CERTs ANNUAL REPORT

YEAR 5

Centers for Education & Research on Therapeutics

AHRQ Agency for Healthcare Research and Quality

Advancing Excellence in Health Care

U.S. Department of Health and Human Services

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Vision

To serve as a trusted national resource for people seeking to improve health through the best use of medical therapies.

Mission

To conduct research and provide education that will advance the optimal use of drugs, medical devices, and biological products.

Values

Public Interest. Research must be conducted to answer important questions that otherwise may not be addressed, with higher priority given to projects that offer better opportunities to achieve our mission and vision.

Public-Private Partnership. For results to apply to the "real world," the research must reflect a collaboration of groups with different perspectives and resources: patients, health care providers, government, academia, delivery systems, payers, purchasers, and manufacturers of medical products.

Multidisciplinary Alliances. The best research harnesses the collective expertise of medical practitioners, biostatisticians, clinical pharmacologists, health services researchers, clinical epidemiologists, pharmacists, clinical researchers, and others involved in health care.

Communication. The information from the Centers for Education & Research on Therapeutics must be made readily available to all relevant audiences.

Education. Education of current and future health care providers, policymakers, and patients is critical to improving health.

Public Policy. Policymakers must be provided with the best available evidence upon which to base policies.

Accountability. Americans should expect the CERTs to be a trusted resource when they need answers to questions about therapies.

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Letter from the Agency for Healthcare Research and Quality

Dear Colleague:

The Agency for Healthcare Research and Quality (AHRQ) has sponsored the Centers for Education & Research on Therapeutics (CERTs) since their establishment in 1999. The CERTs conduct research on the safety and effectiveness of medical therapeutics (drugs, biological products, and medical devices) and examine the benefits and risks of new, existing, or combined uses of therapeutics.

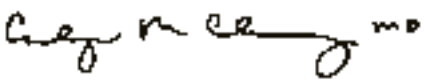
As the health services research agency of the Federal Government, AHRQ works with both public and private sectors to build the knowledge base for what works and what does not work in health and health care. Our aim is to see research translated into everyday practice and policymaking.

In keeping with AHRQ's mission, the CERTs not only engage in research but also reach out to policymakers, health care executives, the medical products industry, clinicians, consumers, and the media. CERTs workshops help put research into the hands of the people who ultimately make the decisions on the use of medical therapeutics. And the value of CERTs research is multiplied as the list of their public and private partners grows.

This report outlines the CERTs' endeavors in their fifth year. We see a focus on understanding the risks associated with frequently prescribed medicines, including COX-2 nonsteroidal anti-inflammatory drugs and erythromycin. Associated with this focus, the CERTs are exploring methods of communicating the risks of certain medications to change prescribing behavior, as well as conducting research on special issues concerning children, pregnant women, and the elderly. Their interest in health information technology continues. And this year a bioterrorism component has been added to the CERTs portfolio.

We are pleased to present this report outlining the CERTs work as a national resource on medical therapeutics.

Sincerely,



Carolyn M. Clancy, MD
Director

Letter from the Steering Committee

Dear Fellow Citizens:

The CERTs are delighted and honored to share the results from our fifth year of work. Our mission is to improve health. We do this by working for the best use of therapeutics and by serving as a trusted national resource. Conducting research and education projects is only the first step toward our goal of improving public health. The essence of our work is to ensure that important information about the best uses of therapeutics gets in the hands of the public, health care providers, and policymakers so that balanced decisions can be made about the risks and benefits of medical therapies.

The studies presented in this report illustrate the breadth and depth of our research. A number of CERTs studies contributed to high-profile health care news this year, including one study that examined the cardiac risks of erythromycin, another that measured frequency of inappropriate medication being prescribed to the elderly, and another about the overabundance of drugs classified as "risky" being used by pregnant women.

Our research reflects the ever-growing role technology plays in health care. Although technology can increase the efficiency and effectiveness of treatment, its use often involves a balance of benefit, risk, and cost. Therefore, CERTs researchers not only examine the use of such technologies; we also look ahead and anticipate the economic implications. For example, we are studying emerging technologies that offer significant benefits for patients but initially can carry a high cost. This kind of research can help policymakers resolve tough questions about improving access to effective treatments and technologies for all Americans.

In addition to our research efforts, a number of CERTs investigators have been tapped to consult on various projects with other leading national groups, such as the Institute of Medicine. For example, CERTs researchers participated in a study about the safety of medical devices used to treat children. These kinds of partnerships continue to forge our presence as a trusted national health care resource.

The collaborative structure of the CERTs enables us to respond quickly and judiciously to important emerging research needs. All of our partners—from academia, government, managed care, industry, health systems, consumer groups, and others—play an integral role with the CERTs, and we thank them for their considerable contributions, leadership, and support.

The CERTs and our partners are committed to meeting the many challenges that lie ahead. We look forward to working with many more of you to ensure that all Americans benefit from advancements in therapeutics.

Sincerely,

Hugh H. Tilson, MD, DrPH
Chair, on behalf of the CERTs Steering Committee:

Lynn A. Bosco, MD, MPH; Robert M. Califf, MD; Georges Benjamin, MD, FACP; Marc L. Berger, MD; Barbara A. Blakeney, MS, APRN, BC, ACP; Susan N. Gardner, PhD; Linda F. Golodner; Harry A. Guess, MD, PhD; James G. Kotsanos, MD, MS; Judith M. Kramer, MD, MS; Richard Platt, MD, MS; Wayne A. Ray, PhD; Kenneth G. Saag, MD, MSc; Marcel E. Salive, MD, MPH; Paul J. Seligman, MD, MPH; Brian L. Strom, MD, MPH; Myrl Weinberg, CAE; Raymond L. Woosley, MD, PhD

Introduction

The Centers for Education & Research on Therapeutics (CERTs) program was created to investigate and research specific areas of therapeutics, and to use this knowledge to educate consumers, health care providers, and policymakers about the risks and benefits of such therapies. The term "therapeutics" refers to the prevention and treatment of illness and disease with remedies such as drugs, medical devices, and biological products.

The CERTs were established in 1999 by the Agency for Healthcare Research and Quality (AHRQ) in consultation with the U.S. Food and Drug Administration (FDA). The program is administered as a cooperative agreement and receives funds from both public and private sources, with AHRQ providing core financial support.

The CERTs consist of a network of research centers, a coordinating center, a steering committee, and numerous partnerships with public and private organizations dedicated to improving the quality and safety of therapeutics. The overarching goals of CERTs research projects are to advance knowledge; inform health care providers, patients, and policymakers about that knowledge; and improve aspects of the health care system related to therapeutics.

CERTs research projects are diverse and represent a wide breadth of areas. For example, projects in this report include examining patterns of use for asthma drugs; exploring the role of nutrition in preventing autoimmune diseases; preventing harmful drug interactions; and establishing better guidelines for managing common diseases such as arthritis and gout.

