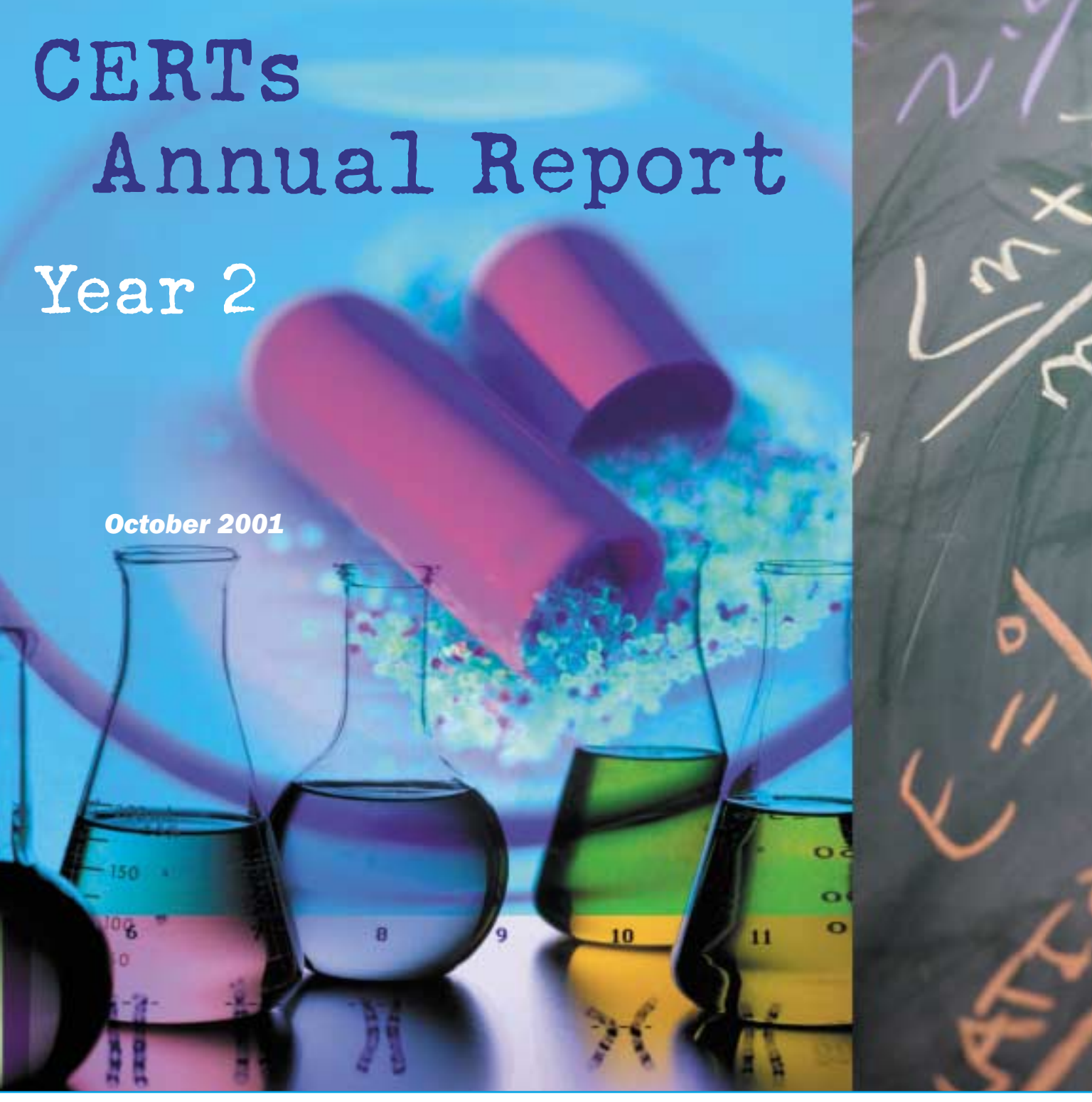
CERTs Annual Report

Year 2

October 2001



Centers for Education & Research on Therapeutics

Agency for Healthcare Research and Quality

This report was developed under the auspices of the Agency for Healthcare Research and Quality (AHRQ) through grant HS10548, although its contents are the sole responsibility of the Centers for Education & Research on Therapeutics (CERTs).

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.

Contents

Glossary

ADE	=	adverse drug event
ADHD	=	attention deficit-hyperactivity disorder
ADR	=	adverse drug reaction
AHRQ	=	Agency for Healthcare Research and Quality
CAD	=	coronary artery disease
CERTs	=	Centers for Education & Research on Therapeutics
CDC	=	Centers for Disease Control and Prevention
CHF	=	congestive heart failure
CME	=	continuing medical education
ECG	=	electrocardiogram
FDA	=	Food and Drug Administration
GIOP	=	glucocorticoid-induced osteoporosis
HIV	=	human immunodeficiency virus
HMO	=	health maintenance organization
NNRTI	=	nonnucleoside reverse transcriptase inhibitor
NSAIDs	=	nonsteroidal anti-inflammatory drugs
PATHs	=	Partnerships to Advance THerapeutics
PBM	=	pharmacy benefits management
PhRMA	=	Pharmaceutical Research and Manufacturers of America
PS	=	postmarketing surveillance
RA	=	rheumatoid arthritis
UAB	=	University of Alabama at Birmingham
UNC	=	University of North Carolina at Chapel Hill
UPenn	=	University of Pennsylvania
VA	=	Veterans Affairs
WHO	=	World Health Organization

Preface

Dear Colleague:

The Centers for Education & Research on Therapeutics (CERTs) program is a national initiative that began in 1999, sponsored by the Agency for Healthcare Research and Quality (AHRQ). The goal of the CERTs program is to increase awareness of the benefits and risks of new, existing, or combined uses of therapeutics through education and research, and thereby improve the effectiveness and safety of the use of therapeutics.

This second annual report documents the progress of the CERTs toward achieving this goal. With seven centers now funded, the CERTs have initiated work on or completed an impressive number of projects. Each of these projects adds to our knowledge base and furthers our understanding of how therapeutics work—and can work more safely and effectively.

In the second year of the program, the CERTs have begun to identify the questions that we, as researchers, must ask ourselves: "Who is affected?" and "How many?" They have examined causal relationships that may help answer the "Why?" question of drug interactions. And they are attempting to build on evidence and research in the field to answer the questions, "What works?," "What doesn't work?," "When?," and "For whom?"

John M. Eisenberg, MD, MBA

AHRQ, a part of the U.S. Department of Health and Human Services, is the lead agency charged with supporting research designed to improve the quality of health care, reduce its cost, improve patient safety, reduce medical errors, and broaden access to essential services. AHRQ sponsors and conducts research that provides evidence-based information on health care outcomes, quality, cost, use, and access. The information helps health care decision-makers—patients, caregivers, health system leaders, and policy-makers—make more informed decisions and improve the quality of health care services.

The CERTs also are identifying effective ways to improve our use of therapeutics and how to communicate and convey research findings so that there is a greater possibility of adoption and dissemination in the field. Finally, the CERTs are synthesizing their findings to translate the results for use in specific clinical settings.

We are very pleased to provide you with this report on the work of the CERTs. We look forward to the continued advancement of our therapeutics knowledge base in the years to come.

Sincerely,

—John M. Eisenberg, MD, MBA,
Director, AHRQ

Letter from the Steering Committee

Dear Fellow Citizens:

We have very good news: The number of CERTs projects has more than doubled, from 40 last year to 98 this year. Even more important, some of these projects already have begun to make a difference in the lives of Americans.

Even though three of our seven centers came on board only within the last quarter of Year 1, we've strengthened our infrastructure, attracted more collaborators, and refined the systems and processes of this multifaceted, national program.

Our unique collaborations with many different groups—government agencies, academic organizations, insurance companies, drug and device companies, caregivers (such as doctors, nurses, and pharmacists), commercial research groups, and consumer groups—also have provided unprecedented opportunities for mutual learning.

The concept of a public-private partnership was largely untested in programs such as CERTs when we began our work. Although new situations will always present themselves, we now have in place a working system for such partnerships, which we hope to expand even more in the years to come.

Most important, there is always a delay between the discovery of new information (which itself takes time) and its application. We continue to perform research on therapeutics and get the results into the hands of people who need them, so that they can take informed action to improve health.

