OVERVIEW OF NOVEL DRUG PLAN AND DRUG REGULATORY PHARMACOSURVEILLANCE INITIATIVES IN THE UNITED STATES, UNITED KINGDOM, AND SELECT OTHER JURISDICTIONS

A background paper prepared for the
Working Conference on Strengthening the Evaluation of Real World Drug Safety and Effectiveness

June 22, 2005

Prepared by
Michael Paterson,
Institute for Clinical Evaluative Sciences

CONTENTS

1. Introduction....3

2. Methods....3

3. United States....3
   3.1. Drug Regulatory Initiatives....3
      3.1.1. Context: FDA guidance for industry on i) good pharmacovigilance practices and pharmacoepidemiologic assessment and ii) development and use of risk minimization action plans
      3.1.2. Data mining of spontaneous adverse drug reaction reports
      3.1.3. FDA post-marketing study commitments
      3.1.4. Office of Drug Safety's Cooperative Agreement Program in Pharmacoepidemiology
      3.1.5. Centers for Education and Research on Therapeutics (CERTs)
         3.1.5.1. Request for input regarding the creation of CERTs
         3.1.5.2. Requests for applications for CERTs
         3.1.5.3. Specifics regarding operation of the HMO Network CERT
   3.2. Health/Drug Plan Initiatives....9
      3.2.1. Context: Guiding Principles of a 'Sound Formulary System'
      3.2.2. Private Plans
         3.2.2.1. Academy of Managed Care Pharmacy (AMCP) Format for formulary submission and access to information
         3.2.2.2. Participation in pharmacoepidemiological research
      3.2.3. Public Plans
         3.2.3.1. Veterans Affairs Administration National Drug Formulary and Pharmacy Benefits Management Strategic Health Care Group
   3.3. Clinician/Researcher Initiatives....12
      3.3.1. Research on Adverse Drug Events and Reports (RADAR) Project

4. United Kingdom....13
   4.1. Drug Regulatory Initiatives....13
      4.1.1. Britain's Yellow Card Adverse Drug Reaction Reporting Scheme and Black Triangle Program
      4.1.2. Medicines Monitoring Unit at the University of Dundee
      4.1.3. General Practice Research Database
      4.1.4. Prescription Event Monitoring Program, Drug Safety Research Unit
   4.2. Health/Drug Plan Initiatives....17
      4.2.1. Product Risk-Sharing Agreements and Outcome Guarantees
         4.2.1.1. Risk-sharing scheme for assessing drugs for multiple sclerosis
         4.2.1.2. Risk-sharing scheme for nicotine replacement therapy
         4.2.1.3. North Staffordshire Atorvastatin Outcome Guarantee

5. Drug Plan Initiatives in other Countries....18
   5.1. France's 2003 policy for assessing the public health impact of new drugs
   5.2. Australian Pharmaceutical Benefits Scheme mechanisms for targeting and monitoring high-cost drug therapies: TNF-alpha inhibitors and human growth hormone

6. Implications for Canada....21
7. References....21
8. Appendices....25

1. INTRODUCTION

This report was prepared for the National Pharmaceuticals Strategy Drug Safety & Effectiveness Working Group to aid in discussions during a conference to be held in Ottawa September 13-15, 2005. It provides an overview of initiatives undertaken by drug regulatory authorities and drug plans primarily in the United States and United Kingdom to improve their understanding of drug safety and effectiveness issues through novel, often collaborative post-marketing research.

Under international regulatory guidelines, establishing the clinical safety of medicines intended for the long-term treatment of non-life-threatening conditions requires data from prospective studies providing a minimum of 100 person-years of drug exposure at dosages expected in regular use. When no serious adverse reactions (ADRs) are observed, this number of patients gives reasonable assurance that the true cumulative one-year incidence is no greater than 3%.<Expert 1995> For less frequent events, spontaneous ADR reporting schemes, such as the Canadian Adverse Drug Reaction Monitoring Program, are a basic regulatory requirement. However, these programs have important limitations, among them: under-reporting; lack of reliable exposure data; and confounding by underlying diseases or drugs. In general, the regulatory initiatives outlined here are novel in their aim to address one or more of these important limitations. Likewise, while patient registries are commonly employed by regulators and manufacturers, their use by drug plans would be considered novel. Throughout this review, we focus mainly upon the practical elements of who's involved in the programs; how are they organized; what has been accomplished; and, where available, what has been learned.

2. METHODS

Our findings were derived from an unsystematic but broad review of the literature conducted in May 2005. The primary focus was upon print material in the public domain, including among other sources, peer-reviewed journals; reports, proposals, and presentations published by foundations and government agencies; industry newsletters; and mass-circulation newspapers. Most material was identified using publicly-accessible search engines (e.g., Google) and databases (e.g., PubMed/Medline), and was ultimately accessed via the World Wide Web. Industry and lay publications frequently gave descriptive information about specific initiatives, but rarely provided detail regarding their operation or evaluation. Occasionally, these details were obtained from program staff or other key informants through verbal or written correspondence. But, generally, the level of information needed to properly evaluate the merits of interventions was limited. These details could be found through key informant interviews or formal requests for access to information that is not typically in the public domain.

3. UNITED STATES

3.1. DRUG REGULATORY INITIATIVES

3.1.1. Context: FDA guidance for industry on: i) good pharmacovigilance practices and pharmacoepidemiologic assessment; and ii) development and use of risk minimization action plans (at www.fda.gov/cder/guidance)

These documents, published March 2005, set standards for industry, including expectations that drug sponsors will identify and characterize safety signals and, in consultation with the FDA, follow-up as appropriate with proper observational research (pharmacoepidemiological studies, registries, and/or surveys). The implication is that sponsors have access data sources and expertise to conduct such research -- see page 6 for more on the U.S. Centers for Education and Research on Therapeutics (CERTs).

3.1.2. Data mining of spontaneous adverse drug reaction reports

(Avigan 2004)

In the context of pharmacosurveillance, data mining typically represents the application of statistical techniques to spontaneous ADR reports or medical records to identify potential associations between drug exposures and outcomes.<Wilson 2004>

In 2003, the FDA's Office of Drug Safety entered into a Cooperative Research and Development Agreement with Lincoln Technologies, Inc., MA to develop a Web-based Visual Data Mining Environment (WebVDME) for safety signal detection using data from the FDA's adverse event reporting system. The main goals were to create a user-friendly program for safety evaluators and epidemiologists to enhance efficiency of signal detection/evaluation; and to determine appropriate applications of the system.

The WebVDME program is currently being pilot tested by staff as part of the Office's surveillance and evaluation activities; and an FDA/PhRMA Working Group is developing recommendations for use. Lessons learned to date include:

- Setting the threshold for signal detection is a compromise between sensitivity and specificity;
- False positive and negative signals are linked to limitations of ADR reporting;
- Quantitative data mining 'scores' may not correlate well with degree of risk; and
- Data mining may have role in signal enrichment, but will never replace the detailed evaluation of case reports.

3.1.3. FDA post-marketing study commitments

(Tufts 2004)

Under the Food and Drug Administration Modernization Act of 1997 (Act), the FDA is required to report annually in the Federal Register on the status of post-marketing study commitments made by sponsors of approved drug and biological products. These studies are mandatory for products for which reviews were 'fast-tracked', and those for which further data are needed to establish safety in children. Other requests are at the discretion of the Agency. In addition to the authority to request post-marketing studies, Section 506B of the Act provides FDA with authority to monitor the progress of studies that an applicant has been required to or has agreed to conduct by requiring the applicant to submit annual progress reports. These reports are required on the anniversary of a product's approval until FDA determines that the study commitment has been fulfilled, or that the study is either no longer feasible or would no longer provide useful information.

The Tufts Centre for the Study of Drug Development recently initiated a five-year research program to evaluate the FDA's post-marketing commitments.<Tufts 2004> Key findings from its first report follow.

- The number of post-marketing commitments per new drug has increased from 2.7 in the 1970s to 3.0 in the 1980s to 4.4 in 1998-2003.
- The median cost of studies rose from $135,000 in the 1970s and 80s to $3.7 million in 1998-2003.
- The completion rate fell from 62% in the 1970s to 17% in the mid-1980s, and then rose to 24% since the implementation of the formal tracking system in 1997.
- The number of patients per study has grown from a median of 30 in the 1970s to 123 in the 1980s to 920 in 1998-2003.

- Requirements for post-marketing commitments vary widely by FDA review division: 100% of all new anti-infectives approved in 1998-2003 involved such studies vs. 36% for analgesics, anti-inflammatories, and ophthalmic drugs.