This report highlights a number of CERTs research and educational projects completed in the past year. It also includes some of the projects currently in progress and in the planning stages. The extent of the CERTs projects offers the public a sense of the challenges and opportunities facing health researchers related to the use of therapeutics.

Medical Therapies

CATEGORY	EXAMPLES
Drugs	Prescription medications; over-the-counter medicines
Medical devices	Coronary stents; blood glucose monitors
Biological products	Vaccines; blood products

The Centers

CENTER	EMPHASIS
Duke University Medical Center	Therapies for disorders of the heart and blood vessels
HMO Research Network	Drug use, safety, and effectiveness in health maintenance organization (HMO) populations
University of Alabama at Birmingham	Therapies for musculoskeletal disorders
University of Arizona Health Sciences Center	Drug interactions that result in harm
University of North Carolina at Chapel Hill	Therapies for children
University of Pennsylvania School of Medicine	Therapies for infection; antibiotic drug resistance
Vanderbilt University Medical Center	Prescription drug use in a Medicaid population

CERTs Progress

Advancing Knowledge

Medical therapies are designed with one goal in mind: to improve health. The underlying challenge is that all therapies invariably involve some degree of risk. The CERTs are providing information to help health care providers, policymakers, and patients understand the risks and benefits of medical therapies in order to maximize those benefits and minimize the risks in their use.

UNDERSTANDING THE RISKS OF ADVERSE REACTIONS TO FREQUENTLY PRESCRIBED MEDICATIONS

Prescription drugs play an important and beneficial role in American medicine. But in some cases, they produce unwanted side effects, ranging from relatively mild allergic reactions to sudden death. The CERTs have undertaken a number of studies to uncover factors that increase risks associated with some frequently prescribed medications.

Popular Antibiotic Raises Risk of Cardiac Arrest[1]

Erythromycin, a commonly prescribed **antibiotic**, has been reported to cause episodes of serious **arrhythmia** or **sudden cardiac death** in both oral and intravenous forms. Previous studies of the association of erythromycin and arrhythmia have focused on the intravenous use of erythromycin, and there has been a perception that oral use of erythromycin is not associated with arrhythmias.

For the study, CERTs investigators examined computerized death certificate and hospital discharge records of patients enrolled in the Tennessee Medicaid program, TennCare, to identify potential cases of sudden cardiac death. They identified 4,404 patients for whom these records suggested occurrence of sudden cardiac death. They found that the association between the use of erythromycin and the risk of sudden death from cardiac arrest applies to the oral use of erythromycin as well as intravenous use.

Even more alarming was the elevated risk associated with using erythromycin in combination with other common medications that inhibit a specific type of drug enzyme known as cytochrome P450 3A (CYP3A). The risk of death for people using both erythromycin and **CYP3A inhibitors** was five times as high as the risk for those who were not using any of the antibiotic drugs from the study or any CYP3A inhibitors.

Among CYP3A inhibitors are the antibiotic clarithromycin (Biaxin®) and certain anti-fungal drugs used to treat toenail fungus and yeast infections, such as fluconazole (Difulcan®), ketoconazole (Nizoral®), and itraconazole (Sporanox®). CYP3A inhibitors slow down erythromycin's breakdown, thereby increasing its concentration in the bloodstream. The higher levels of erythromycin can trigger an abnormal, potentially fatal heart rhythm.

With safer antibiotics, such as **amoxicillin**, readily available, researchers conclude that practitioners should avoid prescribing erythromycin in conjunction with CYP3A inhibitors.

Penicillin Re-Exposure More Common Than Expected[2]

Penicillin is a commonly used **antibiotic** that provokes an allergic response in some people. Approximately 10 to 15 percent of adults report having had an allergic reaction to penicillin, but little was known about how

often such patients are re-exposed to penicillin or the risks caused by such re-exposure.

Most information about **allergic-like reactions** to penicillin has come from hospitalized patients, a population that represents only a small portion of the people who use penicillin. Because it might sometimes be necessary to re-administer penicillin to someone who has previously had an allergic-like reaction, it is important to gather more information about how often such re-exposure to penicillin occurs and the risks of such exposure.

CERTs investigators examined a large group of patients who were not hospitalized but had received prescriptions for penicillin more than 60 days apart. They identified patients who had symptoms similar to those of an allergic reaction on the day of or within 30 days after a prescription. Researchers found that an alarming number of patients were being prescribed penicillin a second time, despite a prior allergic-like event. The data indicated that almost half of those who had experienced such a response to penicillin were later given a second prescription, and in their subsequent use of penicillin, these patients faced a marked increase in the risk of an allergic-like reaction. The absolute risk of an allergic reaction was 0.18 percent following the first prescription, but it increased to 1.89 percent following the second prescription. These data emphasize the necessity for careful prescribing, and specifically the importance of avoiding prescribing penicillin to patients who suffered a previous reaction.

LEARNING MORE ABOUT BACTERIAL RESISTANCE TO ANTIBIOTICS[3, 4]

Antibiotics are a crucial weapon in the arsenal against infectious diseases, and yet widespread use undermines their effectiveness. Now in our fifth year, the CERTs have conducted numerous studies and interventions on the subject of bacterial resistance in an attempt to lower **antibiotic use** in situations where antibiotics are needlessly prescribed. **Bacterial resistance** to these medicines is a persistent problem in our country, and the CERTs are focusing on several different angles of this dilemma.

In one study, researchers looked at the rates of resistance to **penicillin** in **Streptococcus pneumoniae** (S. pneumoniae), which is the most common bacterial pathogen and among the most virulent. Instances in some communities of resistance to penicillin or other drugs recommended by national treatment guidelines raise the possibility that these guidelines may no longer be applicable nationwide. When choosing between prescribing older antibiotics or newer medicines, providers may need to rely less on national guidelines than on up-to-date information about local rates of drug resistance.

A second CERTs study examined data from acute-care hospitals in a five-county area of eastern Pennsylvania to determine whether a specific hospital's rates of antibiotic resistance could be a useful indicator of rates of drug resistance in the surrounding community. The results suggest that the information about drug resistance within one hospital poorly reflects the underlying rate of drug resistance in the community. The study demonstrates the danger that comes with the inability to predict or anticipate local drug resistance rates and the importance of additional research to identify reliable indicators of these resistance rates.

In another study, the CERTs examined long-term trends in resistance to **fluoroquinolone (FQ)** antibiotics among **Enterobacteriaceae**, such as E. coli and Salmonella. These are organisms that cause many inpatient and outpatient infections, including urinary tract infections and bloodstream infections. The data indicated increasing resistance in samples of these bacteria obtained from both inpatients and outpatients. However, the patterns of resistance differed across various Enterobacteriaceae and among clinical settings. The implications are that FQ antibiotics are used frequently to treat these common infections, but that if resistance continues to increase, the usefulness of these antibiotics will become severely limited.

