical studies, from which key evidence can be highlighted in more detail

Evidence tables are always created to allow those decision makers the opportunity to examine the entirety of the evidence. For ease of presentation, summary tables derived from detailed evidence tables may also be desirable or other approaches to presenting information about the magnitude of benefits and harms such as “balance sheets” that provide results in terms of the number of patients who would benefit or be harmed by undergoing a particular intervention can be used. The Center works with the participating organizations and the researchers to make certain that the information provided is arrayed in ways that are most useful to the policy makers that will use it.

As all the evidence is organized into evidence tables, summary tables, and text, reviewers then need to make some assessment of the overall quality and applicability of the evidence. The questions at this stage involve the cumulative quality of the studies (are studies mostly of good quality, mostly of fair or only poor quality, or a mix), the quantity of the data (e.g., numbers of studies and aggregate sample sizes), and consistency (e.g., do the studies show consistent results or are some clearly negative and some positive). Again, the entire body of evidence is often characterized as good, fair, or poor, and typically the limitations of the literature are discussed.

In synthesizing all this information, reviewers may also address a variety of other questions of concern to policymakers. These include but are not limited to:

- What do the largest studies show compared to smaller ones?
- What populations have been studied and are those populations relevant to the question at hand? What critical populations have been excluded or ignored?
- Have "real life" outcomes of concern to patients been studied, or have outcomes been limited largely to biologic or physiologic measures?
- Have risks and harms been reported as thoroughly as benefits?

All these preceding steps will then be assembled into a draft systematic review, complete with background, methods, results, discussion, evidence tables, summary tables, and citations (references). This draft is then subjected to external peer review.

Conducting Peer Review and Revising the Draft into a Final Systematic Review

Peer review is the act of soliciting critiques from national and international experts and potential users of the systematic review. Peer reviewers are asked to comment on factual matters, presentation, interpretation, missing information, readability/usability, and similar matters. The aim is to identify omissions, unwarranted conclusions or inferences, unintentional bias, inadvertent over- or under-emphasis, and unnecessarily tedious, obscure, or misleading writing. Peer review is an integral part of the standards required by the Agency for Healthcare Research and Quality for developing systematic reviews. Comments from reviewers are all given serious consideration.

Peer reviews are solicited through distribution of the draft review to reviewers with expertise in the relevant clinical area outside of the EPC. The draft is also placed on the DERP website to obtain reactions from the public, advocacy organizations, and the industry.

Following peer review the authors of the systematic review begin necessary revisions. All legitimate points raised by the peer review are addressed in the final draft of the systematic review. For example, if reviewers note important missing data or studies, these are obtained and data from them are added to evidence tables and text, as appropriate.

Once the authors have completed the final evidence report, they will then make it available for dissemination as determined by the participating organizations. The authors of the report may also submit the report, or a shorter article summarizing it, for publication in a scientific journal. These journal publications further enhance the credibility and impact of the reports and of the evidence-based process within the scientific community.

Maintaining and Updating Reviews

Even the best information can become outdated, sometimes quickly (within months) and, sometimes, over a longer period (two to three years). The Drug Effectiveness Review Project updates reviews as appropriate given the amount of research being done on the given class. For classes that are experiencing a large amount of research, the updates occur every 6-8 months. Classes with little research taking place may wait for two years to be updated. Each update will consist of a new literature search that seeks additional data or analysis from studies published in the interim; of particular significance will be newly published systematic reviews on the same or a related topic and results from clinical trials or large observational studies.

III. Evidence-Based Practice Centers

Overview

Evidence-based Practice Centers (EPCs) offer a perfect resource for answering complex clinical questions. The EPCs are experienced at the task of evidence-based systematic reviews. They are part of a larger effort devoted to evidence-based analysis overseen by the Agency for Healthcare Research and Quality (AHRQ). As a result, they have access to researchers, peer reviewers, and database searching resources throughout the world.