To date, critics of the current accelerated approval mechanism have charged that the framework makes it difficult to fulfill commitments in a timely manner due to difficulty enrolling patients in post-market studies and to a reduced sense of urgency on the part of manufactures.<Mitka 2003> Others claim the framework has no clear mechanisms for triggering market withdrawal if confirmatory trials are negative. Given that many of the drugs granted accelerated approval are for serious or life-threatening conditions, Roberts and Chabner also fault the program's inability to promote research that helps identify the subpopulations of patients most likely to respond to therapy.<Roberts 2004>

3.1.4. Office of Drug Safety's Cooperative Agreement Program in Pharmacoepidemiology (www.fda.gov/cder/Offices/ODS/AnnRep2003/default.htm)

In June 1998, the FDA Center for Drug Evaluation and Research published a request for applications (RFA) in the amount of $1.4 million for cooperative agreements to study suspected adverse drug events (ADRs).<Federal Register 1998;63(118):33680-33686> At the time, the FDA expected to make up to four 3-year awards for $300,000 per year for access to general population health administrative data bases, and up to two awards for $100,000 per year for special population data bases. The general goals for the program were to collaborate with researchers with access to such data to investigate suspected associations between specific drug exposures and adverse events. Specific objectives were to: 1) provide immediate access to administrative data with the capability of providing assessments of study feasibility; 2) respond to specific drug safety questions within several weeks; and 3) provide complete analysis of those questions deemed feasible within a few months.

The ideal data source was defined as one that would:
1) Capture all drug exposures linked longitudinally to each patient regardless of health care setting.
2) Have the statistical power to identify rare adverse events (< 1 per 1,000 exposures) in the population of interest.
3) Be automated with a computerized system available for linking each patient to all relevant medical care data including drug exposure data, coded medical outcomes, vital status records, cancer registries, and birth defect registries.
4) Have low patient turn-over, thereby permitting long-term longitudinal follow-up of most patients for delayed adverse effects.
Additional credit was given to centres that could link to laboratory test results and readily access medical records for validation studies. This latter criterion was deemed critical.

A defining feature of Cooperative Research Agreements is substantive involvement by the FDA in the research conducted. In this RFA, substantive involvement meant:
- appointment of a Project Officer who would actively monitor the program and collaborate with award recipients;
- participation in the selection and approval of the suspected ADRs and medical events to be studied as predicated by the needs of FDA and the public; and
- collaboration with awardees in study design, data analysis, and report preparation.

The first year of agreements were competitive, with ongoing non-competitive support for year 2 and 3 contingent upon investigators' demonstrated success in collaborating with FDA scientists and other investigators funded through the program.

Six teams/databases were initially funded through September 2001.<Rodriguez 2001>
1) Saskatchewan Health
2) United Health Group – Historical medical and pharmaceutical data from 12 health plans covering about 2.1 million lives and 13.1 million member-years of data since 1990.
3) Harvard Pilgrim Health Care – A Joint Pharmacoepidemiology Program combining populations and resources from three HMOs -- Harvard Pilgrim Health Care, Boston; HealthPartners, Minneapolis; and Fallon Community Health Plan, Worcester, Massachusetts. Each HMO maintains automated record linkage systems, including drug dispensing information, coded diagnoses for ambulatory and inpatient care, and access to medical records.
4) Vanderbilt University - A database containing data from Tennessee Medicaid, a joint federal-state program that finances medical care for low-income patients. In 1997, the program had approximately 1.4 million enrollees. The Medicaid program files include enrollment, pharmacy, hospital, outpatient, and nursing home data.
5) Boston Collaborative Drug Surveillance Program – Which has access to EMR data from the U.K. General Practice Research Database (GPRD (See below for details.)) and the Group Health Cooperative (GHC) of Puget Sound (which merged with Kaiser Northwest). In 1998, GPRD provided data on 4 million patients. The GHC maintained EMR files for 325,000 patients since July 1976, as well as discharge diagnoses from hospitalizations since 1972.
6) Johns Hopkins University - The Johns Hopkins AIDS service is the largest care provider for HIV/AIDs infected persons in Maryland. In 1998 their database included over 3,500 patients from January 1990 and was fully linkable with other Johns Hopkins Health Systems.

In April 2001, a second RFA was released with revised criteria:
- general databases that covered U.S. patients and multiple States;
- at least 1.5 million enrolled patients on December 31, 2000; and
- demonstrated ability to obtain paper copies of anonymized patient medical records for the completion of validation studies.<Federal Register 2001;66(65):17907-17911>

Three teams received ongoing funding: Harvard Pilgrim Health Plan/Fallon Clinic/Health Partners; Vanderbilt University; and United Health Group.

APPENDIX 1 lists a sample of studies completed with support from Cooperative Agreements. Many of these studies have contributed importantly to FDA policy, including safety warnings/Dear Doctor letters, label changes, and outright product withdrawals. An RFA for the next round of Cooperative Agreements is imminent.

3.1.5. U.S. Centers for Education and Research on Therapeutics (CERTs)
(www.certs.hhs.gov)
3.1.5.1 Request for input regarding the creation of CERTs
In 1997, U.S. Congress expanded the authority of the Agency for Health Care Policy and Research (AHCPR) under the Food and Drug Administration Modernization Act to permit the establishment of a three-year demonstration program to conduct research and provide objective information on drugs, biologics, and devices. Accordingly, in November 1998, the AHCPR published a request for input on topics of study and ideas for implementation.<Federal Register 1998;63(212):59313-59315> More specifically, comment was requested on:

- how the centers should be organized;
- the appropriateness of AHCPR or the centers seeking additional funding partners;
- initial areas of emphasis (drawing from a list outlined in the statute);
- high-priority research topics within the suggested initial areas of emphasis;
- whether the Agency should include a list of specific research topics in the RFA to which applicants would respond or whether the RFA should focus primarily on the infrastructure and capacity of applicants and identify specific research issues to be addressed following selection of the centers; and
- other issues that respondents believed need to be taken into account by the Agency in implementing the legislation.

3.1.5.2. Request for Applications for CERTs

In January 1999, the AHCPR invited applications from nonprofit organizations to establish CERTs to evaluate, develop options and methods, and conduct and perform pilot studies.< AHCPR. Request for Applications for Centers for Education and Research on Therapeutics (RFA HS-99-004), January 27, 1999> These studies were to consist of "...state-of-the-art clinical, health services, or laboratory research to increase awareness of the benefits, risks and effectiveness of new uses, existing uses, or combined uses of therapeutics." In addition, the Program sought new and more effective ways to develop, translate and disseminate objective information on therapeutics to health care providers and other decision makers to improve practice. A key long-term goal was to improve care quality while at the same time reduce costs.

For the 1999 RFA, AHCPR was allotted $2 million to support 4-6 centres. In 2004, the budget for 7 CERTs was $5.8 million.<Strom 2004>

Of all the review criteria set forth in the original RFA, infrastructure and research capacity were deemed most important. Capacity was defined as evidence of "...ability to provide rapid production of information, ability to link geographically and demographically diverse sites of care, ability to access a longitudinal and large database, and capability to access and interface with the delivery systems." Core funding was provided for administrative and staff support, and a dissemination program. Research projects also were supported in their initial stages. But it was expected that Centers would ultimately fund their research though other sources. In addition, the RFA asked applicants to make it known if they wished to serve as a Network Coordinator. This job would entail:

- establishing and administering a Steering Committee consisting of members from all of the research centers, AHCPR and FDA, and chaired by a national expert chosen by FDA and AHCPR;
- identifying and employing an individual to act as a data and information coordinator for the Network;
- working with AHCPR Program Officials, FDA representative(s) and the Steering Committee Chair to enhance synergy across the goals and projects of each of the Centers;
- identifying opportunities for engaging research centers in addressing common methodologic and technical challenges;
- identifying opportunities for large-scale dissemination and implement efforts, including developing strategies for knowledge transfer to key "opinion leaders" and "change agents" in the health care system; and
- seeking out opportunities for resource sharing and other economies of scale.

Below are the currently-funded CERTs and areas of emphasis.