EXAMINING THE SAFETY AND EFFECTIVENESS OF TREATMENTS FOR CHILDREN

Oftentimes, adults and children respond differently to medications and treatment regimens. **Children** have different metabolic rates, their bodies change rapidly, and their ability to understand and express information varies widely. The CERTs study how children respond to common medical therapies to enable parents and providers to make more informed decisions about treatment options.

Antipsychotic Medications Can Cause Side Effects in Children[5]

The use of **antipsychotic medications** in children ages 18 and younger for indications other than psychosis or

Tourette Syndrome, such as bedwetting, is controversial. But with the development of newer medications that avoid some of the dangerous side effects of traditional antipsychotic drugs, health care providers may be prescribing these medications more frequently, despite their potential side effects, such as weight gain, diabetes, galactorrhea, and adverse cardiovascular effects, such as life-threatening arrhythmias.

CERTs researchers examined data from children enrolled in TennCare and found that the proportion of these children using antipsychotic medications nearly doubled from 1996 to 2001, with a substantial increase in the use of antipsychotics for **attention deficit hyperactivity disorder (ADHD)** and affective disorders, such as **depression**. Given the risks of serious side effects, the CERTs study demonstrated a clear need for clinical studies to determine whether the benefits of these medications outweigh the risks in children.

Therapeutic Drug Monitoring Helping Children with HIV[6]

The "recommended prescribed dose" of a drug may work very well for many patients but not for others because of underlying differences from patient to patient, including differences in the way drugs are absorbed and metabolized. Less is known about these individual differences in children than in adults. Children may also metabolize drugs differently as they grow and develop. These differences may mean that the "recommended" dose may not have the treatment effect a sick child needs. HIV provides an important example. More than 20,000 children and teenagers in the United States may be infected with **human immunodeficiency virus (HIV)**. How they respond to given doses of anti-HIV drugs such as protease inhibitors may differ from how adults respond.

Therapeutic drug monitoring (TDM) is a way of measuring individual patients' response to drugs and tailoring drug doses to individual patients' needs. The CERTs have assessed the concentrations of protease inhibitors in the blood of children infected with HIV. Concentrations that are too high can be toxic, and concentrations that are too low can cause the virus to become resistant to the drug.

The group used a separation technique (high-pressure liquid chromatography) to develop a test for measuring four of the most commonly used protease inhibitors in blood samples. In a pilot study, they found that in a group of 15 pediatric patients taking at least one of the medications, four children, or 27 percent, had no detectable protease inhibitors in their blood plasma. One child had a suspiciously high concentration, suggesting that the patient had taken an incorrect amount of medication, or that the patient may have had abnormal metabolism of the drug.

The CERTs are now engaged in a larger study to further explore the use of TDM to tailor the treatment of HIV-infected children in order to get the best effect for each child.

Pediatric Guidelines Will Be Promoted

In a collaborative effort with an AHRQ Evidence-based Practice Center, the Ambulatory Pediatric Association (APA) published **guidelines** on three clinical topics: acute otitis media; otitis media with effusion; and

management of the infant with hyperbilirubinemia. The new guidelines are based on evidence developed by AHRQ.

After cataloging the resources identified by the experts who drafted the guidelines, a CERTs-APA team will work with practitioners to devise a set of tools and good practices to promote and disseminate the guidelines as widely as possible.

Informing Providers and Patients

The CERTs are committed to educating and informing health care providers and patients about the results of our research in therapeutics. Understanding the risks and benefits of medical therapies is a critical step to improving the safety and effectiveness of their use. It is also critical to ensure that patients and providers have the knowledge needed to use medical therapies appropriately.

INCREASING AWARENESS OF CRITERIA FOR DRUG USE TO MINIMIZE ADVERSE REACTIONS[7]

A recent and significant health care issue was the voluntary withdrawal of **Vioxx® (rofecoxib)** from the market by its manufacturer, Merck & Co. This action was taken in response to indications that the popular drug increased the risk of cardiovascular events (including heart attack and stroke).

Rofecoxib is a **cyclooxygenase-2 (COX-2)** selective **nonsteroidal anti-inflammatory drug (NSAID)** prescribed for the treatment of arthritis and a variety of musculoskeletal conditions. COX-2 drugs were developed as alternatives for patients needing chronic treatment for pain or inflammation who were at increased risk of gastrointestinal side effects of NSAIDs.

A CERTs study examined rofecoxib use and found that it was frequently prescribed and used at higher than recommended doses. Rofecoxib was approved for chronic treatment of osteoarthritis at doses of 12.5 mg and 25 mg, and for acute pain at doses of 50 mg for up to 5 days. However, in examining prescriptions for rofecoxib among people aged 50 or older enrolled in TennCare, researchers found that the use of high doses (50 mg) of rofecoxib for longer than 5 days was relatively common. This suggests that physicians were prescribing doses approved for acute pain and chronic arthritis interchangeably, despite emerging data and warnings that some COX-2 drugs cause serious cardiac side effects.

USING RISK COMMUNICATION TO CHANGE BEHAVIOR[8, 9, 10]

Another medication with potentially serious risk is **dofetilide (Tikosyn®)**, an oral anti-arrhythmic medicine for patients with **atrial fibrillation** and **atrial flutter**. Because the medication has been associated with **torsades de pointes**, a potentially fatal irregular heart rhythm, the manufacturer developed a distribution and management program to minimize the risks.

The CERTs conducted a study to see whether the **risk management program** was effective in improving compliance with dosing and monitoring recommendations. Researchers examined data for patients receiving either dofetilide or **sotalol** (another drug to treat arrhythmia) in the 12 months after dofetilide became available. Sotalol, like dofetilide, is used to treat atrial

fibrillation and flutter and also carries a risk of torsades de pointes. Sotalol already had been on the market for treatment of ventricular arrhythmias before its approval for atrial fibrillation/flutter, and at the time of the study, no risk management program for its use for atrial fibrillation/flutter was in place.

Comparing the prescribing of dofetilide (with a risk management program) and sotalol (without a risk management program), the researchers found that the starting dose of dofetilide was more often correctly adjusted on the basis of renal function than was the starting dose of sotalol. In addition, baseline and follow-up chemistries and ECGs were more frequently acquired as recommended in patients receiving dofetilide than in those receiving sotalol. This suggests that the dofetilide risk management program was effective in getting prescribers to adhere to dosing and monitoring recommendations on the label.

Yet the study uncovered what may be an unanticipated effect of the risk management program. Dofetilide was used markedly less often than sotalol. This suggests that physicians' avoidance of prescribing drugs with demanding risk management programs may undermine the purpose of such programs.

In another project, the CERTs evaluated the impact of several Federal and industry communication efforts on the risk of **tuberculosis** infections in **rheumatoid arthritis** patients using biological therapies. Following its licensure, potential adverse side effects of **infliximab (Remicade®)** were reported, including tuberculosis. The product prescribing information was changed to recommend a tuberculin skin test before patients received the drug. This was also reinforced by several risk communication efforts.