In short, then, our second year was necessarily a time during which we refined the program, learning several lessons along the way. One of the most important lessons we learned was that, much as we'd like to "do it all," we can't, at least not yet. We've learned to be selective, to focus our efforts on projects that are feasible and that will have a tangible effect on health.

We also continued to take advantage of our several strengths: an experienced coordinating center, strong research and educational centers, committed participants, and a determination to collaborate.

The combination of our strengths and a focused strategy allowed us to complete 40 projects this past year. We're very proud of this, but we know that much work remains.

We are happy to report the many real achievements of Year 2, and we look forward to addressing the many challenges that still lie ahead.

Hugh Tilson, MD, DrPH

—Hugh Tilson, MD, DrPH
Chair, on behalf of the CERTs Steering Committee:
Lynn Bosco, MD, MPH; Robert M. Califf, MD; William H. Campbell, PhD; Lisa Egbuonu-Davis, MD; Linda Golodner; Peter Honig, MD, MPH; Judith M. Kramer, MD, MS; Richard Platt, MD, MSc; Wayne A. Ray, PhD; Kenneth G. Saag, MD, MSc; Marcel Salive, MD, MPH; Brian L. Strom, MD, MPH; Karen Williams; Raymond L. Woosley, MD, PhD

Introduction

The Centers for Education & Research on Therapeutics (CERTs), administered by the Agency for Healthcare Research and Quality (AHRQ), aim to become a trusted national resource for people seeking information about medical products.

As our name implies, we do this through 1) research and 2) education. In other words, first we develop knowledge, then we share it with people who can use it to manage risk, improve practice, and inform policies.

Our 98 projects to date have involved some of the most exciting areas of medical research and education today, but they all can be placed along the broader spectra of research and educational efforts.

On one end of the research spectrum, we have purely descriptive research. "How many teenagers in the U.S. have Type 2 diabetes?" is a question answered by descriptive research. Epidemiology is the predominant discipline involved in this type of research.

Then, there is causal research. As you might expect, this type of research studies possible cause-and-effect relationships. Examples include studying the relation between giving a drug and having a reaction, having a particular gene and being resistant to a therapy, or changing insurance coverage and improving the management of a condition. The dynamic fields of clinical pharmacology, pharmacogenetics, and pharmacoeconomics represent this type of research.

Next we have interventional research. This is the type with which most people may be familiar. Here, prescription or over-the-counter drugs, medical devices, diagnostic tests, or other "interventions" are tested against each other or a placebo, to see whether they are comparable or whether one is better (or worse) than the other.

DID YOU KNOW?

CERTs researchers analyze data from more than 20 unique sources as they work to develop knowledge about therapies and how best to use them. Representing more than 50 million people, these data sources shed light on how therapies are used in practice and highlight opportunities for improvement.

Finally, there is applied research, in which findings are evaluated when used in actual practice situations. This represents a logical progression from the other types.

To tie these together in an example, let's say that we notice that medication errors have increased over the past 10 years (descriptive research). Further study shows that medication errors can be reduced with the use of certain computer software (causal research). We go on to compare various computerized drug-prescribing tools (interventional research). Finally, we "translate" or apply the results into recommendations for individual situations and settings, which then are tested.

Similarly, our educational efforts also have reflected a spectrum of efforts, including teaching modules, seminars, fellowship programs, Internet-based materials, and one-on-one consultations for caregivers, policy-makers, regulators, and patients.

We recognize that people learn differently, but the more personalized and accessible the information is, the sooner people will use it to improve health. We aim to provide material in multiple ways, for multiple audiences.

In this report, we highlight just a few of the CERTs research and educational projects completed over the past year, among the seven centers and by the program as a whole.

Focus on the Centers

Who Is At Risk for Arrhythmias?

www.qtdrugs.org. That's the address for a unique educational and research tool developed by the Georgetown center, which relocated to the University of Arizona Health Sciences Center at the end of Year 2.

This Web site contains a list of 72 drugs (so far) that can cause sometimes life-threatening abnormalities in heartbeat (arrhythmias), with an emphasis on drugs associated with an abnormally long QT interval on the electrocardiogram (ECG). Caregivers around the world can look up specific drugs that might pose a risk to their patients, and submit clinical cases of drug-induced arrhythmias to the registry.

But that's not the most important aspect of this project.

As caregivers submit cases to the registry, they provide clinical information, an ECG tracing, and a swab sample from the inside of the patient's mouth. Why? So that Dr. Raymond Woosley and his colleagues can 1) compile a detailed profile of the people most at risk for drug-induced arrhythmias, and 2) develop a genetic test that can identify them in advance.

The registry remains in the active enrollment phase. So far, 12 patients have been fully enrolled as cases, and another 150 are in the submission phase. Larger samples will be needed for meaningful analysis, however.

"It is critical for individual physicians to realize that each patient they submit helps us develop ways to allow medications to be used with greater safety," says Woosley. "We have designed the Web site's content to make it easier to submit cases and have provided incentives to encourage their participation."

Raymond L. Woosley, MD, PhD

The incentives include a quarterly newsletter, telephone consultations, laminated pocket reference cards, and automatic reporting of their cases to the FDA's MedWatch program, which tracks adverse events associated with drugs.

So that the cases can be compared against a "control" group, the registry also is collecting information from 200 family members and healthy volunteers for analysis.

A genetics core laboratory has begun screening both the case and control samples for abnormalities in six of the known sites of genetic variation.

The first major development from the registry has been reports of cases of drug-induced torsades de pointes (a potentially fatal arrhythmia), prolonged QT interval, and two deaths in patients treated with methadone.

"This may be another example in which the serious toxicity of a prescribed drug escapes detection for too many years," notes Woosley. "But this also is an example of how the CERTs-sponsored registry, qtdrugs.org, can be used to identify signals and further evaluate potential drug-induced toxicity."

"…each patient they (physicians) submit helps us develop ways to allow medications to be used with greater safety."

The investigators suspected that methadone, which is used for pain and to treat heroin addiction, might be acting on the potassium channels in the heart's cells. Potassium is required for normal function of the electrical impulses that coordinate heartbeat.

They examined not only methadone but also morphine and other chemically related substances in the laboratory. Testing human cardiac channels in single cells, they found that methadone was a very potent blocker, severely disrupting the electrical signals.

Methadone has been available for over 45 years, and reports of sudden death emerged almost as soon as it came on the market. These deaths generally were thought to result from underlying drug abuse.

Year 2 Completed Projects, Arizona CERTs *(formerly at Georgetown)*

PROJECT	METHOD	COLLABORATORS
Web-based education about drug interactions, especially in women	Database evaluations, in vitro and clinical research studies, and educational programs	None
Incidence of drug interactions	Retrospective analysis using the AdvancePCS database	AdvancePCS
Educational programs on drug-induced arrhythmia	Web-based educational format	None

The results from this project provide the first systematic evidence of another mechanism for this phenomenon.

More important, the results suggest a strategy for preventing the deaths and arrhythmias associated with this drug.

Woosley and his group have presented information about the registry and its potential effect on public health at two conferences thus far: the Annual Scientific Sessions of the American Society for Clinical Pharmacology and Therapeutics and the annual meeting of the Society for Experimental Biology and Medicine.

Judith M. Kramer, MD, MS

Better Treatment of Heart Failure

Dr. Judith Kramer and her colleagues at the Duke CERTs want to help people with heart failure live longer.

Sometimes, after a heart attack or other injury, the heart becomes less efficient at pumping blood to the body. When this happens, the body doesn't get the oxygen it needs, which results in fatigue. Also, fluid builds up in the tissues of the body, causing swelling and difficulty with breathing. These effects make up the disorder known as congestive heart failure (CHF).

More than 500,000 Americans each year are told that they have CHF. In fact, this is the fastest-growing diagnosis among people enrolled in Medicare, accounting for more expenses than cancer and coronary artery disease (CAD) combined.

"Most strikingly, about half of the people with CHF will die within 5 years," adds Kramer. "Any therapy that can reduce this rate will have a major effect on public health."

Beta-blocking drugs are one such therapy. Unfortunately, they are being underused to treat CHF.

Beta-blockers have been used for many years to reduce anginal symptoms, control blood pressure, and reduce the risk of death or a second heart attack. Until about 1996, though, they had been considered harmful for people with CHF.