RESEARCH CENTER	EMPHASIS
Duke University Medical Center (www.dukecerts.dcri.duke.edu)	Therapies for disorders of the heart and blood vessels
HMO Research Network (www.certs.hhs.gov/centers/hmo.html)	Drug use, safety and effectiveness in HMO populations
University of Alabama at Birmingham (www.uab.edu/certs)	Therapies for musculoskeletal disorders
University of Arizona Health Sciences Center (www.arizonacert.org)	Drug interactions that result in harm to women
University of North Carolina at Chapel Hill (www.sph.unc.edu/certs/index.htm)	Therapies for children
University of Pennsylvania School of Medicine (www.cceb.upenn.edu/cert)	Therapies for infection; antibiotic drug resistance
Vanderbilt University Medical Center (www.certs.hhs.gov/centers/vanderbilt.html)	Prescription drug use in a Medicaid population

As mentioned, a key factor in the success of the CERT program has been funding through public-private partnerships. The Agency for Healthcare Quality and Research -- the Program's current administrator -- works with the centers to establish appropriate agreements to optimize the use and sharing of resources. CERT members are obliged to fully disclose such agreements and to manage potential conflicts of interest in a manner that minimizes the risk of conflict while at the same time maximizing progress to achieve CERTs goals. As academic researchers, CERT investigators maintain control over final decisions regarding study design, analysis, conclusions, and publication, and ensure that all work complies with their respective institutions' conflict of interest guidelines.

CERT projects to January 2005 are listed in APPENDIX 2.

3.1.5.3. Specifics regarding operation of the HMO Network CERT (Platt 2001)
This multicentre group includes nine HMOs plus a coordinating centre at the Harvard Medical School. Each site has a lead investigator, with participation of HMO-based researchers as appropriate. All centres share in the development of policies and procedures, infrastructure, and core collaborative research. New studies are approved by a steering committee, after which centres decide individually whether to participate. Study leadership is decided within each participaing HMO, but all team members contribute to protocol development, work plans, data interpretation, and the preparation of manuscripts. The coordinating centre supports all joint studies, usually by leading in the creation and analysis of study-specific data sets.

According to Platt,<2001> the Network's most important organizational principles are that individual HMO databases reside and remain with the HMOs (rather than creating and supporting a single merged database), and that study-specific data sets are extracted as needs arise. This approach has both advantages and disadvantages. The main advantage is that it ensures that those who know the data best are involved in each project. This is important

because administrative data systems of individual HMOs and the contents of the databases differ substantially due to, among other things, system changes over time and different policies and procedures for benefit coverage, data coding, and data entry. Maintaining data on host systems also avoids the effort and expense of building and supporting a joint database, and ensures that each organization retains control over access to and use of its data.

The main disadvantages of the distributed model are the extra time and inefficiency associated with creating multiple, site-specific datasets; and the extra effort required to ensure quality control. An important quality control measure is the development and use of common computer code that is tested and debugged, and then distributed and tailored for local use. In Platt's experience, however, pooled data sets can be preferable for highly complex analyses. But such data sharing is not permissible in some settings/jurisdictions, even with deidentification.

Other challenges the Network has faced include development of unified approaches to drug identification and drug-disease grouping for comorbidity adjustment. Although all of the HMOs use National Drug Codes to identify drugs in their dispensing databases, each implements the codes differently due to local formatting conventions and use of supplementary codes. Overcoming these challenges has meant significant manual recoding.

3.2. HEALTH/DRUG PLAN INITIATIVES

3.2.1. Context: Guiding Principles of a 'Sound Formulary System', U.S. Healthcare Coalition, 2000 (www.vapbm.org/PBM/formularyprinciples.pdf)

Clinical decisions are based on the strength of scientific evidence and standards of practice that include, but are not limited, to the following:

- Assessing peer-reviewed medical literature, including: randomized clinical trials (especially drug comparison studies), pharmacoeconomic studies, and outcomes research data.
- Employing published practice guidelines, developed by an acceptable evidence-based process.
- Comparing the efficacy as well as the type and frequency of side effects and potential drug interactions among alternative drug products.
- Assessing the likely impact of a drug product on patient compliance when compared to alternative products.
- Basing formulary system decisions on a thorough evaluation of the benefits, risks and potential outcomes for patients; risks encompass adverse drug events (adverse drug reactions and medication errors, such as those caused by confusing product names or labels).

Economic considerations include, but are not limited, to the following:

- Basing formulary system decisions on cost factors only after the safety, efficacy and therapeutic need have been established.
- Evaluating drug products and therapies in terms of their impact on total health care costs.
- Permitting financial incentives only when they promote cost management as part of the delivery of quality medical care. Financial incentives or pressures on practitioners that may interfere with the delivery of medically necessary care are unacceptable.

The formulary system:

- Provides drug product selection and formulary maintenance.
- Provides drug use evaluation (also called drug utilization review (DUR)) to enhance quality of care for patients by assuring appropriate drug therapy. Where DUR is defined as a

process used to assess the appropriateness of drug therapy by engaging in the evaluation of data on drug use in a given health care environment against predetermined criteria and standards.
- Provides for the periodic evaluation and analysis of treatment protocols and procedures to ensure that they are up-to-date and are consistent with optimum therapeutics.
- Provides for the monitoring, reporting, and analysis of adverse results of drug therapy (e.g., adverse drug reactions, medication errors) to continuously improve the quality of care.

3.2.2. Private Plans

3.2.2.1. The Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions and access to information

The U.S. market for healthcare services is characterized by a large private sector dominated by insurers and managed-care providers. Large insurers and HMOs have begun to employ economic analysis of pharmaceuticals to assist them with their formulary decisions. Because this is a task shared by many insurers, the AMCP recently published guidelines for conducting formulary submission assessments that include an economic component (available at www.amcp.org). At present, the *AMCP Format for Formulary Submissions* is use by managed care organizations covering in excess of 100 million lives.<Russo 2005> Although not an official standard, the extent of coverage lends importance to the guidelines. The AMCP guidelines are intended to be a, "... template for pharmaceutical and medical device manufacturers to use to construct a formulary submission dossier designed to make the product evaluation process in formulary development more rational."

A distinguishing feature of the *Format* is its use as an "Unsolicited Request" for all possible clinical and economic information necessary to assess the overall clinical utility and value that a product brings to a specific patient population and health care system. In it, manufacturers are asked to provide all possible published and unpublished studies and information regarding both FDA-approved indications and anticipated off-label uses of the product, improving access to material that has been difficult to obtain in the past under regulatory constraints mandated by the FDA. While no explicit FDA guidance regarding unsolicited requests exists, FDA officials have stated their intention to issue such guidance in the future. In the interim, the FDA has made it clear that it must ensure that: 1) requests for off-label product information are truly unsolicited and unprompted; 2) the information provided is not false or misleading; and 3) the response is specific to the requestor.

3.2.2.2. Participation in pharmacoepidemiological research

As already noted, several large HMOs participate in pharmacoepidemiological research through the HMO Network CERT. Several also collaborate with the FDA through its Cooperative Agreement Program. Most of the studies undertaken by the HMO Network CERT (See APPENDIX 2) have direct implications for health/drug plan policy (e.g., HMO CERT-NCQA collaboration on therapeutic indicators, Pilot study of drug allergy-associated genetic markers in patients with penicillin allergy, and A population-based HMO study of gout pharmacoepidemiology). Whether and how these studies have directly influenced plan policy, however, is not well published. An FDA-Kaiser Permanente cooperative agreement to study the cardiovascular effects of coxibs was clearly of mutual interest to both parties;<Kweder 2004, Graham 2005> this project had enormous impact upon both drug regulatory and drug plan policy across the globe.<Grassley 2005, Centre for Drug Evaluation and Research 2005>

3.2.3. Public Plans

3.2.3.1. U.S. Veterans Affairs Administration National Drug Formulary and Pharmacy Benefits Management Strategic Health Care Group (www.vapbm.org/directive/vhadirective.pdf)

In 1996, the U.S. Veterans Affairs (VA) Administration moved from using more than 170 individual drug formularies to a process that has as its core a single national formulary. The VA National Formulary is augmented by 22 Veterans Integrated Service Network (VISN) Formularies. The migration to a national and regional for mularies has allowed VA to rely more uniformly on evidence-based drug evaluations. The new formulary process has enabled VA to focus on the goals of improving patient safety, appropriate use of drugs, and access to pharmaceuticals; promoting a uniform pharmacy benefit; and reducing drug acquisition costs.