In the CERTs study, patients who had used infliximab were identified from 11 health plans located throughout the United States, and physician claims data were examined to determine whether the patients had received a tuberculin skin test. Over the 30-month time period, the overall tuberculin skin testing rate doubled from 15.4 to 30.9 percent, and the rate of pre-infliximab treatment testing increased from zero to 27.7 percent. Tuberculin skin testing rates were significantly higher in female patients, for those with a diagnosis of rheumatoid or psoriatic arthritis, and for those whose prescribing physician was a rheumatologist.

Although the tuberculin skin testing rate was less than favorable overall, tuberculin skin testing doubled over 30 months of ongoing risk communication efforts. (Under-ascertainment of skin testing likely occurred.) This study demonstrated a significant change in patient care following Federal industry risk communication efforts, a finding that has not been consistently seen in other therapeutic areas.

UNDERSTANDING THE RISK OF ARRHYTHMIA ASSOCIATED WITH METHADONE[11]

Previous work reported in the Year 4 CERTs Annual Report led to the discovery that **methadone** can cause a rare cardiac arrhythmia, torsades de pointes, and in some cases, death. Methadone is a life-saving therapy for heroin addiction and is increasingly used to treat pain for cancer patients. It is important to understand the risks associated with developing torsades de pointes while taking methadone in order to offer

recommendations to practitioners that will enable this drug to continue to be used safely.

The CERTs established a partnership with DrugLogic, formerly QED Solutions, Incorporated, that enables our researchers to use a computer program to more easily access reports of **adverse events** associated with methadone reported to the FDA MedWatch program. Examination of these adverse events suggests that dosages that fall within the recommended range for methadone maintenance treatment (60-100 mg per day) were associated with torsades de pointes and/or a prolonged QT interval. Risk factors that have been previously identified with other drugs known to cause torsades de pointes were included in these reports: female gender, interacting medicines, structural heart disease, hypokalemia (low levels of potassium in bloodstream), and hypomagnesemia (low levels of magnesium in bloodstream).

Based on these results, CERTs researchers suggest that practitioners obtain a thorough history to identify risk factors for torsades de pointes.

PROVIDING VITAL INFORMATION REGARDING THE RISK OF DRUGS

After initial studies revealed that the risk of a potentially fatal cardiac arrhythmia, **torsades de pointes**, was not confined to a particular drug class or type, the CERTs developed a list of drugs that prolong the QT interval and/or induce arrhythmias. This information was made available to practitioners and patients on a Web site, **www.qtdrugs.org**. An e-mail address posted on the site enables the public to ask questions about specific drugs. Over the past 2 years, the lists have been improved and modified to reflect new drugs introduced

in the market and the reevaluation of old drugs as new information becomes known. At the time of publication, the drug lists are visited over 2,000 times per month and have been cited in numerous textbooks and in peer-reviewed journals.

COMBINING OVER-THE-COUNTER MEDICATIONS, HERBS, AND SUPPLEMENTS WITH PRESCRIPTION DRUGS

The use of **over-the-counter medications**, **herbs**, and **supplements** in combination with prescription drugs is of growing concern because of **adverse drug interactions**. The CERTs developed an interactive "virtual medicine cabinet" as a colorful educational tool for health care consumers who visit one of its Web sites: www.azcert.org. The medicine cabinet opens and displays familiar-looking bottles and packages showing generic examples of multiple classes of over-the-counter medications typically found in people's medicine cabinets. Visitors can click on the medicines to find out how safe they are in combination with other drugs and find links to additional information at the National Library of Medicine's Web site, MedlinePlus.gov. Designed specifically to attract and inform busy, non-technical audiences, the virtual medicine cabinet has been visited over 4,000 times since its creation in January 2004.

DISCOVERING THE ROLE OF HERBAL REMEDIES AND SUPPLEMENTS USED BY HISPANIC WOMEN WITH DIABETES

Assessing the use of **herbal remedies** is an important first step in educating patients about the risk associated with combining prescribed medications, herbal remedies, and **supplements**. One CERTs study identified different types of herbal remedies and supplements used by a group of Hispanic women receiving treatment at community health centers in Southern Arizona. The current evidence on efficacy, interactions, and adverse effects associated with the use of particular herbs and supplements was also examined. More than 90 percent of the subjects reportedly used one or more herbal remedies, which underscores the need for practitioners to communicate with their patients about the use of herbal remedies and supplements.

ASSESSING FREQUENCY OF USE OF DANGEROUS DRUGS IN PREGNANCY[12, 13]

The use of medications during **pregnancy** poses a potential risk to both mother and fetus. Because so little is known about the safety of medicines used during pregnancy, health care databases are important tools for identifying possible harm from prescription drug exposures during pregnancy.

Much of what we know to date has come from studies of women who took certain medications during pregnancy and then agreed to have their progress tracked through delivery. These studies, however, can tell us only about certain drugs, and we need to know about the potential effects of many more drugs previously unstudied. CERTs investigators are addressing this problem by using a health care database, the United Kingdom General Practice Research Database, to develop and validate standard definitions of specific birth defects. Once we have standard definitions, we can make them available for use in other large databases to screen for potential adverse pregnancy outcomes from a larger number of drugs.

To assess how often unborn babies are exposed to drugs that may cause them harm, the investigators recorded drug use before and during pregnancy for 152,531 women in eight different U.S. health systems and geographic regions. Of these women, 71,913, or almost half, were prescribed drugs that fall within categories C, D, and X of the **FDA's pregnancy risk classification system**. Drugs in category C have unknown risks in human pregnancy but the benefits may outweigh the risks during pregnancy; those in D have evidence of risk in human pregnancy but the benefits of the drug may outweigh the risks of use during pregnancy; those in X have demonstrated risks and/or positive evidence of risks in human pregnancy, such that the risks clearly outweigh any possible benefit of the drug. The study suggests that a significant number of women become pregnant while taking drugs for which the risks are unknown or demonstrated.

Another CERTs project studied the use of prescription drugs during pregnancy, focusing specifically on drugs in the FDA's **category X**. The group looked at how many of 95,284 pregnant women in TennCare filled prescriptions for category X medications. Within the group, 391 filled such prescriptions, meaning that about 4 in 1,000 fetuses were exposed to potentially harmful medication. Women over the age of 35 and those enrolled in TennCare because of chronic disabilities were at the greatest risk for filling prescriptions for category X drugs. Study results underscore the need to inform both physicians and women so they can consider the risks in taking these medications during pregnancy.

IDENTIFICATION OF POTENTIALLY INAPPROPRIATE PRESCRIBING PATTERNS FOR CHILDREN AND THE ELDERLY[14, 15, 16]

Children are extremely vulnerable to **dosing errors**. In the United States, children visit a physician an average of 1.8 times each year, and in as many as 60 percent of these appointments, they receive prescriptions for medication. Yet despite data showing that each year children experience serious and even fatal consequences from medication errors, little is known about these problems for children outside hospital settings.