The results of several large studies of newer beta-blockers began to change people's minds. What drew particular attention was that deaths were reduced by up to 65% in some studies.

Accordingly, since 1999, the Heart Failure Society of America has recommended the use of one of two beta-blockers—carvedilol or controlled, extended-release metoprolol—for the treatment of CHF, unless there is a reason not to use these drugs. Such reasons include unstable CHF, severe asthma, very low blood pressure, or a very slow heartbeat.

"…about half of the people with CHF will die within 5 years."

In keeping with the CERTs mission, Kramer and her colleagues at the Duke CERTs decided to see how often physicians were prescribing beta-blockers and what effect their use was having on outcomes.

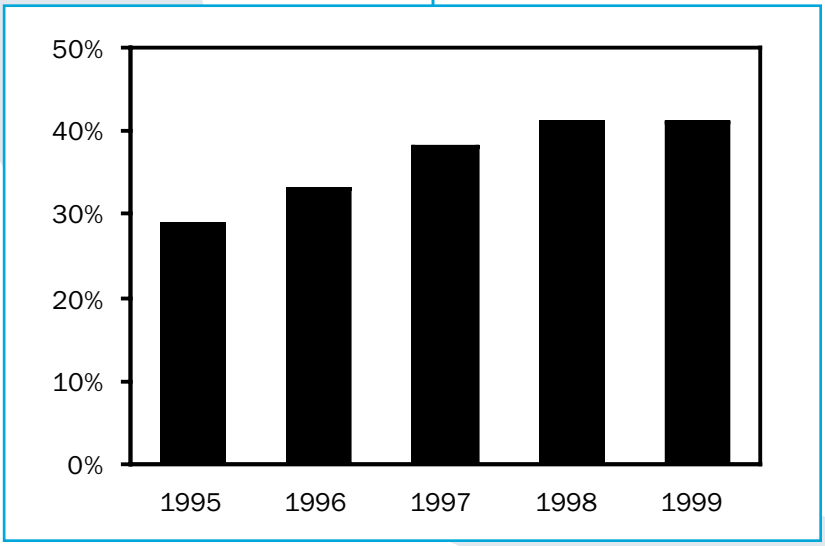
Kramer and Project Manager Dr. Nancy Allen-LaPointe tapped into a local resource, the Duke Databank for Cardiovascular Disease. This is the largest, oldest cardiovascular database in the world, containing the records of every person referred for a heart-related procedure at Duke since 1969. Since 1995, the database also has captured the medicines that these people report taking.

The Duke investigators identified 6652 people in the database who had CHF, and measured how the use of beta-blockers, and the patients' outcomes, changed over time.

First, they found that the use of these drugs increased by only 11% from 1995 to 1999 (figure 1).

Second, compared with people who had never taken a beta-blocker, those who had consistently taken such drugs did significantly better—beta-blocker users had an almost 40% lower risk of death, a ~20% lower combined risk of death or heart attack, and a 15% lower combined risk of death, heart attack, or stroke.

Figure 1: Patients with CHF Taking Beta-blockers



Treating Congestive Heart Failure with Beta-Blockers

What You Can Do To Help Yourself Feel Better

These results represented an opportunity for Kramer and her colleagues. They quickly moved to the next phase of the project: how to increase the use of these drugs.

They designed a comparison of two strategies, one involving a hands-on, intensive outreach program, and the other using a more passive approach. Participants include medical practices in North Carolina, West Virginia, and Virginia that have at least 15 patients with CHF in the Duke Databank.

Both groups are receiving a fact sheet for caregivers and an educational brochure for patients (left). The additional "interventions" in the intensive strategy include:

- A CyberSession™ (an interactive, Internet-based educational conference)
- A toll-free Helpline for caregivers
- An educational videotape for patients
- Feedback of information from the Databank on patients' use of beta-blockers

Year 2 Completed Projects, Duke CERTs

PROJECT	METHOD	COLLABORATORS
Evaluation of beta-blocker use in CHF	Retrospective analysis of the Duke Databank for Cardiovascular Disease	None
Evaluation of beta-blocker use and nonuse in CHF	Patient survey	None
Evaluation of aspirin use in CAD	Retrospective analysis of the Duke Databank for Cardiovascular Disease	None
Evaluation of reasons for aspirin nonuse in CAD	Patient survey	None
Evaluation of the dofetilide risk management program—practitioner perceptions	Practitioner survey	None
Incidence of tardive dyskinesia with metoclopramide use	Retrospective analysis of the Duke Databank for Cardiovascular Disease	U.S. Food and Drug Administration (FDA)
Antiarrhythmic drug use patterns from 1995 to 2000	Analysis of prescription audits and physician survey data	FDA, IMS Health, Inc.
Evaluation of prescribing of concomitant QT-prolonging medications	Retrospective analysis of a pharmacy benefits management (PBM) database *(with Arizona)*	None

"Enrollment" in this phase is nearly complete. When the results are analyzed, Kramer and her group hope to discover what works and what doesn't, when trying to change prescribing behavior.

In the future, they plan to apply the strategy of using a clinical database to evaluate and improve the use of other life-saving therapies.

Sallie-Anne Pearson, PhD (left); Stephen B. Soumerai, DSc

HMOs Can Improve the Use of Therapies

Health maintenance organizations (HMOs) have been around for almost 30 years. They have proven so popular (figure 2) that there are now more than 650 HMOs in the U.S., covering more than one in four Americans.

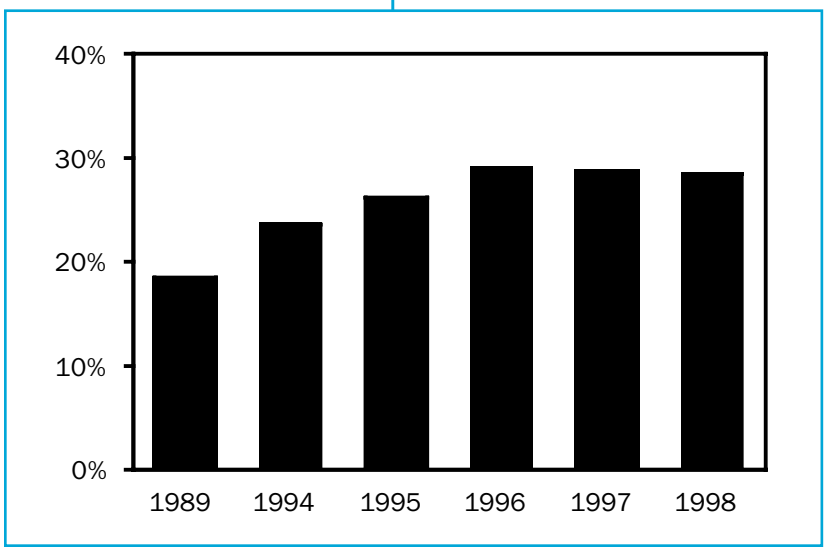
HMOs are responsible for the quality of health care that their members receive. This includes ensuring that they receive appropriate drug treatment for their medical conditions. An example would be receiving beta-blockers after a heart attack to reduce the risk of death.

To ensure appropriate therapy, HMOs collect and examine extensive information about their members' medical conditions and treatment. They also capture and analyze information about the caregivers providing such treatment.

The CERTs at the HMO Research Network is going to put this information to good use.

Although HMOs have developed several ways to help caregivers prescribe the right drugs for the right patients, and to help patients to take these drugs, there is no organized source of information about which strategies have been tried, how well they work, or how they compare with other approaches. Thus individual HMOs often "reinvent the wheel" when trying to decide which are the best treatment strategies.

Figure 2: Americans in HMOs



Dr. Stephen Soumerai, of the HMO Research Network CERTs; Dr. Sallie-Anne Pearson, project coordinator; and their colleagues are addressing this need by reviewing both published and unpublished studies of approaches used to improve medication use among HMO members.

They are organizing this information into a database that will allow patients, caregivers, and HMO planners to determine what type of strategies have been tested, the conditions for which they have been used, and their impact.

By means of the main CERTs Web site, the research team will make the information available to all. The group also is preparing a report that summarizes this information, to serve as a guide.

"This will be the first comprehensive review of the effectiveness of drug-related interventions in managed care organizations," notes Soumerai.