Considerations that support the use of EPCs in the Drug Effectiveness Review Project include:

- EPCs realize the importance of getting the question right – making sure that research is relevant and properly focused for use in policymaking.
- EPCs have access to extensive peer review resources.
- EPCs are experienced in working with both public and private customers.
- EPCs have experience working in public settings. Their work is virtually always used and reviewed in public settings.
- EPCs have a proven record of performing to contract requirements.
- EPCs have high standards regarding conflict of interest. They strive to avoid even the appearance of conflicts of interest.
- EPCs have experience helping local decision-making groups understand the research process and assisting these groups in appropriately using research products.
- EPCs have the flexibility to produce the type of report needed—from Cochrane-type reports to technology assessments, systematic reviews, and other decision aids.

EPC Background and History

In 1997, the Agency for Healthcare Research and Quality (AHRQ, known previously as the Agency for Health Care Policy and Research) launched its initiative to promote evidence-based practice in everyday health care through establishment of 12 Evidence-based Practice Centers (EPCs). The EPCs develop evidence reports and technology assessments on clinical topics involving conditions or health services that are common, expensive, and/or are significant for the Medicare and Medicaid populations. With this program, AHRQ became a "science partner" with private and public organizations in their efforts to improve the quality, effectiveness, and appropriateness of health care by facilitating the translation of evidence-based research findings into clinical practice.

AHRQ is the lead federal agency for enhancing the quality, appropriateness, and effectiveness of health care services and access to such services. In carrying out this mission, AHRQ conducts and funds research that develops and presents evidence-based information on health care outcomes, quality, cost, use and access. Included in AHRQ's legislative mandate is support of syntheses and widespread dissemination of scientific evidence, including dissemination of methods or systems for rating the strength of scientific evidence. These research findings and syntheses assist providers, clinicians, payers, patients, and policymakers in making evidence-based decisions regarding the quality and effectiveness of health care.

Since 1997, the EPCs have conducted more than 100 systematic reviews and analyses of scientific literature on a wide spectrum of topics. Summaries of EPC reports may be reviewed by visiting AHRQ's website, www.ahrq.gov. EPC evidence reports and technology assessments have been used by systems of care, professional societies, health plans, public and private purchasers, states, and other entities, as a scientific foundation for developing and implementing their own clinical practice guidelines, clinical pathways, review criteria, performance measures, and other clinical quality improvement tools, as well as for formulating evidence-based policies related to specific health care technologies.

The EPC Program is an essential component of AHRQ's support for evidence-based systematic reviews, analyses, and research. AHRQ intends that evidence reports, technology assessments, and research flowing from EPCs will be useful to a broad array of stakeholders— consumers, providers, employers, policymakers—and be more rapidly available than previous evidence-based efforts.

In June 2002, AHRQ announced the award of new five-year contracts for EPC II to 13 Centers in the US and Canada to continue and expand the work performed by the original EPCs.

Development of Reports

The EPCs develop evidence reports and technology assessments based on rigorous, comprehensive syntheses and analyses of relevant scientific literature on clinical, behavioral, organizational, and financing topics, emphasizing explicit and detailed documentation of methods, rationale, and assumptions. These scientific syntheses may include meta-analyses and cost analyses. All EPCs collaborate with other medical and research organizations so that a broad range of experts participates in the development process.

The resulting evidence reports and technology assessments are used by federal and state agencies, private sector professional societies, health delivery systems, providers, payers, and others committed to evidence-based health care. In addition, the EPCs:

- Update existing reports;
- Provide technical assistance to professional organizations, employers, providers, policymakers, and others to facilitate translation of the reports into quality improvement tools, evidence-based curricula, and reimbursement policies; and
- Undertake methods research by comparing and studying the outcomes of various research methodologies. Profiles of Evidence-based Practice Centers Likely to be used in Project

The following are profiles of the three EPCs that produce systematic reviews for the DERP.

PROFILE - Oregon Evidence-based Practice Center

The Oregon Evidence-based Practice Center based at Oregon Health & Science University, (OHSU) in Portland, Oregon, serves as a resource center for the production of systematic reviews and related projects in evidence-based medicine for federal and state agencies and private foundations. These reviews report the evidence from clinical research studies and the quality of that evidence for use by policymakers in decisions on guidelines and coverage issues.