The Pharmacy Benefits Management Strategic Health Care Group (PBM) -- the national formulary's oversight body -- is comprised of clinical pharmacists, data analysts, and administrative pharmacy personnel. In cooperation with a Medical Advisory Panel (MAP) and the VISN Formulary Leaders Committee, the PBM is responsible for facilitating and coordinating the VA National Formulary process. MAP members provide physician oversight to the PBM on formulary management issues. VISN Formulary Leaders (VFL) Committee members provide clinical, strategic and operational input to the PBM on VA National Formulary management issues. The VFLs Committee is comprised of pharmacist and physician representatives from each of the 22 VISNs. In consultation with the MAP and VISN VFLs Committee, the PBM is responsible for:

a) Supporting, implementing, maintaining, and updating the VA National Formulary (available at www.vaww.pbm.med.va.gov;
b) Monitoring non-formulary use and providing utilization data and reports to the VISN Formulary Committees;
c) Monitoring drug utilization variation among VISNs and providing data and reports to the affected VISN Formulary Committees;
d) Recommending to the MAP necessary actions identified while conducting drug utilization analyses;
e) Monitoring compliance with access to VA National Formulary items in closed therapeutic classes and sub-classes and selected therapeutic classes and sub-classes by facilities and reporting variation to VISN Directors, VISN Clinical Managers, and VISN Formulary Committees for action;
f) Providing VISN Formulary Committees with data on the drug formulary status designations for drugs in the facility drug files;
g) Developing and distributing criteria for addition of drugs to and removal of drugs from VISN formularies;
h) Developing a template for quarterly VISN Formulary Committee reporting of drugs added to or removed from the VISN formulary and non-formulary approvals and disapprovals by VISNs; and
i) Developing a system-wide approach for TI (therapeutic interchange) when a VA National Formulary initiative requires TI.

Examples of recent national VA drug use evaluation (DUE) studies include: (www.vapbm.org/PBM/National%20Database%20Reviews%20and%20AUEs.pdf)

- Antipsychotic agents in dementia: evaluating stroke event rate;

- HMG-Co-A reductase inhibitor use with fibrates, verapimil and amiodarone;
- Fluoroquinolone and glycemic control;
- SSRIs and concomitant use with codeine-containing products; and
- Oxycodone Use/Misuse.

Individual VISN Formulary Committees also undertake independent research with the assistance of VA-funded research centres. One such collaboration exists between the Veterans Intergrated Service Network of New England (VISN1) and the Massachusetts Veterans Epidemiology Research & Information Center (MAVERIC; www.maveric.org/route/maveric/Home.asp). MAVERIC exists as a collaboration between the VA Cooperative Studies Program, the VA Boston Healthcare System, and the Harvard University Schools of Medicine and Public Health. In 2004, the Team was awarded a 5-year grant from the VA Cooperative Studies Program. Initial projects include:

- Evaluation of the potential for drug-to-drug interactions with Simvastatin based on recent labeling changes;
- Use of a VA pharmacoepidemiology database to define the scope of the problem of steroid-induced fractures;
- Duration of naltrexone and disulfiram use for alcoholism treatment by veteran patients in VISN1;
- Long-duration oxycodone/acetoaminophen (Percocet) prescribing in VISN1: patterns and clinical correlates; and
- Is concurrent prescribing of benzodiazepine and opioid drugs to patients associated with consequential outcomes?

3.3. CLINICIAN/RESEARCHER INITIATIVES

3.3.1. Research on Adverse Drug Events and Reports (RADAR) Project (Bennett 2005)

The RADAR project focuses on identifying, evaluating, and disseminating information about serious ADRs characterized as those resulting in death, severe organ failure, or precipitating major therapeutic interventions. The project is funded by grants from the National Heart, Lung, and Blood Institute, the National Cancer Institute, the American Cancer Society, and the Department of Veterans Affairs (VA). Pharmaceutical manufacturers do not provide financial support, but are asked to provide relevant clinical information on the ADRs under study. The core RADAR team, which holds weekly operational meetings, is led by a hematologist/oncologist/health services researcher, and consists of 25 core investigators with training in internal medicine, various medical subspecialties, clinical pharmacology, epidemiology, statistics, and pharmacy. Other co-investigators with expertise relevant to specific ADRs participate as required.

RADAR investigations are initiated when a clinical event that represents a possible serious ADR is seen by or reported to a RADAR investigator. Senior members of the team review the indicator event and oversee a review of the published literature and relevant package inserts to determine if the event represents an instance of a severe and previously unreported ADR. If they agree that further investigation is warranted, queries for additional case reports are submitted to the FDA, a more extensive literature review is initiated, and institutional review board approvals are requested at the collaborating institutions. The FDA reports are subject to a preliminary review to inform hypothesis generation and refine data collection and case classification forms. These forms are adapted based on input from investigators at the weekly conferences. World Health Organization criteria are used to score the strength of evidence for causality. After

reviewing a sample of cases (50 to several hundred), the RADAR team meets to refine hypotheses about the pathophysiology of the ADR and identify additional data sources that might include further information on cases with the suspected ADR. These include abstracts or peer-reviewed papers that describe published clinical trials, physicians at medical centers that treat large numbers of patients who either receive the relevant drug or receive treatment for the suspected ADR, relevant drug companies, and other federal agencies. Information from these case reports is abstracted and entered into a relational database for cross reference and integration with ADRs that are identified from the review of FDA reports and duplicates are excluded. Finally, complete case profiles are then compared against hypotheses-based sources of pathophysiologic evidence of causality for individual types of ADRs by clinical pharmacologists (for class effects), immunologists (for hypersensitivity cases such as interstitial pneumonitis, hepatitis, and antibodymediated pure red cell aplasia [PRCA]), hematologists (for TTP, thromboembolism, PRCA, and hemorrhage), gastroenterologists (for hepatic sinusoidal obstructive syndrome and hepatitis), and pathologists (for drug-eluting coronary stent hypersensitivity). When possible, reporting rates are estimated using whatever data are available.

Once RADAR investigations are completed, comprehensive reports are prepared and presented at national medical conferences and to the FDA and post-marketing surveillance programs of the relevant pharmaceutical companies. These reports have lead to the distribution of 'Dear Doctor' letters and/or revisions to product labels and package inserts. Between 1998 and 2004, RADAR investigations identified new serious ADRs associated with 16 drugs that affected 1699 patients, 169 of whom died.<Bennett 2005> These were found a median of 3 years after the drugs' market authorization (range: 0-17 years). In 9 instances the ADRs occurred when the drugs were being used for off-label indications.

4. UNITED KINGDOM

4.1. DRUG REGULATORY INITIATIVES

4.1.1. Britain's Yellow Card Adverse Drug Reaction Reporting Scheme and Black Triangle Program

The Pharmacovigilance Subcommittee (SCOP) advises the UK's Committee on Safety of Medicines on safety and risk-benefit considerations relating to marketed medicines and has particular responsibility for oversight of the Yellow Card Scheme – Britain's system for voluntary reporting of suspected ADRs. This eight-member committee meets every two months and is comprised of pharmacists, pharmacologists, physicians and researchers. It is the Committee on Safety of Medicines' (COSM) responsibility to:

- provide advice to the Licensing Authority on whether new products (new active substances) submitted to the UK Medicines and Healthcare products Regulatory Agency (MHRA) should be granted a marketing authorisation (in close collaboration with the MHRA's Licensing Division); and
- monitor the safety of marketed medicines, in close association with the MHRA's Post-Licensing Division, to ensure that medicines meet acceptable standards of safety and efficacy.

The COSM and MHRA also establish working groups to undertake detailed assessments of specific issues relating to the quality, efficacy or safety of medicines. These working groups are usually established where concerns have arisen over classes of medicines rather than individual products (e.g., hormone replacement therapy, SSRIs, and coxibs).

Although health professionals are encouraged to report all suspected ADRs, under the Yellow Card Scheme's Black Triangle program, new drugs and vaccines -- those typically within two years of market authorization -- receive more intensive surveillance. Black triangle symbols (▼) must be present wherever new active substances are advertised -- adjacent to product entries in the British National Formulary and Nurse Prescribers' Formulary, in the ABPI Compendium of Datasheets, and in Summaries of Product Characteristics and advertising material. However, products containing previously licensed active substances also may be 'black listed' if they:

- represent a new combination of active substances;
- are administration via a novel route/delivery system; or
- are being used for a new indication which may alter the drug's risk/benefit profile.

A 2004 independent review of the Yellow Card Scheme made numerous recommendations relevant to this report.<Metters 2004> Several follow.

- While it is essential for the Scheme to maintain its focus upon serious ADRs and black triangle products, greater clarity is needed about the meaning of 'serious' and which other ADRs should be reported.
- The Scheme and the reasons for it should receive much greater emphasis during the clinical training of all health professionals, should be included as part of their continuing professional development, and emphasis should be placed on the professional duty to report ADRs.
- For reporters and potential reporters, the MHRA should develop a communication strategy to improve professional and public education and provision of information about the Yellow Card Scheme. This must clarify:
    - the types of ADRs that should always be reported;
    - the role of Regional Monitoring Centres (RMC);
    - local feedback to reporters where there is no RMC; and
    - how all those with an interest in emerging ADRs can obtain up-to-date information.
- The role of Regional Monitoring Centres should be clarified. A protocol should be agreed to define the relationship, respective responsibilities and working practices between the MHRA and the Centres.
- A system should be set up for patients to report ADRs directly to the MHRA. Different approaches to managing patient reporting should be tried but, initially, patient reports should be kept separate from those of health professionals through a parallel system until experience indicates the best method of linking patient and Yellow Card reports to the same ADR.
- Pilot studies should be undertaken to identify the best ways of raising ADR reporting rates and to inform and educate health professionals and patients about the Scheme. Direct patient reporting systems should be tested through local pilot studies.
- The MHRA should open access to the Yellow Card database and should maximize the release of data from the Scheme for independent research, subject to appropriate safeguards.