Kenneth G. Saag, MD, MSc

Improving Management of Steroid-induced Osteoporosis

Caregivers have not followed expert recommendations for people receiving long-term glucocorticoid treatment. So concludes a study from the University of Alabama at Birmingham (UAB) CERTs that appears in the June 2001 issue of the *Journal of Rheumatology*.

Glucocorticoids, a class of steroid drugs, have been used for more than 50 years to reduce inflammation and suppress the immune system. Prednisone and cortisone are examples of glucocorticoids.

These drugs are invaluable in the treatment of rheumatoid arthritis (RA), lupus erythematosus, and other inflammatory and autoimmune disorders. They are not without risk, however.

One of their side effects is to cause bones to break down more rapidly. They also act directly on the cells that form bone tissue. Together, these two effects can render the bone less dense, and thus weaker, than it should be. This condition is known as osteoporosis.

Glucocorticoid-induced osteoporosis (GIOP) can be managed by periodically measuring bone mass and using appropriate preventive and therapeutic compounds. These compounds include calcium or vitamin D supplements, estrogens, and newer nonhormonal drugs to prevent bone loss, such as alendronate and residronate.

"…only a minority of physicians are addressing this critical problem."

Since 1996, guidelines from the American College of Rheumatology have recommended the strategies described above for prevention and treatment of GIOP. With support from partners Aetna U.S. Healthcare, U.S. Quality Algorithms, and Merck & Co., Inc., the UAB CERTs examined how well caregivers have followed these recommendations.

They studied 2378 HMO members who, over a 3-year period, had received a new prescription for at least a 3-month supply of glucocorticoids.

The news, although better than in previous studies, remains discouraging. Overall, only 9% of the members had undergone bone-mass measurement, and only 21% of the members had been prescribed any kind of treatment for osteoporosis.

"Our findings are regrettably consistent with past studies in showing that only a minority of physicians are addressing this critical problem," said Amy Mudano, MPH, lead author of the study.

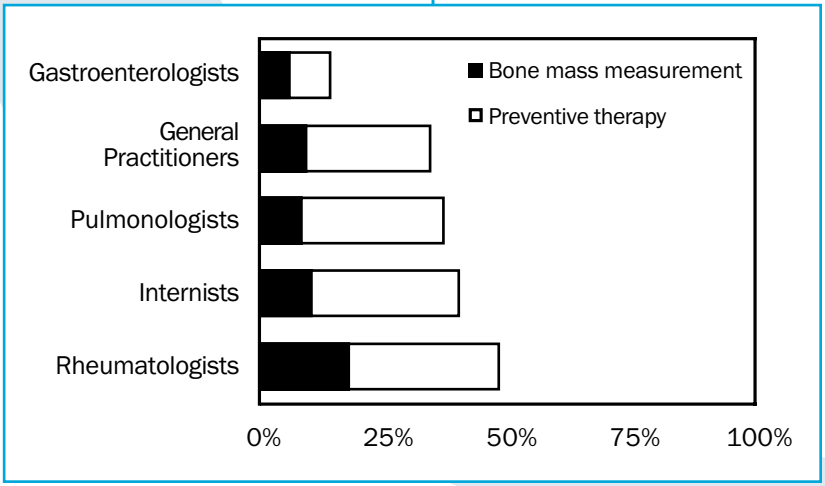
Women over the age of 50 fared somewhat better: 16% had undergone measurement of bone mass overall, and 41% had been prescribed preventive therapy independent of testing.

Although rheumatologists were most likely to have followed the guidelines (figure 3), still, only 18% of them had ordered a bone-mass measurement and only 30% had prescribed the appropriate therapies.

Clearly, there is a need for education of caregivers and patients.

The UAB CERTs now is conducting a project to test how outcomes are affected by different interventions designed to increase the use of these agents.

Figure 3: Caregivers Following GIOP Guidelines



Year 2 Completed Projects, UAB CERTs

PROJECT	METHOD	COLLABORATORS
Variations in practice patterns in glucocorticoid-induced osteoporosis (GIOP)	Characterize glucocorticoid usage and patterns of osteoporosis preventive therapies among a large national cohort	Aetna U.S. Healthcare, U.S. Quality Algorithms, Merck & Co., Inc.
Racial variations in osteoporosis management	Determine self-reported prevalence of osteoporosis risk factors and treatment type in a large managed-care population; determine racial variations in osteoporosis management, knowledge, and attitudes	United Healthcare of Alabama, Merck & Co., Inc.
Rating glucocorticoid-associated adverse effects versus fractures in RA	Determine patient preferences, using rating-scale and time-tradeoff methods	National Institutes of Health

"We intend to use well-tested methods developed at UAB for changing physician behavior," says Dr. Kenneth Saag, principal investigator of the UAB CERTs.

The interventions will include a Web-based resource for physician education, feedback on performance, and printable materials on prevention and treatment of GIOP.

Reporting Adverse Drug Events in Infants, Children, and Adolescents

A voluntary system for reporting adverse drug events in hospitalized youngsters is starting to pay off at the University of North Carolina at Chapel Hill (UNC).

The World Health Organization (WHO) has defined an adverse drug reaction (ADR) as an effect that is "noxious and unintended, and that occurs at doses used in man for prophylaxis, diagnosis, or therapy." More recently, the term "adverse drug event" (ADE) has been proposed, as it is more comprehensive. It has been defined as "real or potential injury resulting from medical intervention related to a drug."

"The data have proven invaluable in our efforts to improve patient safety."

These two types of events carry huge costs, in both human and financial terms. Inpatients who have an ADE or ADR have almost twice the risk of dying during hospitalization compared with people who don't, and these events translate into costs of more than $136 billion per year in the U.S. alone.

The risk of a potential ADE/ADR can be up to three times higher in pediatric inpatients than in adult inpatients. Systems that improve the process of using medicines (prescribing, dispensing, administering, and monitoring) can greatly reduce this risk, saving lives and resources. That's what the UNC CERTs aims to develop.

Since 1996, the UNC Hospitals have collected data on ADEs and ADRs from hospitalized infants, children, and adolescents. The UNC CERTs initiative resulted in revision of the Pediatric Adverse Drug Event and Reaction reporting system.

The UNC CERTs decided to adapt this reporting system in order to strengthen the pediatric focus. The overall goal was to develop a comprehensive, convenient reporting system that would not penalize caregivers. Ideally, the system would improve both reporting and patient care, while maintaining confidentiality and protection of the information.

The group, led by Project Leaders Dr. Rowell Daniels, Dr. Tina Hussey, and Jim McCallister, developed a new reporting form that was easy and convenient to complete. The new program also included a pediatric ADE/ADR specialist, more data-entry resources, and a multidisciplinary review committee.

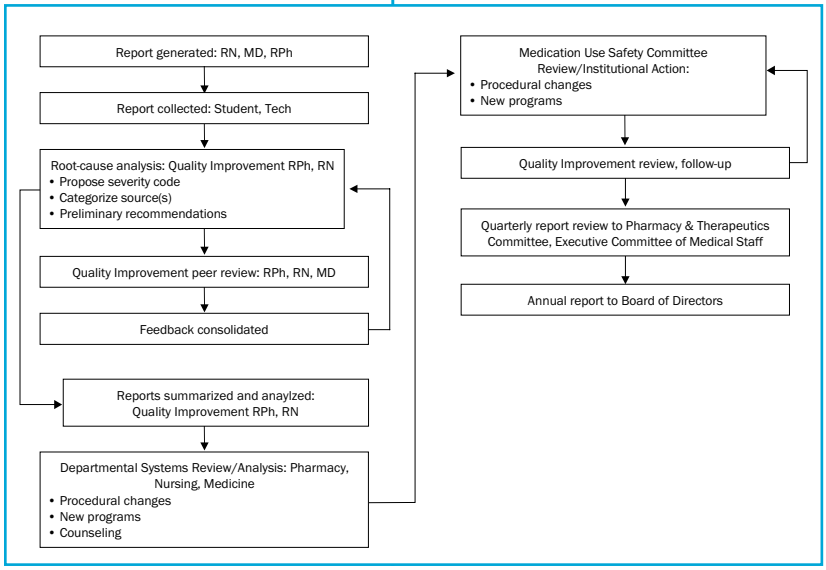
After 6 months of effort, they implemented a pilot version of the new reporting program in the pediatric units in February 2000. It has remained in place ever since (figure 4).

"We have been very excited at the volume of information generated through this process," notes Daniels. "The data have proven invaluable in our efforts to improve patient safety."