To determine the frequency of dosing errors in the outpatient setting, the CERTs examined records for 1,933 randomly selected children who had been dispensed new prescriptions for commonly prescribed medications. The study found that dosing errors occur frequently in outpatients. Approximately 15 percent of children were dispensed a medication that constituted a potential dosing error, almost evenly divided between potential overdoses (8 percent) and underdoses (7 percent). **Analgesics**, or drugs for pain relief, were the most likely to be overdosed. This is a matter of concern because analgesics have a higher than average

likelihood of serious adverse effects associated with improper dosing. Prescriptions for anti-epileptic drugs were the most likely to be underdosed.

The risk of medication errors is higher for the youngest patients, those least equipped to alert parents or providers to problems. The study found that children under 4 were 50 percent more likely to be prescribed a potential overdose than children ages 4 to 12, with **asthma and allergy medications** and **antibiotics** the most likely to be associated with medication errors in this youngest age group. The study underscores the need for more work on the impact of these errors and on effective strategies to prevent them.

Also vulnerable to dosing errors are **people 65 years of age and older**, who make up less than 15 percent of the U.S. population but account for nearly one-third of prescription drug consumption. The chance of adverse reactions to drugs increases with age, a factor complicated by the fact that many older people take several medications simultaneously.

In order to determine rates of **inappropriate medication use**, the CERTs examined records for 157,517 patients age 65 and older in a nationally representative managed care population. The study examined the use of 33 potentially inappropriate medications over an 18-month period. The list includes a range of pain killers, antidepressants, and muscle relaxants classified as risky for elderly consumption.

From January 2000 to June 2001, almost 1 in 3 of those surveyed received at least 1 inappropriate medication, with about 5 percent receiving at least 1 of the 11 medications classified by an expert panel as "always avoid." Overall, the use of inappropriate medications was greater among women (32.4 percent)

than among men (24.2 percent), a gender difference consistent with previous studies' findings.

The manner of use of drugs specified as "always avoid" highlights the importance of additional educational interventions designed to improve appropriate use of drugs among the elderly.

In a similar study, the CERTs used the database of a national pharmaceutical benefits manager (PBM) to examine inappropriate prescribing in a group of 765,423 outpatients age 65 or older. One in five (21 percent) of the subjects filled a prescription for one or more drugs of concern in 1999, and half of those were for drugs that carry the risk of severe adverse effects. More than 15 percent of subjects filled prescriptions for two drugs of concern, and 4 percent filled prescriptions for three or more of the drugs within the same year. These results reinforce the need to monitor prescription patterns for elderly patients more closely. The study also shows that PBM databases can be an important tool for identifying potentially dangerous prescribing patterns.

EVALUATING THE ASSOCIATION OF VITAMIN D INTAKE WITH A REDUCED RISK OF RHEUMATOID ARTHRITIS[17]

Rheumatoid arthritis is one of the most common forms of arthritis and affects more than 2 million Americans, primarily women. It is a chronic, debilitating autoimmune disease in which the body's own immune system attacks healthy joint tissue, causing inflammation and joint damage.

Vitamin D plays an important role in **bone health**. In observational studies it has been shown to suppress the development of **autoimmune diseases**. In an effort to determine whether Vitamin D might help protect the body against rheumatoid arthritis, the CERTs examined data from more than 29,000 women ages 55 to 69 enrolled in the Iowa Women's Health Study. Researchers found a connection between higher levels of Vitamin D intake and a reduced risk of rheumatoid arthritis. These results support the hypothesis that Vitamin D might reduce the risk of immune disorders, and should be a subject for future research.

LEARNING HOW COMMUNICATION CAN AFFECT THE PATIENT-PROVIDER RELATIONSHIP[18]

Effective **communication** between patients and providers is a vital part of delivering effective health care. The CERTs have conducted a number of studies to examine the intricacies of these relationships and to measure how outside factors affect patient care.

How physicians handle discussions with patients about **medical errors** has been the subject of one CERTs study. Medical errors can range in severity from mild discomfort to a life-threatening issue. The researchers surveyed a random group of 1,500 adults in a New England-based health plan to determine their attitudes toward medical error disclosure. They measured responses to questions following eight hypothetical situations, each of which had the description of a medical error, the clinical outcome of the error, and the patient-physician dialog after the event.

The survey results indicate that full disclosure of errors increased patient trust and satisfaction, and also reduced the likelihood that patients would change physicians. The survey also found that patient responses could be influenced by the details of the

case and the severity of the outcome. Researchers found in some cases that full disclosure may not lessen a patient's desire to seek legal advice.

Improving the System

The CERTs' broadest and potentially most beneficial efforts are those that improve aspects of the health care system. Our studies work to improve the efficiency of health care, make therapies safer, and give health care providers better access to current treatment information.

USING TECHNOLOGY TO REDUCE PRESCRIBING ERRORS[19]

Pharmacists play a critical role in health care, especially when monitoring potentially harmful interactions between medications prescribed for the same patient. Examining the daily habits of community pharmacists for a set amount of time, the CERTs studied their responses to **drug-drug interaction alerts (DDIAs)**. The study found that alert systems produce many DDIAs that pharmacists frequently override. In many cases, the override occurs because the pharmacist can see that the alert involves a drug the patient is no longer taking or that the medication is a refill and the alert was examined previously. However, the study suggests that reducing the abundance of DDIAs in order to concentrate on more serious interactions could reduce the risk that important DDIAs are overridden and overlooked by pharmacists.

Voluntary error reporting programs help practitioners, patients, and organizations learn from mistakes, either through single case reports or from larger, systematic analyses. A case report developed by CERTs researchers on the U.S. Pharmacopeia Error Reporting System **MedMARX℠** showed that even a very minor change in operating procedure can cause harm by creating errors in dosages when system checks and safeguards are not in place. This serves as an example of when a subtle change in well-established routines opens the same possibility for harm that arises when practitioners are learning to use new tools. Therefore, measures should be taken to check and recheck materials and procedures to prevent errors.

It is also important to develop standard definitions for reporting errors to help correctly identify adverse events when they occur. For example, CERTs researchers are using a database containing all South Carolina emergency room discharges over a 3-year period to develop and validate a standard definition of **anaphylaxis**, which is a severe, life-threatening reaction to drugs.

ESTABLISHING STANDARDS OF CARE FOR GOUT AND ARTHRITIS[20, 21]

There are significant gaps in health care that directly affect **arthritis** and **gout** treatment, and change is necessary to improve the quality of care for these painful diseases that significantly hamper the daily activities of millions of Americans. The problem is that there is little consensus about the way in which to treat either condition.

Gout is a form of arthritis in which a buildup of uric acid causes sudden, severe inflammation, swelling, and pain in one or more joints, often the big toe. It affects more than 2 million Americans, mostly men over 40.

Gout is an understudied disease, and there is little consensus on the best ways to manage it, leaving patients vulnerable to medication-related errors and less than optimal care. Further, there are no systematic guidelines for informing patients about the risks of common medications used to relieve arthritis pain.