4.1.2. Medicines Monitoring Unit at the University of Dundee and the National Health Service's Information and Statistics Division (Evans 1999)

Scotland has two major record-linkage initiatives. The Medicines Monitoring Unit (MEMO) was established by the University of Dundee to conduct post-marketing drug safety research. The Information and Statistics Division (ISD) of the NHS also works on record-linkage studies, although their main contribution to pharmacovigilance has been to collaborate with MEMO. MEMO record-links data for the population of Tayside, Scotland. This is possible through the

region's uniform use of Scotland's Community Health Index Number (CHNo) -- a unique, specific 10-digit number assigned to residents when they register with a general practitioner. Tayside has a population of just over 400,000 residents, and a demographic and health status profile broadly similar to that of the rest of Scotland.

Record-linkage at MEMO has both deterministic and probabilistic elements. Deterministic because the Community Health Index is validated and maintained centrally by the Tayside Health Board, and MEMO makes use of multiple datasets that are already indexed by the CHNo. However, MEMO also exploits numerous patient-specific databases that do not contain CHNo by linking probabilistically on other personal identifiers. Pivotal to MEMO's research are an 'exposure' database of dispensed prescriptions and an 'outcome' database of hospital admissions. The exposure database is compiled from records of all prescriptions dispensed in Tayside community pharmacies. The CHNo is added by MEMO. This database currently contains records for over 15 million prescriptions dispensed since 1989 (all drugs dispensed since January 1993 and selected drugs prior to this). The hospital admission database is the Tayside Scottish Morbidity Record 1 (SMR1), supplied to MEMO annually by ISD. For each episode of care, a record is generated that contains the CHNo, personal and demographic data, hospital administrative data, and clinical data in the form of up to six ICD9 diagnosis codes and up to four OPCS4 operation or procedure codes. Some admissions are stored in separate datasets, such as the SMR2 (maternity admissions), SMR4 (mental health admissions) and SMR11 (neonatal admissions); and these are accessed by MEMO as studies require. The CHNo also permits linkage with cancer registrations and laboratory tests conducted in Tayside hospitals.

While MEMO's databases have been useful for both flagging problem prescribing behaviours <Hayes 1996> and evaluating more frequent drug safety signals, such as hospitalization for upper GI bleeding,<Carson 1987, Evans 1995> the size of underlying population is too small for accurate quantification of the risks of less frequent events (either because the drugs are rarely prescribed or because the reactions themselves are rare). To overcome this problem, MEMO, ISD, and the country's Pharmacy Practice Division are in the process of undertaking pilot studies to explore the feasibility of using probabilistic methods to develop a linkable drug exposure database for the entire Scottish population (approximately 5.1 million).

4.1.3. General Practice Research Database, Medicines and Healthcare Products Regulatory Agency, London (Wood and Martinez 2004; www.gprd.com)
Formerly known as the Value Added Medical Products Research Databank, the General Practice Research Database (GPRD) was created in 1987 and donated to the Department of Health in 1994. Since 1999 it has been managed by the Medicines and Healthcare products Regulatory Agency (MHRA) and is operated on a not-for-profit basis by a division of the Agency which delivers GPRD-related services to researchers both within and outside the Agency. The GPRD is currently the world's largest computerised database of anonymized longitudinal clinical records from general practice, comprising over 35 million patient-years worth of data collected from about 9 million patients.

Access to GPRD data is provided under license from the MHRA. Protocols for research that is published or communicated to third parties require prior approval from a GPRD Scientific and Ethical Advisory Group. Further information on Group's Terms of Reference is available on the GPRD web site (www.gprd.com). Conditions for using the data are standard for all users, including the MHRA's Post-Licensing Division. New data access options have recently been

introduced by the MHRA, including academic fees for non-commercially-funded research to support wider academic use.

Data from the GPRD are widely used to triage safety signals identified through spontaneous reporting schemes by providing ready background incidence rates for diseases and drug exposure. Typically, data from the GPRD have been used to strengthen or refute signals, to quantify absolute and relative risks, and to identify sub-populations at risk. As of January 2005, studies using the GPRD have resulted in over 400 peer-reviewed publications (see www.gprd.com for complete references). Recently, the FDA awarded a 5-year contract to the GPRD Division for full access to the database to support its pharmacovigilance program. Planned future applications of the GPRD include its use for signal detection, as a data source for pharmacovigilance planning, and for assessing the impact of regulatory policy.

4.1.4. The Prescription Event Monitoring Program, Drug Safety Research Unit, Southampton (Mann 1998)

Prescription Event Monitoring (PEM) is an active approach to pharmacovigilance, but remains observational. Most U.K. residents are registered with a general practitioner (GP) who provides primary health care and issues prescriptions (FP10s). When prescriptions are dispensed, pharmacists must send the FP10 to a central repository -- the Prescription Pricing Authority (PPA) -- for reimbursement. Under a long-standing agreement with the PPA, the Drug Safety Research Unit (DSRU) receives an electronic copy of all prescriptions for drugs targeted for PEM -- typically those likely to be prescribed by GPs on a widespread basis. Each PEM study starts as soon as possible after the target drug has been marketed in England, and each study aims to collect clinically useful data on a minimum of 10,000 patients. For each study patient, the DSRU prepares a longitudinal record of all prescriptions dispensed to the individual for a period of 3-12 (usually 6) months from the date of the index prescription. The prescriber is then sent a 'green form' questionnaire seeking information on any 'events' which may have occurred since the drug was first prescribed. This takes place on an individual patient basis, but no more than four green forms are sent to an individual physician in any given month. The Form asks the prescriber to confirm: the patient's sex and date of birth; the prescribed drug, dose, and indication; date initiated and stopped, if applicable; reason for stopping, if applicable; and any 'events' that occurred while taking the drug. The Form defines an EVENT as "...any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, an suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint which was considered of sufficient importance to enter in the patient's notes (e.g., a broken leg is an EVENT)."

Doctors are not paid to complete the Green Forms; it is done in the interests of drug safety. The program allows for contact between doctors and the DSRU, and this facilitates the collection of any follow-up data that may be considered necessary by DSRU. All pregnancies during treatment or within 3 months of stopping the drug being monitored, and any deaths for which the cause is unknown or may be related to the medication, are followed-up by contact with the GP. With the GP's permission, access to a patient's medical record, death certificate or other records can be granted, if necessary.

In the 58 PEM studies described by Mann in 1998, the DSRU achieved an average response rate of 58% (range: 40-74%). Interim analyses are done and results are summarized after every 2,500 patients; and these analyses are typically shared with the Product Licence holder so that reporting

obligations can be fulfilled. PEM is undertaken in a collaborative, never commissioned relationship with manufacturers. But, the DSRU is heavily supported by industry donations.

4.2. HEALTH/DRUG PLAN INITIATIVES

4.2.1. Product Risk Sharing Agreements and Outcome or 'No Cure-No Pay' Guarantees

These agreements, typically between drug manufactures and payers, are relevant here to the extent that drug utilization and outcomes data must be collected and monitored as a condition for reimbursement. Although none of these agreements are terribly well publicized, a few (described below) have recently received attention in the UK lay press and peer-reviewed literature. More on several 'no cure-no pay' agreements can be found in a recent review by Moldrup.<2005>

4.2.1.1. Risk sharing scheme for assessing drugs for multiple sclerosis

The U.K. Department of Health (DoH) and the National Assembly for Wales (NAW) first asked the National Institute for Clinical Excellence (NICE) to appraise new MS treatments in August 1999. By July 2000, the appraisal committee had held its second meeting and circulated a final appraisal determination to consultees recommending that beta-interferons not be prescribed on the NHS. Eight consultees appealed against various aspects of the Determination. Their main issue was with the assessment of cost-effectiveness. NICE decided to commission new economic models. After considered the new models, the appraisal committee held a further round of consultation. NICE announced in January 2002 that the appeals had not been upheld and issued its final guidance in February 2002, reiterating its previous advice not to prescribe the new MS treatments on the NHS.