"After results are reviewed by our Medication Use Safety Committee, the information is then passed on to the Pharmacy and Therapeutics Committee, Medical Executive Committee, and Board of Directors. This ensures full disclosure within the Health Care System," continues Daniels.

The group recently reviewed 14 months of data gathered from the program. The results are very promising.

Figure 4: UNC ADE Reporting Program



First, the rate of pediatric ADE reporting jumped 500% during this period, to an average 5.85 reports per day and 232.5 per month. Pharmacists submitted more than 80% of the reports.

More than 70% of the reported ADEs were only *potential* adverse events, such as prescribing an incorrect dose, that never reached the patient because a nurse or pharmacist intervened.

When broken down by category, ADEs related to prescribing (30%) and order processing (40%) accounted for most of the reports during the first two quarters. Since then, events related to prescribing (25%), order processing (20%), dispensing (25%), and delivery (20%) have accounted for most reports.

The most common classes of drugs involved in ADEs have been antibiotics (48%), H_2-blocker antacids (10%), opium-like drugs (10%), anticonvulsants (10%), and glucocorticoids (9%).

The Pediatric Adverse Drug Event and Reaction reporting system is now part of a peer-reviewed process for continuous quality improvement at UNC Hospitals.

As Daniels says, "The results of this program have been so successful that we recently have received additional budgetary support to further expand the pediatric program into all patient-care areas at UNC. We hope that this program will serve as a model and can be replicated at other institutions as a mechanism for improving patient safety."

(l–r) Rowell Daniels, PharmD; Tina Hussey, PharmD; and Jim McCallister, MS

The group has identified trends in the results and is using them to develop further, targeted interventions. Primary projects for improvement include: missing doses from the Pyxis® dispensing system, missing doses of oral syringes, prescribing errors, processing of orders on the units, pediatric and neonatal total parenteral nutrition, and errors in pump and infusion rates.

In the second phase of the project, the group will assess the effect of these interventions on the ADE reporting rate, the rate of ADEs themselves, costs, and, most important, the outcomes of the infants, children, and adolescents.

Year 2 Completed Projects, UNC CERTs

PROJECT	METHOD	COLLABORATORS
Pediatric ADE, ADR reporting program	Create system that improves reporting and patient care while protecting confidentiality	None
NC asthma improvement project	Statewide educational effort to share knowledge: 3-hour interactive continuing medical education (CME) session and a learning collaborative within a NC Area Health Education Center region	GlaxoSmithKline, AccessCare
Drug metabolism in children with and without cystic fibrosis	Urine assays for caffeine and dextromethorphan and metabolites to assess differences in drug clearance	None
Tailored implementation strategy for pediatric therapeutic guidelines	Cross-sectional, multilevel assessment of guideline types and tools for tailoring and adapting guidelines for different settings	None
Efficacy, safety, and pharmacokinetics of drugs in pediatric human immunodeficiency virus (HIV) infection	High-pressure liquid chromatographic method to develop sensitive, specific, practical assay for any of the four most commonly used protease inhibitors (indinavir, ritonavir, saquinavir, and nelfinavir) in human plasma samples	Columbus Children's Hospital, Cincinnati Children's Hospital
MedMARx monitoring and surveillance project	Evaluation of inpatient error-reporting system	United States Pharmacopeial Convention, Inc.
Prevalence of vitamin D-deficient rickets in minority infants	Physician survey; proposal for state public health policy change	Bowman Gray School of Medicine, Wake Forest University Baptist Medical Center
Fellowships and Education Programs: Pediatric pharmacology, pediatric clinical trials, public outreach	Educational activity	Quintiles Transnational Corporation
CERTs Summer Institute: Using the evidence on therapeutics to enhance quality of care	Educational activity	National Initiative for Children's Healthcare Quality

Tetracycline Use and Bacterial Resistance

David J. Margolis, MD, MSCE

Antibiotics save lives; this fact is not in dispute.

Recently, though, their popularity among patients and caregivers has far exceeded their rational use against infection. A primary danger with the inappropriate use of these drugs is that bacteria and other organisms that cause infection can become resistant to the drugs.

Prescribing antibiotics to treat such conditions as upper respiratory tract infections, acute bronchitis, and acne, for example, might predispose patients to developing bacteria that will resist antibiotic treatment in the future.

Indeed, many strains of certain bacteria now are resistant to all but one antibiotic drug, and strains of at least three others do not respond to treatment with *any* known antibiotic.

The costs of resistance are high, in both financial and human terms. Estimates range from $75 million to $7.5 *billion* per year for the financial costs of resistant infections. In addition, the Centers for Disease Control and Prevention (CDC) estimate that drug-resistant infections carry at least twice the risk of serious illness and new or prolonged hospitalization compared with infections susceptible to drugs.

The University of Pennsylvania (UPenn) CERTs is conducting a series of studies intended to make the use of these drugs more rational. As an example, one study is assessing the possible link between long-term tetracycline use for acne and the development of both antibiotic resistance and infections. Dr. David Margolis, a dermatologist and pharmacoepidemiologist, is leading the efforts at UPenn.

“Patients with acne often take oral antibiotics for many years,” notes Margolis, “but the effect that the antibiotics may have on the health of these individuals or their families is not fully known. The current study is a first step in exploring this.”

People with acne generally are treated with topical or oral medications. Tetracycline is the most commonly prescribed oral treatment, and topical agents often include tetracyclines as well. The oral antibiotics, though, may be more likely to result in bacterial colonization, especially of resistant bacteria, and possibly even infections.

The goal of the UPenn study, then, is to see whether the long-term use of oral tetracycline for acne will affect the presence and drug resistance of bacteria, in the throat specifically.

Dr. Margolis and colleagues are recruiting patients with acne from the outpatient dermatology clinic at the Hospital of the University of Pennsylvania. The patients must have been taking an oral tetracycline for at least 3 months before enrollment.

The comparison group consists of people with acne who have not used oral tetracyclines for at least 6 months before enrollment in the study.

All study subjects have throat cultures taken, to measure the presence of two bacteria—*Staphylococcus aureus* and *Streptococcus pyogenes*—in the throat. If one or both of the bacteria is present, further tests are conducted to assess the resistance to tetracyclines.

So far, 44 patients have been recruited, of whom 34% were using an oral tetracycline. Of the people taking tetracycline, 5 of 13 had *S. pyogenes* present in the throat, 4 of 5 cases of which were resistant to tetracycline (table 1). Five of 12 patients taking tetracycline also showed *S. aureus* in the throat, 1 of 4 cases of which were resistant to tetracycline.

Table 1: Incidence and Resistance of Two Types of Bacteria in Patients with Acne

	Taking Tetracycline (n = 13)	**Not Taking Tetracycline** (n = 30)
S. pyogenes	38.5%	21.4%
Resistant	80%	12.5%
S. aureus	41.7%	23.3%
Resistant	25%	42.9%