Recognizing the severity of the problem, the CERTs designed a study to develop **quality-of-care indicators** for gout management. Using a combination of evidence reported from previous gout research and the opinions of two panels of experts, the study produced 10 quality indicators for minimal standards of care. These guidelines touched on the use of anti-inflammatory medications, behavioral modifications, and ways to lower levels of uric acid.

Having these standards in place will result in many benefits for gout patients, such as helping their providers avoid medication errors. The standards also provide a basis for future research of an understudied but painful disease.

Arthritis is the country's leading cause of disability, affecting as many as 70 million people. As part of the **Arthritis Foundation Quality Indicator Project**, the CERTs conducted a study to assess the safe use of prescription and over-the-counter analgesics, including NSAIDs, aspirin, and acetaminophen. These medications are commonly used to relieve arthritis pain, but they can produce harmful side effects, particularly to the gastrointestinal tract and kidneys.

CERTs researchers synthesized previous guidelines and updated quality-of-care indicators with current knowledge. The 10 indicators developed in the study can help providers and patients balance the pain-relieving benefits of analgesics with the risks of harmful side effects.

ASSESSING THE EFFECTS OF ECONOMIC ISSUES ON HEALTH CARE

The economic implication of quality health care is of vital concern to consumers, health care providers, and policymakers. Many CERTs projects focus on the **economic issues** that will help inform better decision making on the part of policymakers.

Examining the Costs of Prescription Drug Benefits[22]

In one study, the CERTs examined the effects of increased cost-sharing of **prescription drugs** for patients with a chronic illness requiring medication. The study selected 13,407 adults with diabetes mellitus who faced an increase in the copay for medications. The researchers compared their use of **oral hypoglycemic (OH)** medications over a 12-month period with use by patients whose copay was not increased.

The comparison showed that increases of more than $10 for a 30-day supply were associated with significantly reduced OH use, while more modest increases ($1-$10) were not. The decrease in OH use was independent of age, gender, concurrent insulin use, or income.

Researchers noted that over several years, underuse of OH medications can lead to a significant increase in complications. Further study could help determine whether the effects of higher cost-sharing will be significant in the long run.

Studying the Economic Effects of Coronary Heart Disease Drugs[23]

Drugs known as **beta-blockers** have been shown to improve outcomes for patients with heart failure, but many patients with heart failure are still not treated with this therapy. In one study, the CERTs researchers looked specifically at the economic effects of beta-blocker therapy from the perspectives of society, Medicare, hospitals, physicians, and patients.

They found that beta-blocker therapy for heart failure increased survival by 0.3 years per patient and reduced societal costs by $3,959 per patient over 5 years. **Medicare** costs declined $6,064 per patient, primarily due to fewer hospitalizations. From the perspectives of the hospital and physician, however, revenue decreased. With no clear **financial incentives** for hospitals and physicians to support increased beta-blocker use, systems need to be created to encourage optimal use of beta-blockers that take into account these economic issues.

Reviewing Economic Effects of Coronary Heart Disease Devices[24]

The CERTs also examined a similar cost-related issue involving the introduction of a **drug-eluting coronary stent**. The new drug-coated stent is more effective at preventing a coronary artery from narrowing again and decreases the need for further procedures. However, it is more expensive than uncoated stents, and it has been unclear whether a proposed increase in Medicare hospital reimbursements would cover the increased costs for the new stent.

The study reviewed the estimated **costs and reimbursements** and found that the proposed increase would not completely cover the hospital costs. It also acknowledged the ethical dilemmas posed by expensive new technologies. For example, these technologies can shift cost burdens so rapidly that it is difficult for those setting reimbursement policy to respond in a timely manner. The study suggests the need for carefully constructed, evidence-based simulation models to help physicians, patients, hospitals, policymakers, and manufacturers work through the dilemmas posed by new technological devices.

PROTECTING THE PUBLIC AGAINST BIOTERRORISM AND EMERGING INFECTIOUS DISEASES[25, 26]

As concerns increase about **bioterrorism**, it is important to assess the capacity of the U.S. health system to handle such events. Effective **communication** between providers and public health officials is essential in recognizing and responding effectively to emerging infections or to deliberate attacks with biologic agents. However, little is known about which sources providers rely on for this kind of information. The CERTs examined sources of information about bioterrorism that are available to front-line health care providers, particularly emergency physicians.

In the 3 months following the 2001 anthrax attacks, most emergency physicians had access to specific protocols for management of **anthrax**, but only a quarter of them had access to protocols for treating smallpox. The researchers conducted a telephone survey of randomly selected emergency physicians in Pennsylvania; 97 physicians participated in the 10-minute interviews. The survey found that most

respondents had read official public health updates on bioterrorism, including the new Health Alert Network developed by the Centers for Disease Control and Prevention (CDC) that distributes public health emergency notifications among government entities and health care organizations. This suggests that electronic alert networks, including broadcast faxes, e-mails, and the Web, are useful means for distributing official public health guidelines.

A majority of the respondents who used the Web accessed information from the CDC Web site, while 27 respondents contacted public health agencies by telephone, usually calling local or State health departments. The study concluded that Health Alerts are perceived as highly credible and that this system is useful in conveying important information. However, it is important that the alerts be presented in a concise, user-friendly format.

Researchers also detected a need for regional public health plans to address the large influx of patients that could be triggered by an attack using **biological agents**. In an effort to help assess preparedness for an attack involving the **smallpox virus**, the CERTs surveyed pediatric emergency health care workers to determine their willingness to receive a smallpox vaccination. The anonymous survey found that almost three-quarters of the respondents were willing to be vaccinated, although many of the respondents reported ambivalent or contradictory attitudes toward the vaccine. These inconsistent attitudes might explain poor participation in a subsequent smallpox vaccination program organized by the CDC for emergency health care workers.

This kind of survey is extremely useful in enhancing the success of future efforts to prepare health care workers for possible bioterrorism or emerging infectious diseases.

Referenced Projects

CENTER	PROJECT	PAGE
Vanderbilt University Medical Center	Oral erythromycin and sudden cardiac death	8
University of Pennsylvania School of Medicine	Re-administration of antibiotics in patients with history of allergy	8-9
University of Pennsylvania School of Medicine	Risk factors for drug-resistant Pneumococcal pneumonia	11
University of Pennsylvania School of Medicine	Risk factors for infection due to fluoroquinolone-resistant Enterobacteriaceae	11
Vanderbilt University Medical Center	Trends of increasing antipsychotic medication use in children	11-12
University of North Carolina at Chapel Hill	Efficacy, safety, and pharmacokinetics of drugs in pediatric HIV	12
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Duke University Medical Center	Evaluation of the dofetilide risk management program	13-14
Duke University Medical Center	Evaluation of national market uptake of dofetilide	13-14
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University of North Carolina at Chapel Hill	Medication/vaccine safety studies using the general practice research database	16-17
HMO Research Network	Prescribing safely during pregnancy	17

CERTs Program Resources

ADHD Online Toolkit for Providers, Patients, and Families: Web Tool
nichq.org/resources/toolkit