Capabilities

Mark Helfand, MD, MS, MPH, associate professor of medicine and medical informatics & clinical epidemiology, directs the Oregon EPC; Heidi D. Nelson, MD, MPH, associate professor of medical informatics & clinical epidemiology and medicine, serves as co-director. Associate Director Merwyn Greenlick, PhD, is professor and chair emeritus of the Department of Public Health and Preventive Medicine and was the former director of the Kaiser Permanente Center for Health Research. EPC Associate Director William Hersh, MD, chair of the Department of Medical Informatics & Clinical Epidemiology, is one of several OHSU faculty involved with the Cochrane Collaboration.

Oregon EPC investigators have a particular interest in diagnostic technology assessment, prevention effectiveness, women's health issues, Medicare coverage, evidence-based informatics, systematic drug class reviews, patient safety, and behavioral counseling in the primary care setting. Since 1998, the Oregon EPC has produced systematic reviews of prevention, screening, and behavioral counseling topics to inform recommendations of the US Preventive Services Task Force.

Collaboration

The Oregon EPC is collaboration between Oregon Health & Science University, the Kaiser Permanente Center for Health Research, which has strong expertise in the areas of prevention effectiveness, health economics, and managed care, and the Portland Veterans Affairs Medical Center. Investigators at OHSU come from a wide variety of disciplines within the Schools of Medicine and Nursing. The EPC has also worked with investigators

from the University of Washington, the University of Colorado Health Sciences Center, the Portland Shriners Hospital, and Griffith University in Queensland, Australia.

Additional Information

All inquiries related to the Evidence-based Practice Center at Oregon Health & Science University should be directed to e-mail address: epc@oshu.edu. The Center's Web site is http://www.ohsu.edu/epc, or contact:

Mark Helfand, MD, MS, MPH
Oregon EPC Director
Oregon Health & Science University
Department of Medical Informatics and Epidemiology
3181 SW Sam Jackson Park Road
Portland, OR 97239-3098

Phone: (503) 494-4277 Clinical
Fax: (503) 494-4551
E-mail: helfand@ohsu.edu

PROFILE - Research Triangle Institute and University of North Carolina at Chapel Hill Evidence-based Practice Center

Research Triangle Institute, in collaboration with the five health professions schools and the Cecil G. Sheps Center for Health Services Research at the University of North Carolina at Chapel Hill, operates the RTI International*-University of North Carolina at Chapel Hill (RTIUNC) Evidence-based Practice Center for the Agency for Healthcare Research and Quality. The RTI-UNC EPC is headquartered at the North Carolina campus of Research Triangle Institute, a short distance from the UNC-Chapel Hill campus.

The RTI-UNC EPC will:

- Foster the development and dissemination of systematically developed, authoritative evidence reports (or technology assessments) on critical health care topics affecting all population groups.
- Work with science partners in the public and private sector, which will use these reports to improve clinical practice; help clinicians, patients and their families, payers and purchasers, and policymakers and to make better decisions and choices of effective and appropriate health care technologies; and improve patient and population health and well-being.
- Enhance methodologies for evidence reports and technology assessments.

- Determine the effects of such materials on health care practices and patient outcomes.

Capabilities

The RTI-UNC EPC brings extensive assets from five significant clinical and public health areas: dentistry, medicine, nursing, pharmacy, and public health. It also combines expertise in health services research and policy analysis with depth of technical skills in all forms of quantitative, qualitative, and social sciences methodology. The RTI-UNC Center can marshal appropriate and appreciable resources to study issues on a full range of clinical topics, from prevention and screening through diagnostic testing to therapy, rehabilitation, counseling, and palliative care.

The EPC is prepared to:

- Carry out rigorous review and critique of the clinical and biomedical research literature in a timely and efficient way.
- Conduct all forms of relevant analysis (such as meta-analysis or cost-effectiveness analysis).
- Produce useful materials for and provide technical assistance to all interested parties and provider, patient, and consumer groups.
- Perform small or large projects to evaluate the use, implementation, and impact of evidence reports and similar tools and products on the delivery, costs, quality, and outcomes of health care in the United States and elsewhere.