Year 2 Completed Projects, UPenn CERTs

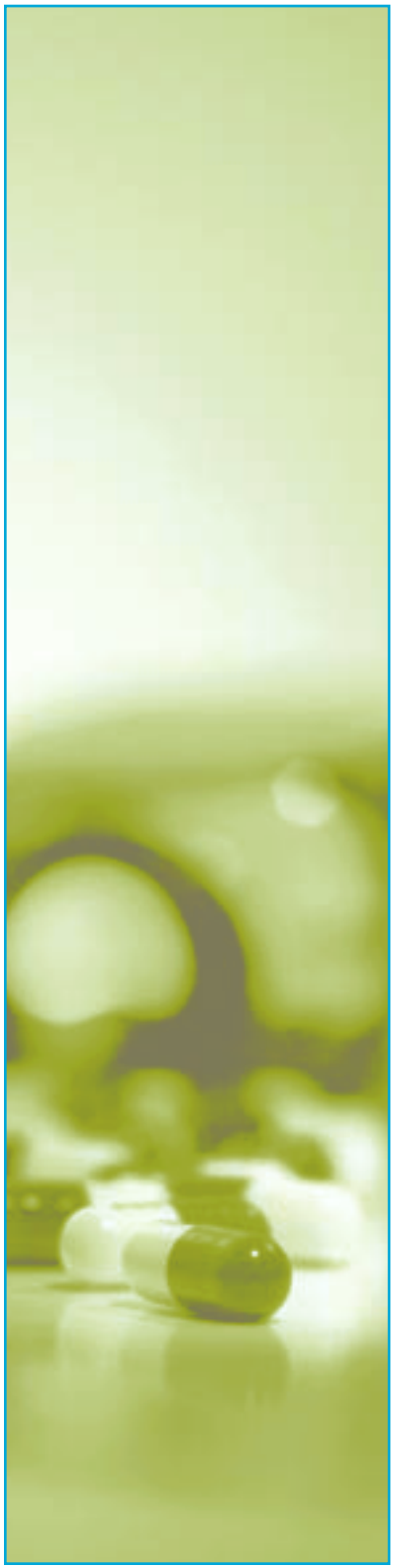
PROJECT	METHOD	COLLABORATORS
Increased use of meta-analysis to study rare side effects of antibiotics	Computer simulations of various data-analysis approaches to these analyses	None
Risk factors for infection by fluoroquinolone-resistant *E. coli* and *Klebsiella pneumoniae*	Case-control study	Infectious Diseases Society of America, Roche Laboratories, Presbyterian Medical Center
Adherence to protease inhibitor treatment for HIV	Observational cohort study	Agouron Pharmaceuticals, Inc.
Fluoroquinolone resistance in infection by extended-spectrum ß-lactamase–producing *E. coli* and *Klebsiella pneumoniae*	Case-control study	National Institute of Diabetes and Digestive and Kidney Diseases
Risk factors for drug-resistant urinary tract infections	Case-control study	Department of Veterans Affairs (VA)

Among the control group, *S. pyogenes* was present in only 6 of 28 people, and only 1 case was resistant. For *S. aureus*, only 7 of 30 patients had the bacteria present in the throat, and 3 cases were resistant to tetracycline.

Additional subjects are still being enrolled, and information about infections of the upper respiratory tract must still be analyzed.

Follow-up projects will include a longitudinal assessment of the bacteria in the upper respiratory tract and the resulting propensity for infection in this area among acne patients, as well as a similar evaluation of people in close contact with acne patients.

This sequence of projects should contribute greatly to the UPenn CERTs overall goal of optimizing the risk/benefit balance in the use of antibiotics.



Do Some Medicines Cause Sudden Death?

Some commonly prescribed drugs—antidepressants and antibiotics among them—can affect the electrical properties of the heart. Concern has increased in recent years that these drugs actually may trigger very serious arrhythmias, often causing sudden death.

This has been a difficult area to research because many of these drugs have been used for many years and generic versions are available, which has limited funding from industry for research. The drugs continue to be used by millions of people each year, however, so the subject remains very important to the public health.

The Vanderbilt CERTs aims to tackle this issue.

Dr. Wayne Ray, Project Coordinator Sarah Meredith, and their colleagues are conducting a series of studies of certain medications and the rates of sudden cardiac death among people who take them.

Using a unique database developed and maintained by the CERTs, they first assembled a group of over 400,000 people who had nearly 1.3 million person-years of medication use.

From this group, Ray and colleagues identified nearly 1500 cases of sudden cardiac death. They confirmed the cases through careful review of the circumstances surrounding the deaths.

Then the group put the data to work.

The first of their studies, completed this year, examined the class of drugs called antipsychotics. These are medicines used to treat schizophrenia and other serious mental illnesses.

In an analysis to be published in the November 2001 issue of the *Archives of General Psychiatry*, the group compared the incidence of and risk factors for sudden cardiac death with the use of these drugs.

Compared with people who had never used these medicines, those who were taking high doses were more than twice as likely to die suddenly from cardiac causes (figure 5).

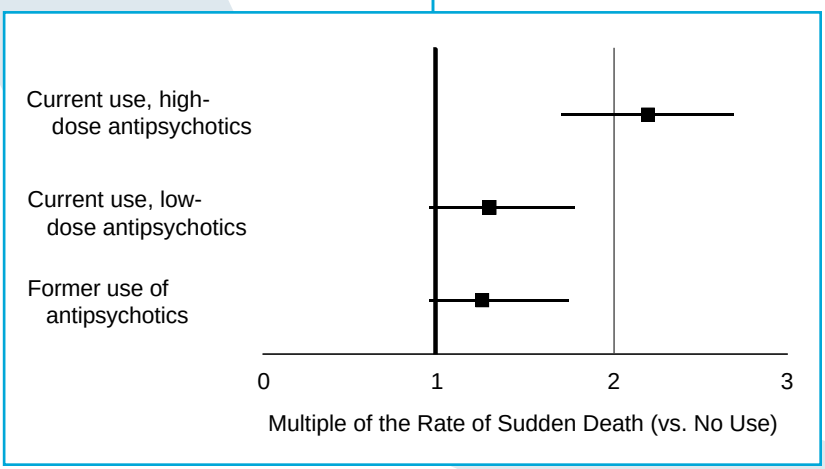
Further, people with severe cardiovascular disease had an even higher rate of sudden cardiac death if they were taking high doses of antipsychotic drugs—more than three times higher than among people who had never taken these medicines, in fact. People who had moderate or mild heart disease also showed proportionally higher rates of sudden cardiac death.

This study illustrates the valuable synergy that can result from interactions between the individual CERTs centers. Much of the basic work in identifying the drugs that can cause sudden death has come from studies by Drs. Raymond Woosley, David Flockhart, and their colleagues at the Arizona center. This center has a systematic program for identifying drugs, including those in development, that can affect the electrical properties of the heart.

Dr. Ray and colleagues will continue to leverage the findings from the Arizona program, next studying the risk of sudden death with antidepressant and antibiotic drugs.

Their findings could, in turn, feed into an overall CERTs initiative to develop a core curriculum for caregivers (see *On the Horizon*). This is an example of one of the many synergies that the CERTs organization makes possible.

Figure 5: Increase in Sudden Cardiac Death with Antipsychotic Drugs



Year 2 Completed Projects, Vanderbilt CERTs

PROJECT	METHOD	COLLABORATORS
Antipsychotic drugs and the risk of sudden death	Retrospective cohort study	Janssen Pharmaceutica, Inc.
Improving medication use in home health care	Randomized controlled trial	John A. Hartford Foundation
Evaluating regulatory policy changes	Retrospective cohort study	FDA, HMO Research Network, UnitedHealth Group
Risk of hip fractures with "statin" drugs	Observational study	None
Educational program to reduce adverse events with nonsteroidal anti-inflammatory drugs (NSAIDs): nursing home	Randomized controlled trial	AHRQ
Educational program to reduce adverse events with NSAIDs: community	Randomized controlled trial	AHRQ
Possible medication errors in home health care	Prevalence cohort	John A. Hartford Foundation
Evaluating treatment effects outside randomized controlled trials	Methods study	None
Exposure to systemic corticosteroids in childhood	Prevalence cohort	FDA
Early exposure to erythromycin and infantile hypertrophic pyloric stenosis	Nested case-control study	FDA
Fetal exposure to erythromycin and infantile hypertrophic pyloric stenosis	Retrospective cohort study	FDA
Effect of misclassification of time-dependent drug exposure on risk estimates	Methods study	None
Tricyclic antidepressants and the risk of sudden cardiac death	Retrospective cohort study	Janssen Pharmaceutica, Inc.
Nonselective NSAIDs and concurrent cytoprotective therapy	Prevalence cohort study	None

Year 2 Peer-reviewed CERTs Publications

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Rosebraugh CJ, Flockhart DA, Yasuda SU, Woosley RL. Visual hallucination and tremor induced by sertraline and oxycodone in a bone marrow transplant patient. J Clin Pharmacol 2001;41:224–7.