One week before the NICE judgment, the Department of Health (DoH) announced it had reached a 'risk-sharing' agreement with the drugs' manufactures. Under the scheme, all UK patients meeting prespecified clinical criteria were eligible to receive the new MS drugs (interferon beta, glatiramer, or azathioprine) and have them reimbursed by the NHS. On entering the scheme, each patient would be assessed by a neurologist to confirm eligibility and establish a baseline for comparison. Each patient would be monitored annually to permit the DoH to track the cost-effectiveness of the drugs; the effects of each to be determined every two years by comparison with expected disease progression without treatment derived from a Canadian cohort. Target treatment effects were agreed with the drug companies, and if these were not achieved, drug costs will be reduced to maintain cost-effectiveness at £36 000 per QALY over 20 years. In total, some 7,500-9,000 MS patients in England and Wales are expected to be enrolled in the program, which may involve assessing up to 30,000 patients. However, as of November 2003, just 3,000 patients had been enrolled -- at least 30% behind targets set for the end of 2003.<Pharmaceutical Journal 2003> Key in the delay has be a shortage of neurologists to perform baseline assessments.

Critics of the agreement point to numerous limitations, including the absence of a concurrent (preferably randomised) control group, acceptance of previously-treated patients, failure to follow-up patients who discontinue therapy, and assumptions about the future discounting of costs and benefits.<Sudlow 2003> Others argue that the development of new MS therapies will make it unlikely the government will ever see the rebates it expects.<Crinson 2004>

4.2.1.2. NHS risk sharing scheme for nicotine replacement therapy

Through a 2003 agreement between the NHS and three pharmaceutical companies (GlaxoSmithKline, Novartis Consumer Health, and Pfizer), primary care trusts (PCTs) are

distributing free nicotine replacement therapy (NRT).<Pharmaceutical Journal 2003> Under these agreements, the exact workings of which have not been revealed for commercial reasons, thresholds were decided for the use of smoking cessation products, including Zyban (bupropion). Prescribing figures will be analysed quarterly and, if the thresholds are exceeded, the companies will provide free NRT to PCTs on a proportional basis. Deliveries of stock will be made every six months, and it will be up to the individual PCTs to decide how supplies will be distributed to pharmacies/clinics. The Department of Health expects that free NRT sufficient to help 10,000 smokers will be made available under the agreement.<Pharmaceutical Journal 2003>

4.2.1.3. North Staffordshire Atorvastatin Outcome Guarantee (Chapman 2003, 2004)

In 1999, the North Staffordshire Health Authority, Parke-Davis (now Pfizer), and Keele University entered a pilot collaboration to provide an outcomes guarantee for statins. The health authority had identified cardiovascular disease as a local priority and was looking for ways to promote best practice, without making excessive demands on itself or its general practitioners. The outcomes guarantee was aimed at protecting the health service from paying for a drug if it did not work -- e.g., because it was inappropriately prescribed or less effective than claimed. The claimed performance for atorvastatin was defined in terms of a matrix derived by Parke-Davis/Pfizer from the results of clinical trials, indicating the percentage of patients expected to reach target low density lipoprotein (LDL) concentrations at specific dosages, depending on the patient's baseline concentration and allowing for 20% non-compliance. Thus, the outcomes guarantee was a measure of the claimed effectiveness of the product against agreed performance targets. The basic terms of the guarantee were that:

1) practices would enroll patients with a history of coronary heart disease who had not achieved a target LDL $\leq$ 3 mmol/L;

2) participants would attend 4 quarterly clinics at which drug compliance would be determined and meet a target of at least 80%; and

3) the proportion of patients satisfying these criteria would reach their LDL target as predicted.

If patients did not achieve their predicted LDL targets, the sponsor would refund the cost of 'unsuccessful' treatment. In the end, 27 practices and 877 patients were recruited to participate in the program, and 669 (76%) completed it. All treatment targets were met or exceeded; thus, no monies were owed.

5. HEALTH/DRUG PLAN INITIATIVES IN OTHER JURISDICTIONS

5.1. France's 2003 policy for assessing the public health impact of new drugs

(Abenhaim 2004)

According to a report by Abenhaim,<2004> in May 2003 an agreement was reached between the French government's Health Product Economic Committee (CEPS) and the Association of Drug Enterprises (LEEM) that provides for assessment of the public health impact of drugs being considered for reimbursement by the public drug plan. In short, whenever a drug is likely to be used on a large scale, under the agreement, pharmaceutical companies must present a pre-reimbursement assessment and organize a post-market evaluation of the drug's public health impact. Requirements include:

- A description of the treated population and comparison with the target population for the drug. Estimation of the fraction in whom disease is poorly controlled with previous treatments and who should therefore receive the new product.
- Evaluation of the effect of co-prescriptions, comorbidities, and other risk factors.
- Epidemiological assessment of the impact of the new drug on the incidence and prevalence of complications of the treated disease in populations, including morbidity and mortality associated with treated disease and side-effects and risks of the drug.

- Assessment of the impact of other new comparative drugs in the same population.
- Evaluation of the impact of the new drug on the health system (medical and hospital services, use of diagnostic procedures and other treatments, including other drugs)

An early example for the policy was a 2001 request for an independent cohort study of 40,000 patients treated with rofecoxib, celecoxib, or traditional nonsteroidal anti-inflammatory drugs. Since then, more than 50 such studies have been agreed, some including limits to the size of the population for which the drug should be reimbursed. A full report on the effects and efficiency of the policy is expected shortly.

5.2. Australian Pharmaceutical Benefits Scheme mechanisms for targeting and monitoring high-cost drug therapies: TNF-alpha inhibitors and human growth hormone
(www.health.gov.au/pbs)
The Pharmaceutical Benefits Scheme (PBS) provides universal subsidised access to prescription drugs for roughly 20 million Australians. Consumers make a co-payment of $A23.70 per prescription ($A3.80 for concessional patients) for medicines that cost the government more than this amount, and pay in full for medicines that cost less than $A23.70. Applications for inclusion on the PBS formulary are assessed by the Pharmaceutical Benefits Advisory Committee (PBAC), which evaluates the incremental cost-effectiveness of candidate products compared with other treatments that the new product could replace. The PBAC may recommend drugs be granted Restricted Benefit status or an Authority Required listing, which requires prior authorization. Products estimated to have a first year cost of $A10 million or more require cabinet approval.<Cookson 2000>

Difficulties perceived by stakeholders and/or reported in the literature in getting higher-cost drugs listed on the PBS have included requirements for randomised trial data; issues of cost and price; high cost-effectiveness ratios; 'leakage', both in terms of problems with identification of the target populations and usage outside of defined populations; logistics and organizational problems with the approval process; and problems with the lack of transparency of coverage decisions.<Brown 2003> Recently, the Commonwealth Government implemented policies requiring the PBS to undertake special approval and audit procedures for the subsidized use of several high-cost therapies covered under its Highly Specialized Drugs Program (www.hic.gov.au/providers/forms/pbs/medical_practitioners.htm). These include:

- Imatinib -- for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours;
- Herceptin -- for the treatment of breast cancer;
- Bosentan -- for the treatment of pulmonary hypertension; and
- tumor necrosis factor (TNF)-alpha inhibitors (such as Etanercept and Infliximab) -- for the treatment of rheumatoid arthritis and related disorders.

<u>TNF-alpha inhibitors</u>
In the case of the TNF-alpha inhibitors, ideas for the drug approval and surveillance framework grew out of a unique collaboration between PBAC, the sponsor of Etanercept (Wyeth Pharmaceuticals), rheumatologists, and consumers -- specifically, the Arthritis Foundation of Australia and Arthritis Research Task Force. Originally termed the Quality Use and Outcomes Measurement for Biological Agents for Rheumatoid Arthritis Registry, the project's primary aims were:

- to ensure appropriate patient selection for subsidized prescription of the drug based on objective criteria and in a manner that minimized prescriber bias;
- to ensure that patient response to the drug would be measured;
- to ensure that continuation of therapy would be based on objective response to treatment;
- to ensure quality use of biological agents over time based on high-quality data collection and analysis; and
- to use the data to optimize treatment guidelines.<Brown et al. 2002>

After debating issues of efficacy, safety, cost effectiveness, and access; the group agreed to eligibility criteria for initial prescription and continuation of treatment beyond three months. Prescribing rights were limited to rheumatologists, and evidence was required that patients agreed to abide by a decision to stop treatment at three months if response criteria were not met. A early feasibility study for the Registry gave operating cost estimates in the range of $A200-$A400 per patient per year; equivalent to roughly one week of Etanercept therapy. PBAC believed that the product would achieve acceptable cost-effectiveness if listed under these conditions. At the time of listing, the government predicted the annual expenditure for etanercept could reach $A140 million. However, Wyeth believed that they would not exceed $A100 million and agreed to pay for expenditure above this. This agreement provided incentives to the sponsor to promote the drug responsibly.<Lu et al. 2004> PBS expenditures for Etanercept for the year ending June 2004 were $A12,240,040 (www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-pubs-pbbexp-jun04.htm/$FILE/bookp21.pdf).