Arthritis Outcomes Initiative Resource for Patients and Families: Web Resource
www.engalitcheff.uab.edu

Arthritis Self-Help for Patients: Web Site
www-cme.erep.uab.edu/arthritispatient/welcome.html

Beta-Blocker Fact Sheet
dukecerts.dcri.duke.edu

Drug Interaction Card: Reference Guide
www.drug-interactions.com

Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes
www.qtdrugs.org

Head and Chest Colds: Patient Education Brochure
www.penncert.org

Preventable Adverse Drug Interactions – A Focus on Drug Interactions: Education Module
www.arizonacert.org/medical-pros/education/module01.htm

Safer Use of Nonsteroidal Anti-Inflammatory Drugs: Online Continuing Medical Education Course
www-cme.erep.uab.edu/nsaids/nsaids.html

Saving Lives with Beta-Blockers: Duke CERTs Cybersession
dukecerts.dcri.duke.edu

Tools and Techniques of Improved Medication Use for Health Care Professionals: Web Resource
www.aahp.org/redirect/improvedmedicationuse.htm

Treating Congestive Heart Failure with Beta-Blockers: Patient Education Videotape
dukecerts.dcri.duke.edu

Treating Congestive Heart Failure with Beta-Blockers: What You Can Do To Help Yourself Feel Better: Patient Education Brochure
dukecerts.dcri.duke.edu

Understanding the QT Interval – A Duke CERTs Educational Program: Internet-Based Module
qtmodule.mc.duke.edu

NOTE: For additional information about CERTs program resources, please e-mail the CERTs Coordinating Center at certs@mc.duke.edu.

CERTs Partnerships and Collaborations

Public-private partnerships are one of the core values of the CERTs. Collaboration among groups sharing different perspectives and resources is essential in carrying out the mission of the CERTs. In addition to the many partnerships that enable the research centers to study important therapeutics issues, the CERTs have established several program-wide initiatives in collaboration with other public and private organizations.

Risk Series

An important goal of CERTs research is to increase awareness of the benefits and risks of therapeutics. Equally important is ensuring that people understand how to apply new knowledge in order to increase the benefits of therapeutics and reduce the risks. In 2001, the CERTs established the Risk Series to identify research issues that could improve the Nation's ability to assess, communicate, and manage therapeutic risk.

Experts from the government, consumer groups, the medical products industry, the media, health care, and academia convened for a series of workshops called "Think Tanks" to review how the risk associated with different medical products is assessed, communicated, and managed.

Since the last Annual Report, the results from the Think Tank on risk assessment have been published. The workshop, which included academic, industry, government, and constituency-based leaders, discussed ways to improve the post-approval phase of marketed pharmaceuticals and other therapeutics.

The group agreed that improving the system will involve research into methods to improve risk assessment, enhancement and consolidation of data-handling systems, education of health care workers, allocation of financial resources, and building of constituencies. There is need for leadership on multiple levels for global coordination of risk assessment. Only with better assessment of risk can interested groups like the CERTs begin to fill gaps and produce benefits for industry, health authorities, government agencies, health care providers, and most important, the public.

Manuscripts from the Think Tanks on risk communication and the media and risk management have been accepted for publication next year.

Partnerships to Advance THerapeutics (PATHs)

The CERTs organize annual meetings with our public and private partners at PATHs and Government Day.

The PATHs program was created in 2001 as a means of cultivating partnerships between organizations interested in advancing the optimal use of therapeutics. Each spring, the CERTs host a meeting of leaders from a variety of public and private organizations concerned about the quality and safety of health care. Partners and participants include organizations representing a range of constituencies, such as consumers, health care providers, government, academia, delivery systems, payers, purchasers, and manufacturers of medical products.

Working together and in collaboration with public and private partners, the CERTs program is in the process of determining the strategic initiatives to pursue during the next few years to improve the public health through optimal use of therapeutics.

At the PATHs meeting in March, entitled "National Strategic Initiatives to Improve the Public Health Through Therapeutics," the CERTs received input from PATHs partners on potential initiatives to undertake in the following areas: (1) CERTs Risk Series recommendations; (2) health care provider education and training; (3) technology-assisted decision-making; (4) safe use of marketed therapeutics; and (5) informed coverage decisions. These areas had been identified by Steering Committee members earlier in 2004 as some of the key areas of potential impact for the CERTs.

During breakout sessions, PATHs partners shared different perspectives on the issues, which helped facilitate a productive discussion and generated strategic suggestions about next steps. The meeting also generated ideas about specific projects, including the improvement and implementation of computerized provider order entry (CPOE). The initiative was to develop standards for CPOE content based on scientific evidence and practical considerations.

The PATHs program is a visible example of the strength and value of the CERTs public-private partnership to improve public health through therapeutics. A registry of educational and research projects of the PATHs organizations is published and can be accessed through the CERTs Web site at www.certs.hhs.gov/partners/paths/regis/.

PATHs Partners

We would like to thank the following organizations for participating in *National Strategic Initiatives to Improve the Public Health Through Therapeutics:*

Academy of Managed Care Pharmacy

Advanced Medical Technology Association

Agency for Healthcare Research and Quality

American Academy of Pharmaceutical Physicians

American Association of Colleges of Pharmacy

American Association of Retired Persons

American College of Cardiology

American College of Clinical Pharmacology

American College of Clinical Pharmacy

American College of Physicians

American College of Preventive Medicine

American Health Quality Association

American Medical Association

American Nurses Association

American Public Health Association

American Society for Clinical Pharmacology and Therapeutics

American Society of Health-System Pharmacists

America's Health Insurance Plans

Department of Veterans Affairs

Eli Lilly and Company

Institute of Medicine

International Society for Pharmacoepidemiology

Merck & Co., Inc.

National Committee for Quality Assurance

National Consumers League

National Council on Patient Information and Education

National Patient Safety Foundation

National Pharmaceutical Council

National Quality Forum

Pharmaceutical Research and Manufacturers of America

Society for Women's Health Research

United Mine Workers of America Health & Retirement Funds

United States Pharmacopeial Convention, Inc.

U.S. Food and Drug Administration

Government Day

At Government Day, CERTs investigators have an opportunity to discuss their projects and collaborative opportunities with individuals from government agencies. The 2004 meeting focused on the Nation's public health priorities as set forth by Healthy People 2010 and other national plans. Presentations were made about the strategic priorities of AHRQ, Centers for Medicare & Medicaid Services, FDA, National Institutes of Health, and the Department of Veterans Affairs Center for Medication Safety. Participants discussed ways in which the CERTs ongoing work and the expertise of CERTs investigators could contribute to national public health priorities, such as the evidence-based implementation of electronic technology to improve patient care.

Conclusion

The CERTs were established to conduct research and provide education to advance the best use of drugs, medical devices, and biological products. From educating women about the risks of certain medications during pregnancy, to helping physicians better prescribe to the elderly, our research is diverse and has the potential to help every citizen, no matter what race, age, or geographic location. The work that CERTs researchers are doing directly impacts the lives of U.S. citizens every day.