The RTI-UNC Center can call on up to 450 clinical, substantive, and methodologic experts for studies and activities done for the AHRQ evidence-based practice program, for other public sector agencies at both the Federal and State levels, and for an array of private sector organizations such as professional societies and associations, patient and consumer groups, managed care organizations and insurers, and pharmaceutical firms.

Its Co-Directors are Kathleen Lohr, PhD, of RTI and Timothy S. Carey, MD, MPH, of the Sheps Center at UNC-CH.,

The RTI-UNC Center has numerous collaborators representing important constituencies, populations, and perspectives on health care. An initial list includes: the American Pharmaceutical Association; American Society of Health-System Pharmacists; Center for Clinical Quality Evaluation; Center for Health Services Research in Primary Care, Department of Veterans Affairs Medical Center (Durham VAMC); Center for Quality of Care Research and Education at Harvard; IMCARE (the Internal Medicine Center to Advance Research and Education); Kaiser Foundation Hospitals; Morehouse University Medical Treatment Effectiveness Center; Paralyzed Veterans of America; The Permanente Medical Group Research Institute, and Urban Health Institute at Harlem Hospital Center and Columbia College of Physicians and Surgeons.

*RTI International is a trade name of Research Triangle Institute. *Southern California-RAND*

PROFILE - Southern California Rand Evidence-based Practice Center

The Southern California Evidence-based Practice Center conducts systematic reviews and technology assessments of all aspects of health care, performs research on improving the methods of synthesizing the scientific evidence and developing evidence reports and technology assessments, and provides technical assistance to other organizations in their efforts to translate evidence reports and technology assessments into guidelines, performance measures, and other quality-improvement tools.

Capabilities

The Southern California EPC brings together a breadth and depth of methodological and clinical expertise and can staff multiple simultaneous task orders. The EPC is also the natural progression of more than 20 years of work (dating back to 1972 and the beginning of the RAND Health Insurance Experiment) by RAND and its affiliated institutions in reviewing the biomedical literature for evidence of benefits, harms, and costs; using meta-analysis, decision analysis, and cost-effectiveness analysis to synthesize the literature; developing measures of clinical appropriateness and practice guidelines; developing and assessing medical review criteria; and developing and assessing performance measures and other tools for translating evidence-based knowledge into clinical practice. The hallmark of this work has been: (1) its multi-disciplinary nature: RAND and its affiliated institutions combine the talents of clinicians, health services researchers, epidemiologists, statisticians, economists, and advanced methods experts in meta-analysis and decision analysis; (2) the advancement of knowledge about the methods for performing literature reviews, synthesizing evidence, and developing practice guidelines or review criteria; and (3) the emphasis on developing and evaluating products for use in the real world of health care delivery.

Collaboration

The Center combines the talents of RAND and its five affiliated regional health care institutions:

- University of California, Los Angeles
- University of California, San Diego
- Cedars-Sinai Medical Center/ZYNX Health
- University of Southern California
- Children's Hospital Los Angeles.

In addition, through the VA/RAND/UC Field Program "Center for the Study of Health Care Provider Behavior," two Department of Veterans Affairs (DVA) Healthcare Systems collaborate with the Center:

- Greater Los Angeles VA Healthcare System
- San Diego VA Healthcare System

The Center is also affiliated with five health services research training programs, and the International Cochrane Collaboration.

IV. Pharmaceutical Companies: Communication and Involvement

The Center for Evidence-based Policy (Center) and the Evidence-based Practice Centers (EPCs) seek a fair and constructive relationship with the pharmaceutical industry. This document outlines the methods available to the pharmaceutical industry to inform the process of the Drug Effectiveness Review Project. The goals of the Center in relating to the industry include:

1. Obtaining the best evidence relevant to the key questions identified by the participating organizations for each drug class chosen.
2. Obtaining this evidence in a timely fashion.
3. Giving pharmaceutical companies an equal opportunity to provide evidence to the systematic review process.
4. Providing to participating organizations, policy makers, the public and pharmaceutical companies full disclosure of the source and content of all evidence considered in the systematic review process.
5. Providing a standardized, efficient, and open process for pharmaceutical company submission of evidence.