Human growth hormone
(www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-general-supply-hghapplication)
Human growth hormone (hGH) is available as a Pharmaceutical Benefit under Section 100 of the Australian National Health Act 1953 for patients who meet prespecified criteria. In 2000/01, the PBS spent $A21 million on hGH.<Brown 2003> The Growth Hormone Program is operated by the Commonwealth Department of Health and Ageing with the assistance of the Growth Hormone Advisory Committee (GHAC), an independent panel of paediatric endocrinologists appointed by The Australasian Paediatric Endocrine Group. While an officer of the Department administers the program according to guidelines, GHAC deliberates on cases which do not clearly fulfil the guidelines, where eligibility is uncertain, or where there is dispute about an eligibility decision.

The Growth Hormone Program is primarily concerned with the growth-promoting effects of hGH, but will also subsidize its use for neonatal hypoglycaemia associated with growth hormone deficiency. The Program's broad aim is to allow a trial of treatment with hGH and possible ongoing hGH therapy in children who are likely to benefit. Specific aims include promoting short-term catch-up growth in short children; enhancing long-term linear growth in short children; and ensuring therapeutic safety.

Ongoing subsidization requires that patients be reviewed by the treating physician every 3 months, and that information requested on a *Growth and Treatment Record* be provided to the Department of Health and Aging every 6 months. A radiological assessment of skeletal age must be submitted every 12 months, and applications to continue treatment are assessed by a pharmacist according to response criteria outlined in the Guidelines. For safety and effectiveness

assessment, key data elements are entered to a national database -- OZGROW -- housed and managed by a research team at the Children's Hospital at Westmead, Sydney, NSW (www.chw.edu.au/research/groups/endocrinology.htm). As part of the application for subsidization, informed consent is obtained from the patient's parent/guardian for the Department of Health and Aging to release specific information to OZGROW. The data transferred to OZGROW are de-identified and allocated an OZGROW non-identifiable patient number to maintain patient confidentiality. In addition to generating growth outcome data, OZGROW seeks information on potential adverse events. Thus, events thought to be attributable to treatment with hGH are collected and reported to OZGROW, in addition to routine reporting to Australia's Adverse Drug Reaction Advisory Committee.

6. IMPLICATIONS FOR CANADA

This review shows that there are important lessons for Canada within existing frameworks for real-world drug safety and effectiveness research in other countries. Models exist for productive, sustainable collaboration between, among others, clinicians/academics, drug regulatory/drug plan decision-makers, manufacturers, and funders. While details are needed about exactly how these programs are funded, governed, and function, and whether stakeholders believe they are worthwhile; as we work toward a made-in-Canada approach, the general models provide fodder for setting priorities for further discussion and research. The review identifies several tools with which we have limited experience in Canada (such as prescription event monitoring and ADR data mining); but also highlights areas where, given our health care system, data resources, and expertise, Canada could lead. These include the use of linked health administrative data for real-world drug and drug policy evaluation; and innovative, perhaps conditional, drug coverage research agreements that take advantage of Canada's unique resources. By building upon these strengths, we may also be in a better position to help others. For instance, the U.S. CMS and FDA will soon be seeking input regarding analysis of data from its Medicare Prescription Drug Benefit.<CMS 2005>

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APPENDIX 1: SAMPLE OF PUBLISHED STUDIES SUPPORTED BY FDA COOPERATIVE AGREEMENTS

Evaluation Of Drug Safety Signals

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Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. Clin Pharmacol Ther. 2004 Mar;75(3):234-41. Department of Preventive Medicine, Division of Pharmacoepidemiology, Vanderbilt University School of Medicine, A-1124 Medical Center North, Nashville, TN 37232, USA.

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Evaluation Of Regulatory Policy
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Other Studies
Rawson NS, Nourjah P, Grosser SC, Graham DJ. Factors associated with celecoxib and rofecoxib utilization. Ann Pharmacother 2005;39:597-602.

Cooper WO, Hickson GB, Ray WA. Prescriptions for contraindicated category X drugs in pregnancy among women enrolled in TennCare. Paediatr Perinat Epidemiol 2004;18:106-11.

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APPENDIX 2: CERT PROJECTS: PROPOSED, ONGOING, AND COMPLETED (as of December 13, 2004 at www.certs.hhs.gov)

Proposed Projects

Last Projects Update 12.13.04

Arizona | Duke | HMO Research Network | Penn | UAB | UNC | Vanderbilt

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University of Arizona Health Sciences Center		
Project Name	**Project Description**	**Partners**
Effect of academic detailing on drug-drug interactions.	A case control study comparing those physicians who receive academic detailing by clinical pharmacists to those who do not receive consults.	AdvancePCS
Internet health information seeking skills for women at the UA National Center of Excellence in Women's Health (CoE).	Patient education to improve health information literacy among patients at the Women's Health Resource Center (WHRC) utilizing a facilitator and computer work station in the clinic waiting room. AZCERT will develop curriculum and provide technical assistance for patient education in using the computer and internet for seeking health-related information.	University of Arizona National Center of Excellence in Women's Health (CoE)

To Top

Duke University Medical Center		
Project Name	**Project Description**	**Partners**
Evaluation of the Tracleer access program.	Evaluate patient and provider perceptions of the Tracleer access program.	Food and Drug Administration
Impact of external academic consultants on hospitals' success in improving adherence to evidence-based therapies as assessed by the American Heart Association's "Get with the Guidelines" program.	Compare the performance of the hospitals that are participating in the Duke Infection Control Network (DICON) with a peer group of hospitals in the state of North Carolina not participating in DICON with respect to results on AHA's Get with the Guidelines program.	Duke Infection Control Network (DICON), American Heart Association
Evaluation of medication labeling representations for dosage adjustments in patients with impaired renal function.	Evaluate the effectiveness of the current and new ways to represent dosage adjustments for patients with impaired renal function.	Duke Department of Psychology, Food and Drug Administration
Analysis of the utilization of the QT Module	Evaluate the utilization of the QT module following its public launch.	
Meta-analytic study of intermediate and long-term rates of death, Myocardial Infarction and revascularization with drug-	Using meta-regression analytical techniques on published and forthcoming results of randomized trials of drug-eluting stents, we will compare	

eluting stents versus bare metal stents.	intermediate and long term rates of death, MI, and revascularization with drug-eluting stents versus bare stents. If data are available, stents coated with different anti-proliferative agents will be compared.	

To Top

HMO Research Network		
Project Name	**Project Description**	**Partners**
Antibiotic use and PCV7: impact on childhood infections	Study changes in the incidence of serious bacterial illnesses as a result of decreasing antibiotic use in primary care settings, in the context of introduction of introduction of pneumococcal conjugate vaccine	
Health plan member/physician education for judicious antibiotic use in children.	Collaborate with HMO Research Network CERTs health plans, Council for Affordable Quality Healthcare (CAQH) and the Association of American Health Plans (AAHP). Dissemination to parents, clinicians and provision of templates to health plans for physician and practice-level prescribing reports.	American Association of Health Plans, Council for Affordable Quality Healthcare
Lab alert: enhancing medication safety through electronic interventions to improve laboratory monitoring.		
Talking to patients about medical errors.		National Patient Safety Foundation
A population based HMO study of gout pharmacoepidemiology.	A retrospective cohort of gout patients. Develop an algorithm based on claims data to identify patients with recurrent gout attacks.	University of Alabama at B irmingham CERTs, TAP Pharmaceuticals
Enhanced identification of adverse drug events.	Develop and test population-based systems for early identification of adverse drug events and characterization of unsafe prescribing practices.	Pfizer
HMO CERT NCQA collaboration on therapeutic indicators.	Participate in collaboration with NCQA to test and develop quality of care indicators.	National Committee for Quality Assurance
Effects of prior authorization of atypical antipsychotic agents among patients with schizophrenia.		Centers for Disease Control, Eli Lilly Foundation