As we conclude our fifth year, it is clear that there continues to be great need for the CERTs. We remain committed to our mission, always with the overriding objective of improving the Nation's health. We have only begun to address the important questions, and much work remains. The CERTs are committed to continuing to share our latest research evidence in the field of therapeutics in the years to come.

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Principles of CERTs Public-Private Partnerships

Issues of Public Interest. CERTs is a national initiative to foster the optimal use of therapeutics through research and education activities that are in the public interest but would not otherwise be done.

Public-Private Partnership. CERTs is a public-private partnership on two levels: (1) between the U.S. Department of Health and Human Services and the CERTs centers; and (2) between CERTs centers as representatives of the government-sponsored CERTs program and other research-sponsoring organizations. In the latter relationship, the CERTs centers seek useful, appropriate interactions with private organizations to support and enhance education, research, and demonstration projects. AHRQ works with the centers to establish appropriate agreements to optimize use and sharing of resources.

Conflicts of Interest. Public-private partnerships typically present the potential for conflicts of interest. While these potential conflicts of interest cannot be completely avoided or eliminated, a CERTs center has an obligation to disclose fully and to manage conflicts in a manner that minimizes the risk of those conflicts, while at the same time permitting as much progress as possible to achieve CERTs goals within the constraints of maintaining respected research activity.

Academic Integrity. As academic researchers, individuals conducting projects under the CERTs umbrella maintain final decision making about study design, analysis, conclusions, and publication in any partnership with other organizations, and ensure that their work complies with their respective institutions' conflict of interest rules.

Activities. CERTs activities are defined as projects supported in whole or in part by AHRQ funds under the CERTs cooperative demonstration program. Such activities are subject to processes established for the CERTs program such as the review of potential conflicts of interest by the Public-Private Partnerships Committee, a subcommittee of the CERTs Steering Committee made up of representatives from the CERTs centers, government, and the private sector. Individuals affiliated with the centers also conduct education and research activities outside of CERTs that are not subject to CERTs processes.

CERTs Project Partners

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Academic Medicine and Managed Care Forum

AccessCare, Inc.

Advanced Medical Technology Association

Aetna Inc.

Agency for Healthcare Research and Quality

Agouron Pharmaceuticals, Inc.

Alabama Practice-based Continuing Medical Education and Research Network

Alabama Department of Public Health

American Academy of Family Physicians

American Academy of Pediatrics

American Association of Colleges of Pharmacy

American College of Cardiology

American College of Clinical Pharmacy

American College of Rheumatology

American Heart Association

American Pharmacists Association

American Pharmaceutical Association Foundation

America's Health Insurance Plans

Amgen

Arizona Area Health Education Centers

Arthritis Foundation

Arthritis Foundation, Alabama Chapter

Arthritis Foundation, Maryland Chapter

AstraZeneca

Aventis

Berlex, Inc.

Bowman Gray School of Medicine

Brigham and Women's Hospital

Bristol-Myers Squibb Company Worldwide

Caremark

Center for Health Care Policy and Evaluation

Centers for Disease Control and Prevention

Centers for Disease Control Foundation

Centers for Medicare & Medicaid Services

Children's National Medical Center

Cincinnati Children's Hospital Medical Center

Columbus Children's Hospital

Community Health Centers

Conceptis Technologies, Inc.

Crohn's & Colitis Foundation of America

Council for Affordable Quality Healthcare

Department of Veterans Affairs

Duke Clinical Research Institute

Duke Heart Center

Duke Infection Control Outreach Network

Duke University Department of Psychology

Duke University Health System

Eli Lilly and Company

Express Scripts, Inc.

Fallon Community Health Plan

General Practice Research Database/EPIC

Genentech

Georgetown University

GlaxoSmithKline

Group Health Cooperative of Puget Sound

Harvard Pilgrim Health Care

Harvard School of Medicine

Harvard School of Public Health

Harvard Vanguard Medical Associates

Health Resources and Services Administration

HealthPartners

Henry Ford Health System

IMS Health

Infectious Diseases Society of America

Institute for Healthcare Improvement

Institute of Medicine

Integrative Pain Center of Arizona

International Society for Pharmacoepidemiology

Iowa Women's Health Study

Janssen Pharmaceutica

John A. Hartford Foundation

Kaiser Permanente Colorado

Kaiser Permanente Georgia

Kaiser Permanente Northern California

Kaiser Permanente Northwest

La Frontera Hope Center

Massachusetts Department of Public Health

Massachusetts Division of Medical Assistance

Medco & Co., Inc.

Medical Review of North Carolina, Inc.

Medtronic, Inc./Diabetes Management Subsidiary MiniMed, Inc.

Nanogen, Inc.

National Committee for Quality Assurance

National Health and Medical Research Council Clinical Trials Centre, Sydney, Australia

National Initiative for Children's Healthcare Quality

National Institutes of Health/ National Cancer Institute

National Institutes of Health/ National Institute of Allergy and Infectious Diseases

National Institutes of Health/ National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institutes of Health/ National Institute of Diabetes & Digestive & Kidney Diseases

National Institutes of Health/ National Institute of General Medical Sciences

National Institutes of Health/ National Institute of Mental Health

National Institutes of Health/ National Institute of Nursing Research

National Institutes of Health/ National Institute on Aging

National Institutes of Health/Office of Research on Women's Health

National Patient Safety Foundation

North Carolina Association of Pharmacists

North Carolina Department of Health and Human Services

North Carolina Medicaid

North Carolina State Children's Health Insurance Program

North Carolina Women, Infants & Children

Office of Women's Health

Ortho-McNeil Pharmaceutical, Inc.

Pediatric Research in Office Settings

Pennsylvania Department of Public Health

Pennsylvania Pharmaceutical Assistance Contract for the Elderly

Pfizer Inc.

Pharmaceutical Research and Manufacturers of America

Pharmacogenetics Network

Premier

ProVantage Health Services, Inc.

QED Solutions, Incorporated

Robert Wood Johnson Foundation

Roche Laboratories Inc.

RTI Health Solutions

RTI International

Society for Healthcare Epidemiology of America

Society for Women's Health Research

Society of Thoracic Surgeons

TAP Pharmaceutical Products, Inc.

TennCare Medicaid

Tennessee Department of Health

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United States Pharmacopeial Convention, Inc.

UnitedHealth Group

UnitedHealthcare

UnitedHealthcare of Alabama

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University of Illinois at Chicago

University of Massachusetts Medical School

University of Pennsylvania Health System

University of Texas Health Science Center at San Antonio

U.S. Food and Drug Administration

U.S. Quality Algorithms, Inc.

Wake Forest Baptist Medical Center

Walgreens

Wellpoint

Whitehall-Robins Inc.

Wyeth-Ahearst Laboratories

Peer-Reviewed Publications:

October 1, 2003 - September 30, 2004

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