Note: All information submitted to the center will be available to the public at cost upon the release of the related draft systematic review or draft update.

The DERP provides the following opportunities for the pharmaceutical industry interaction with the Project.

- The primary process for pharmaceutical companies to transfer evidence to the Project will be by dossier submission. Submitting a correctly completed dossier will ensure that the evidence submitted by a company will be fully reviewed. Good quality evidence that is relevant to the key questions will be integrated into the Project reports and updates. Local decision makers will have the benefit of considering dossier information in the full context of other evidence.
- The Center will make available, at cost, copies of any evidence submitted in the Project dossier process at the time of release of the relevant draft report or update. This will enable all interested parties to assess the evidence submitted and its use in the systematic review process.
- The Center and the EPC will make every effort to ensure that all relevant evidence is considered in the systematic review process by conducting thorough searches of

the appropriate databases, review of dossiers, and any other appropriate sources of evidence. The Center and the EPC cannot ensure that evidence submitted by pharmaceutical manufacturers outside the dossier format will be included in the systematic review process. The Center will adhere to the timelines articulated in the initial report and update processes in order to provide an efficient and predictable product to local decision makers. Questions regarding the Project, any specific report, or update should be addressed to the Center for Evidence-based Policy as outlined below. Substantive communication will be scheduled in sessions open to the public. EPC staff will not meet with industry representatives regarding substantive issues outside of these public sessions.

- The Center and the Evidence Based Practice Centers host an annual conference for industry representatives to discuss the process, answer questions, and receive input on how to improve the dossier process.

Dossier Submission

Note: Any information submitted as confidential will be rejected. The Dossier submission process includes the following steps:

- A description of the Drug Effectiveness Review Project dossier submission process is provided to all pharmaceutical companies licensed to do business in the United States and Canada.
- The Center notifies pharmaceutical companies of the initiation of an evidence-based report or an update by certified mail. Notice is sent to the company CEO. Key questions in the initial systematic review or update are provided in the notice.
- Companies have eight weeks from the date notification is mailed to submit a dossier for an initial systematic review. Deadline for submission of a dossier for an update is four weeks from the date notice is mailed.
- To be considered, dossiers must be sent to the Center for Evidence-Based Policy, Oregon Health & Science University, 2611 SW 3rd Ave, MQ280, Portland, Oregon 97201-4950.
- Notice of this process is also provided on the Project web site.
- Only evidence relevant to the key questions is considered.
- To ensure that their evidence is considered, companies must submit evidence in the format provided by the Center including:
    - Indicating whether the company asserts their product is superior, equivalent or has unknown performance compared to other products in the class for the issues identified by the key questions contained in the initial systematic review or the update
    - Providing the current label for their product.

- Summarizing the submitted evidence in a table that includes study name/number, indication, population, and duration of exposure, endpoints, location, key results, and publication.
- Submitting electronic copies of the full text of any studies referred to in their dossier. An electronic copy of the bibliography for the dossier is also required. Illegible submissions will be rejected.

Center Submission to EPCs

The Center for Evidence-based Policy:

- Notifies pharmaceutical companies as described above.
- Receives dossiers, log their receipt, and distribute them as outlined below.
- Screens for required elements and legibility, and inform companies of dossiers not meeting these requirements.
- On the business day, following the dossier submission deadline provides 2 copies of each dossier to the EPC assigned to the initial report or update and a single copy to the coordinating EPC.
- Retain the master copy.
- Logs all dossier submissions by class, creating a specific entry for each submission that includes date received, company, whether the dossier complied with requirements, and any follow up communication with company.
- Coordinates the entry system with the coordinating EPC using EndNote software.
- Holds information submitted after the deadline for consideration in the update process.

Center Process for Release of Evidence

All materials submitted to the Center are available to the public upon the release of a draft systematic review or update. All evidence included in the report or update is listed in the report.

The Center for Evidence-based Policy:

- Maintains a file of all accepted dossiers.
- Maintains a master copy of all dossiers.
- Makes copies of dossiers available at cost and upon request at the time of release of the related draft initial report (16 weeks after dossier submission due) or draft update (13 weeks after dossier submission due).