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Key:

= cardiovascular

= education

= clinical pharmacology

= health policy

= infectious disease

= mental health

= metabolic disorders

= musculoskeletal disorders

= pediatrics

= pharmacoepidemiology

= pulmonary disorders

= quality of health care

= safety management

= statistics

Ongoing Projects

ARIZONA CERTs (formerly Georgetown)

International registry for drug-induced arrhythmias

National medication-errors survey of third-year medical students, internal-medicine clerkship, and residency programs

Incidence of drug interactions

Incidence of and education about drug interactions, especially in women

Curriculum for therapeutics in women's health

Role of heart rate correction in QT analysis of drug action

Fourth-year medical school course on therapeutics

Genetic predictors of drug-induced QT interval prolongation

DUKE CERTs

Prospective demonstration project to improve use of beta-blockers in CHF

Evaluation of antiarrhythmic prescribing patterns, including dofetilide, in atrial fibrillation

Evaluation of physicians' understanding of the QT interval and drugs that can affect it

The effect of beta-blockers in CHF: a meta-analysis

Evaluation of the dofetilide risk management program—adherence to guidelines

Educational module on QT-prolonging drugs

Determine critical postmarketing surveillance (PS) questions, explore novel PS solutions for cardiovascular devices

PS of transmyocardial revascularization

Evaluation of beta-blocker use in a VA medical center

Economic implications of changes in treatment of cardiovascular disease

HMO RESEARCH NETWORK CERTs

Antibiotic use in children

Antiasthma drug use

Development of algorithms to identify patients with Churg-Strauss syndrome

Systematic review of drug interventions in managed care

UAB CERTs

Medical errors in the management of gout *(with UPenn)*

Cost-effective treatments for osteoporosis

Improving primary care with hand-held computers

Monitoring the long-term safety and toxicity of NSAIDs

Outcomes of elderly-onset RA

Interactive CD-ROM for arthritis patient education

Arthritis quality indicators

UNC CERTs

Evidenced-based tools to assess pediatric populations

Prevalence of Type 2 diabetes in childhood and adolescence

Attention deficit-hyperactivity disorder (ADHD) project

Prescribing patterns of drugs for ADHD and depression in adolescents

Reporting program for pediatric adverse drug events and reactions

Skeletal effects of oral replacement of vitamin D and calcium in adolescents with cystic fibrosis

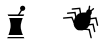
Optimizing prescribing and treatment for otitis media

NC immunization registry

UPENN CERTs

Reducing the outpatient use of antibiotics for acute bronchitis

Effect of formulary changes on resistance patterns of *E. coli* and *Klebsiella*



Use of tetracycline for acne in an outpatient clinic, effects on antibiotic resistance patterns

Risks of antibiotic use for drug-resistant *S. pneumoniae* infection

Adherence to nonnucleoside reverse transcriptase inhibitor (NNRTI) treatment for HIV

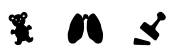
Research sponsorship and the statistical power to detect adverse effects of newly approved drugs

Patient versus public health values in generalists' use of antibiotics

Risk factors for drug-resistant pneumococcal pneumonia

Expansion of curriculum on therapeutics in medical school

VANDERBILT CERTs



Loss of Medicaid enrollment and asthma medication compliance

Use of beta-blockers, aspirin, and lipid-lowering drugs after heart attack

Clinical outcomes of NSAIDs

Effect of mental-health coverage changes on outcomes

Focus on the Program

The Risk Series

Because no medical product is absolutely "safe," the U.S. system of developing medical products involves trade-offs—a certain amount of risk given a certain amount of benefit. Products approved for marketing thus reflect a balance between the known benefits and the known risks as used in a specific population.

When products are used inappropriately, however, or their use is not monitored properly, the risk of adverse effects can increase. In more and more cases, continued inappropriate use or inadequate monitoring has resulted in the removal of products from the market, thereby reducing treatment options for all of us.

The CERTs program as a whole is working to reverse this trend. In partnership with FDA, the Pharmaceutical Research and Manufacturers of America (PhRMA), and AHRQ, we are tackling the issue of risk through a series of expert workshops. These workshops are focusing on three broad categories related to risk: communication, assessment, and management.

The ultimate goal of the Risk Series is to put forth an agenda for research priorities relating to the risks of medical products.

COMMUNICATING RISK: WHERE IS THE DISCONNECT?

Information about risk traditionally has been provided to caregivers by including more detailed information in the drug's packaging, by including "black box" warnings in the packaging (figure 6), and by mailing "Dear Healthcare Professional" letters. These interventions have been shown to be only minimally effective at changing prescribing behavior, however. Clearly other methods are needed.

Dr. Bill Campbell, principal investigator of the UNC CERTs, is leading the effort to improve communications about risk. The group's first accomplishment was the coordination of a workshop this past spring.

Figure 6: Sample "Black-box" Warning

WARNING

When used orally, **DRUG X** has been associated with liver toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See **WARNINGS** and **PRECAUTIONS** sections.

Coadministration of **DRUG Y** with **DRUG X** is contraindicated. Rare cases of serious cardiovascular adverse events, including death, ventricular tachycardia, and torsades de pointes have been observed in patients taking **DRUG X** concomitantly with **DRUG Y**, due to increased **DRUG Y** concentrations induced by **DRUG X**. See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** sections.

William H. Campbell, PhD

"It was both sobering and stimulating to be part of this workshop; sobering because there is a paucity of research to guide decisions, but also stimulating because all stakeholders agree on the critical importance of developing new and more effective methods of risk communication," says Campbell.

Experts were gathered from government, academia, and industry for this workshop, entitled "Improving Communication of Drug Risk Information to Prevent Patient Injury."

The two objectives of the workshop were to survey the status of risk communication approaches and to create a research agenda for communicating the risks of medical products.

The attendees agreed that the system, as it stands, is not working.

"Despite the recent emphasis placed on the risks of therapeutics, very little energy has been devoted to changing the status quo," notes Dr. Rob Califf, principal investigator of the CERTs Coordinating Center.

Several promising outcomes emerged from the workshop. For example, FDA and pharmaceutical industry representatives agreed to collaborate in developing more effective approaches to communicating the risks of prescription drugs.

There also was a consensus to identify approaches deserving the highest priority. The group agreed that the real-life concerns of caregivers, patients, regulators, and industry groups should guide development of risk-communication methods.

The group is preparing the proceedings of the workshop for publication, which will put forth the group's conclusions and recommendations about research priorities.

One such priority is to assess how risk is communicated (or not communicated) by the mass media, because this can determine how risk is perceived by patients and caregivers.

For example, a sensational "lead" can obscure the facts behind the situation. "Drug X Increases Stroke Risk by 100%!" is a typical headline or soundbite. What is less typical, though, is being given some context for this statistic, namely, that the strokes occurred in 2 of the 5000 patients treated with Drug X versus 1 of the 5000 patients treated with Drug Y. Or perhaps the study included only people who had a very high risk at baseline. It even might be that both Drug X and Drug Y *reduce* the risk of stroke compared with the background rate of stroke in the population studied. Clearly the presentation of risk information can affect its perception.

Califf and colleagues are tackling this aspect of the Risk Series. Their first goal is to gather interested parties from academia, industry, regulatory agencies, and the media to answer several critical questions during a 1-day workshop:

- Who performs research on the media and on how the risks of medical products are depicted?
- What does the "typical" citizen know about risks and probabilities?
- Who decides which stories to report, who does the reporting, and what gets included/excluded?
- What do organizations do to get the press interested and particular reporters to cover the story?
- How do organizations attempt to influence the final interpretation of a story about risk?

Robert M. Califf, MD

- How can we assess the effect of stories on the perceived risks of medical products?
- Does the medium (newspaper, television, Internet) matter?
- What can industry, academia, and regulatory agencies do to enable the press to depict the risks (and benefits) of medical products more accurately and effectively?

The answers to these questions and others will be used to develop a research agenda, which will be disseminated to the public. This workshop is slated to take place during Year 3.

The media are a crucial mechanism for distribution of information, which is part of the CERTs mission. By working together, we can provide more accurate and complete information to those who need it.

RISK/BENEFIT ASSESSMENT: FINDING A BALANCE

The American system for developing medical products balances the possible benefits against the possible risks. Accurate, comprehensive information about both is critical to inform decisions about product approval. It wasn't always this way.

Safety has long been a priority. Since 1938, manufacturers have been required to show the safety of prescription drugs before they can market them in the U.S. It wasn't until 1962, though, that manufacturers also had to show a drug's effectiveness, or benefit, before marketing.

The requirement to show a benefit brought forth a host of issues, including the definition of "benefit" itself. Another question was how to measure benefit, however defined, across different types of patients and geographic locations. Differences in definitions can provide confusing and conflicting study results and can affect the design and interpretation of future research.

Over time, it has become clear that the ideal measures of both benefit and risk would be quantifiable, objective, standardized, and, most important, clinically meaningful.

How best to assess risk, and how best to assess benefit, will be covered in two more CERTs workshops, chaired respectively by Dr. Brian Strom, of the UPenn CERTs, and Califf.