- Notifies the requesting party of the cost of the request within 3 business days of the request. Cost will include a flat charge, a per-page copying fee and a shipping charge.
- Ships dossiers to the requesting party within three business days of receipt of payment.

Note: The Center will release only the full set of dossiers submitted for a drug class. Individual dossiers will not be copied and released.

Evidence Submitted to Local Decision Making Processes

When information is submitted to the local decision-making process, neither the Center nor the EPCs can ensure that the information will be considered in the relevant systematic review or update. The Center will:

- Inform all participating organizations of the process for submitting evidence to the Center and provide the participating organization with written instructions to give to pharmaceutical companies desiring to have their information considered.
- Encourage participating organizations to ask pharmaceutical companies to submit a dossier to the Center for inclusion in the review process and to give them the written instructions on how to do so.
- Review requests from participating organizations to review information submitted in local decision making processes, and determine whether the information has already been considered in the systematic review, and if not, the best way for that information to be reviewed.
- Track requests for review of additional information from participating organizations, the disposition of those requests.
- Notify all participating organizations of requests for additional information and the disposition of those requests.
- When appropriate, refer the additional information to relevant EPC to determine if the information meets the inclusion criteria for the related systematic review. If deemed not relevant the Center will inform the local decision maker within ten business days of receiving the information.
- If information is relevant to the key questions, the Center will forward the information to the appropriate EPC.
- If the information is relevant, submitted prior to the due date for the dossier submission, and submitted in the required dossier format, the evidence will be included as a dossier.

- If the information is relevant, submitted in the required dossier format, but submitted after the due date of the dossier process, the dossier will be included in the next update process.
- If the information is related to adding to or otherwise modifying the key questions, the evidence will be referred to the next governance group discussion regarding key questions for the update of the class.
- The Center will provide copies of evidence submitted in any local decision making process to any interested party upon their request following the same procedure as outlined for dossiers.

Note: All information submitted to the Center via a localized decision-making process will be available to the public on request.

Yearly Conference for Pharmaceutical Companies

The Center and EPCs will organize a conference on an annual basis for pharmaceutical companies and other interested parties. The conference goals will be to describe the current processes related to the Project, answer questions regarding these processes and provide a venue for industry participants to suggest improvements.

The conference will be held at a time and place designated by the Center and EPCs. The Center will notify pharmaceutical companies licensed to do business in the US and Canada 12 weeks prior to the conference of the time, place, cost and registration process. The Conference will be open to the public. The cost of the conference will be covered solely by registration fees. Any significant balance remaining in the conference account will be returned to participants on a pro rata basis. Center and EPC staff will be compensated for their time related to the conference from Center and EPC operating budgets, not the conference budget. Center and EPC support staff with dedicated time to the Conference will be compensated for that time from the Conference budget. Any travel expenses for Center and EPC staff related to the conference will come from the conference budget rather than operating expenses. The Center and EPCs reserve the right to cancel the conference if there is not sufficient registration to cover the cost of the conference. Participating organizations will be invited to attend the conference at their expense.

Ad Hoc Communication with the Center and EPCs

Pharmaceutical companies desiring to communicate with the Center and EPCs regarding the Project should contact the Center first. The Center will determine the nature of the inquiry and the appropriate next steps. If the contact involves the submission of evidence, the Center will provide the information required to integrate that submission into the dossier process. Any contact with the EPCs attempting to communicate or commenting on evidence will be made public. EPC staff will direct pharmaceutical inquiries to the Center.

John Santa MD will be responsible for responding to inquiries from scientific staff. Mark Gibson will be responsible for responding to inquiries from governmental affairs staff.

Note: Those wishing to have input into the Project cannot be assured their information will be included unless it is submitted according to the processes and guidelines outlined above.

Web Site

The Center and EPCs will maintain a web site for the Project. The web site will be updated on a regular basis regarding the Project including timelines, status reports, draft reports, updates, and key questions. If the web site is not available, the Project will make Center staff available by phone to answer questions.

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