The goal of these additional workshops, as in previous sessions within the Series, is to set a research agenda. To accomplish this goal, the attendees will discuss what is known and unknown and what research already has been done.

The group first hopes to draw some lessons from recent cases of product risk, considering both medical products specifically (drugs) and consumer products in general (airbags).

The group also will review current and traditional methods of measuring risk and benefit. These include everything from animal studies to reporting systems for adverse events in people.

The pros and cons of newer methods for assessing risk and benefit also will be covered. With advances in analytical methods, data collection, and software, researchers have more powerful tools at their disposal to detect and quantify risk.

After risk and benefit have been quantified, though, comes the hardest question of all: What is the "right" balance between the two? How much risk is too much?

Going back to the cases mentioned above, the group will attempt to identify the gaps in knowledge and processes that resulted in excess risk. From there, they will develop a program for research projects to address these issues.

Attendees of the workshops, which will held during Year 3, will include representatives from academia, industry, regulatory agencies, and other interested groups.

Brian L. Strom, MD, MPH

RISK MANAGEMENT: PUTTING IT ALL TOGETHER

After the other workshops have been completed, we plan to hold one more. The goal of this final workshop will be to meld the output of the previous sessions in the Series, along with new input, into a cohesive, comprehensive research agenda about risk.

Dr. Judith Kramer, of the Duke CERTs, will chair this concluding workshop, which is to be held in Year 3.

The agenda from this workshop will set forth priorities for research, to be sure, but the other half of the CERTs mission is education. To this end, the group also will discuss methods of educating caregivers about risk communication, assessment, and management.

"…very little energy has been devoted to changing the status quo."

"One of the keys to managing risk will be to educate young professionals about therapeutics while they are still in school, and then to help them apply this knowledge throughout their professional careers," notes Kramer.

One possible strategy for such education is the development of a core curriculum for caregivers (see *On the Horizon*). In keeping with our collaborative approach, the curriculum would reflect several perspectives, including those of regulators, caregivers, clinical pharmacologists, medical-product manufacturers, and patients.

With this series of workshops, and the resulting research, CERTs hopes to offer practical and effective strategies to assess, manage, and communicate the risks associated with medical products.

PATHs to Knowledge

Fostering collaborations is a core value of the CERTs. Its importance has expanded over the past 2 years, so much so that creation of a separate group was required to do it justice.

As the proverb says, "Many hands make light work." In Year 2, we began development of an offshoot of CERTs, the Partnerships to Advance THerapeutics (PATHs), that will cultivate public-private partnerships across the United States.

In March 2001, Dr. Hugh Tilson, chair of the CERTs Steering Committee, led the first meeting of this group in Washington DC.

Attendees included representatives of ~40 organizations interested in advancing the best use of therapeutics, including government agencies, caregivers, consumers, and insurers, among others.

Several Congressional staff members also attended, to learn more about CERTs and opportunities for collaboration in promoting the optimal use of therapeutics.

As a result of this meeting, the PATHs will be developing an Internet-based registry of educational and research projects, as an aid to pairing worthy projects with interested partners. The registry has several purposes:

- to serve as a resource of current and planned projects that aim to optimize the use of therapies;
- to identify and aid in partnerships around these projects; and
- to provide a list of participating organizations and their priorities relative to the optimal use of therapies.

The registry will include the project list, organizational summaries, and models for public-private partnerships. The registry is to be posted during Year 3.

The PATHs program is an important step in aiding collaborations that will improve the use of therapeutics. These collaborations will help us achieve our vision that much faster.

On the Horizon

As our name states, we are the Centers for *Education* & Research on Therapeutics. Through educational efforts, we intend to change the way caregivers obtain and apply information about therapeutics in the treatment of their patients—from the time they are in school throughout the time they are in practice.

Our future plans include development of a comprehensive, core curriculum for caregivers, which would impart the critical safety issues related to the use of medical products. The curriculum would incorporate the results of the Risk Series and other CERTs efforts.

The Arizona, UPenn, and UNC CERTs already have made progress in this effort, respectively developing curriculum components for therapeutics in women's health, pharmacoepidemiology, and pediatric therapeutics. The Duke and UAB centers also have done extensive work in CME programs. Further resources beyond CERTs will be needed, however.

Notes Dr. Judith Kramer, of the Duke CERTs, "Such an educational initiative is likely to be most successful if we can form partnerships with organizations that have common goals: professional societies, medical specialty groups, and schools of pharmacy, nursing, and medicine."

The CERTs group as a whole would develop the core curriculum, and all CERTs centers would test it. When refined, the curriculum then could be offered to medical, pharmacy, and nursing schools and to professional groups for CME programs.

In the future, an Internet-based "virtual library" could make such a core curriculum universally accessible. People could "check out" the material, adapt it as needed, and return the adapted material as their contribution to the library. This truly would be a collaborative effort.

Conclusion

We have accomplished much this year, and we have even bigger goals for next year. In the end, though, we won't have achieved our vision until there is "a CERTs in every pot," so to speak.

Why? To be trusted, a resource must be credible, local, personal, and easily accessible. The most direct way we can become such a resource is to expand our collaborative pool to cover new areas of the country, new types of practices, new sources of support, new methods of education, and new groups of patients. The PATHs will help achieve this goal, by extending the reach of CERTs through a national network of collaborations.

In addition to increasing our local presence, we also hope to change the way caregivers receive, incorporate, and apply information about medical products. We intend to start this tremendous undertaking by fundamentally changing the education of doctors, nurses, and pharmacists about therapeutic options—from the time they begin their education through the time they are in practice.

As we noted in last year's Annual Report, no one should have doubts about the medical products they prescribe or use. With our collaborators in research and in education, we are seeking the knowledge that will dispel such doubts. Armed with this knowledge, all of us then will be able to take informed action to improve our health.

—The CERTs Group

CERTs

Developing knowledge
Managing risk
Improving practice
Informing policies

The CERTs Organization

Administration

Agency for Healthcare Research and Quality, Rockville, MD

Program Coordination

Duke University Medical Center, Durham, NC

Centers

Duke University Medical Center, Durham, NC

HMO Research Network, Boston, MA

University of Alabama at Birmingham

University of Arizona Health Sciences Center, Tucson
(formerly at Georgetown)

University of North Carolina at Chapel Hill

University of Pennsylvania, Philadelphia

Vanderbilt University Medical Center, Nashville, TN

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National Pharmaceutical Council

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University of Arizona Health Sciences Center

Bookmarks

AHRQ
www.ahrq.hhs.gov

CERTs Program
www.certs.hhs.gov

Arizona CERTs (formerly Georgetown)
http://georgetowncert.org/; http://www.torsades.org; http://www.qtdrugs.org; http://www.drug-interactions.com

Duke CERTs
http://dcri.mc.duke.edu/research/fields/certs.html

UAB CERTs
http://www.uab.edu/certs/

UNC CERTs
http://www.sph.unc.edu/health-outcomes/certs/index.htm

UPenn CERTs
http://www.penncert.org

Partners

We gratefully acknowledge our partners for their expertise and support of the CERTs efforts. They have helped create a model for future public-private collaborations:

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AdvancePCS

◗ Agouron Pharmaceuticals, Inc.

Aetna U.S. Healthcare

American Association of Colleges of Pharmacy

American Pharmaceutical Association

American College of Cardiology

AstraZeneca LP

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◗ Children's Hospital Medical Center of Cincinnati

Cincinnati Children's Hospital

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◗ Conceptis, Inc.

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◗ Department of Veterans Affairs

◗ DuPont Pharmaceuticals Company

◗ Epidemiology and Pharmacology Core (EPIC, UK)

GlaxoSmithKline

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◗ Health Care Financing Administration (now the Centers for Medicare & Medicaid Services)

◗ F. Hoffman-La Roche, Ltd.

◗ Immunex Corporation

◗ IMS Health Inc.

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◗ Iowa Women's Health Study

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U.S. Food and Drug Administration

U.S. Quality Algorithms

United States Pharmacopeial Convention, Inc.

UnitedHealth Group

United Healthcare of Alabama

University of Illinois Chicago College of Pharmacy

◗ University of Iowa

◗ University of New Mexico

◗ Wake Forest University Baptist Medical Center

Wyeth-Ayerst Laboratories

◗ = *new partner this year*