To Top

University of Pennsylvania School of Medicine		
Project Name	**Project Description**	**Partners**
Validation of a modified clinical pulmonary infection score in children.	To validate a modified Clinical Pulmonary Infection Score (CPIS) in children. This validation will emphasize assessing the score's negative predictive value, as a prelude to designing a larger intervention trial to limit unnecessary antibiotic use in critically ill children and thereby reduce antibiotic resistance in the PICU.	
Impact of non-antibiotic antimicrobial soap and toothpaste on antibiotic resistance.	A cross-sectional study with multiple samplings per subject, to estimate the incidence of new colonization with antimicrobial resistant organisms in subjects using triclosan-containing hygiene products.	
Estimating odds ratios under misclassification of the outcome in a large database cohort study when medical records are sampled.	Large sample sizes are needed to study rare diseases and events; misclassification of the outcome is common and verification of all presumptive cases not feasible. Our goal is to extend previously-developed methodology by this group for adjustment for misclassification, which uses all or most exposed cases but only a sub-sample of unexposed cases, to accommodate multivariable adjustment for cofounders and other covariates. The approach will be based on data-based weights applied in a logistic regression. A simulation study will be developed to examine the properties of the method.	
A Pilot Study of Drug Allergy-Associated Genetic Markers in Patients with Penicillin Allergy	This is a Nested Case Control Molecular Epidemiology study with 2 aims. Specific Aim 1: To determine the feasibility and logistics of testing whether polymorphisms of IgE, IL-4, IL-5, IFN-y, IL-1, TNF-a, platelet activating factor are associated with penicillin allergy identified by skin testing, Specific Aim 2: To determine the feasibility and logistics of testing whether polymorphisms of cytochrome P450 genes, including CYP3A4, are associated with penicillin allergy identified by skin testing	Southern California Kaiser Permanente Allergy Department

To Top

University of Alabama at Birmingham		
Project Name	**Project Description**	**Partners**
Improving care in Gout Management through patient interventions (D.5.2 sub-project 1)	Assess the current medical approach to gout treatment in a retrospective epidemiological study.	
Improving care in Gout Management through	Improve quality and safety of	

patient interventions (D.5.2 sub-project 2)	medications used to prevent gout attacks in chronic recurrent gout.	
Cardiac outcomes associated with anti-tumor necrosis factor (TNF) therapies.	Compare the incidence of MI among RA and Crohn's patients exposure versus non exposure to anti-TNF agents.	
Preferences for Total Joint Replacement (TJR) and other musculoskeletal therapeutics among ethnic/racial minorities.	Compare preference of TJR and medical anti-rheumatics interventions in persons with RA.	NIH, University of Texas Health Sciences Center at San Antonio
Disparities in the treatment and outcomes for African Americans with rheumatoid arthritis in a Managed Care.	National study to examine disparities in the treatment and outcomes for African Americans with rheumatoid arthritis.	
Osteoporosis treatment in the home health care setting.	Using patient data from the Alacare home healthcare agency we propose to assess quality of care delivered to home care recipients with osteoporosis.	Alacare Home Health Care, Eli Lilly
Outcomes of vertebroplasty/kyphoplasty versus medication management among nonelderly with vertebral compression fracture.	Prospective medical record and claims data examination of long-term outcomes and utilization post vertebroplasty or kyphoplasty among adults with a primary osteoporotic VCF.	HHS/FDA/Center for Devices and Radiological Health, Blue Cross/Blue Shield of Alabama

To Top

University of North Carolina at Chapel Hill		
Project Name	**Project Description**	**Partners**
Impact of antibiotic resistance on the management of childhood infections: a community evidence-based approach. 2-diarrheal pathogens	Aiding practitioners in understanding and preventing resistance.	
Impact of antibiotic resistance on the management of childhood infections: a community evidence-based approach. 4-clinical proje ct III.	Aiding practitioners in understanding and preventing resistance.	
Improving quality of care: change behavior to minimize adverse drug events.	Understanding system-level context of errors.	National Initiative for Children's Healthcare Quality (NICHQ)
Ambulatory psychotropic use by children and adolescents: a cohort study of medications and behavioral health.	Helping providers understand patterns of psychotropic prescribing.	Center for Health Care Policy and Evaluation, UnitedHealthcare

National conference on pediatric risk communication at all levels.	Synthesizing best research on communication at patient and system level.	

To Top

Vanderbilt University Medical Center		
Project Name	**Project Description**	**Partners**
Atypical antipsychotics and sudden cardiac death.	Retrospective cohort study of new antipsychotic agents and risk of sudden cardiac death in VA population.	
CPOE to improve pharmacotherapy for hospitalized patients.	Interrupted time series analysis of efficacy of CPOE.	
CPOE to improve cytoprotection in NSAID users.	Interrupted time series analysis of efficacy of CPOE to improve NSAID user safety.	
Improving pharmacotherapy for state-custody children.	Interrupted time series analysis of efficacy of CPOE to improve care state-custody children.	
Effects of TennCare enrollment cuts.	Analysis of the effect of a policy change.	

Ongoing Projects

Last Projects Update 12.13.04

Arizona | Duke | HMO Research Network | Penn | UAB | UNC | Vanderbilt

University of Arizona Health Sciences Center		
Project Name	**Project Description**	**Partners**
Web-based education about drug interactions, especially in women.	Database evaluations, in vitro and clinical research studies, and educational programs.	
International registry for drug-induced arrhythmias.	Web-based registry and genotyping study to evaluate pharmacogenetic risk factors for drug-induced arrhythmia.	National Institute of General Medical Sciences, Pharmacogenetics Network, QED Solutions, Inc.
Curriculum for therapeutics in women's health.	Survey of literature and development of curricular content.	HHS Office of Women's Health, FDA/Office of Women's Health, Health Resources and Services Administration, NIH/Office of Research on Women's Health, Public Health Service, American Association of Colleges of Pharmacy, American College of Clinical Pharmacy, American Pharmaceutical Association, University of Illinois at Chicago
Educational programs on drug-induced arrhythmia.	Web-based educational format.	Food and Drug Administration
Role of heart rate correction in QT analysis of drug action.	Clinical protocol.	
Effects of herbal remedies in diabetic Hispanic women in the Southwestern US.	Qualitative evaluation, development of a clinical tool, chart review.	
Interactive online logic model of patient- and prescriber-generated factors leading to ADEs in primary care settings.	Interviews of patients and prescribers, development of composite online logic model showing participants' views of factors contributing to ADEs and research evidence supporting these factors.	Arizona Area Health Education Program; local Community Health Centers.
Relationships between Cytochrome P450 genotype, methadone dose and QT prolongation in humans.	Identify the risk factors for methadone-induced heart rhythm disorders and death.	LaFrontera Hope Center
Community pharmacy factors associated with drug interactions.	A postal survey of community pharmacies linked to data from PBM's to evaluate the community pharmacy structure and how that contributes to	AdvancePCS, Express Scripts, added 11/25/03 Caremark, Wellpoint

	adverse drug interactions.	
Evaluation of computerized physician order entry with Veterans Affairs Medical Centers.	Evaluation of VA Medical Center facility characteristics, prescriber satisfaction and pharmacy data to determine the impact of computerized physician order entry on adverse drug interactions.	Department of Veterans Affairs
Prescriber factors associated with drug-drug interactions.	A postal survey of prescribers who operate in an ambulatory setting linked with PBM data to evaluate adverse drug interactions.	AdvancePCS, Express Scripts
Gender differences in medication use.	Examination of gender differences in prescription drug use for top 200 most commonly prescribed medications using pharmacy data.	Walgreens
Interviews with patients to identify medication-taking practices and characteristics of two groups of consumers of prescribed methadone: opiate addicts and chronic pain patients.	Accurate assessment of prescribed and unprescribed medication use to guide educational strategies for reducing the risk of ADEs among these two groups of prescribed methadone consumers.	Integrative Pain Center of Arizona; La Frontera Center, Inc.
Development of internet drug information webliography	An internet-based printable resource for patients and proiders to imrpve ability to identify reliable, accurate online drug information.	

To Top

Duke University Medical Center		
Project Name	**Project Description**	**Partners**
Retrospective evaluation of beta-blocker use in patients with heart failure.	Determine prevalence of beta-blocker use, predictors of beta-blocker use, and consequences of beta-blocker use from the Duke Databank for Cardiovascular Diseases.	
Prospective demonstration project to improve use of beta-blockers in patients with heart failure.	Develop and implement a multi-faceted intervention for an ambulatory setting to increase beta-blocker use in appropriate heart failure patients.	Duke Heart Center, AstraZeneca, Conceptis Technologies, GlaxoSmithKline
CERTs Prescribing Safety Program: Safety of use of QT prolonging drugs.	In collaboration with the HMO Research Network CERTs, evaluate co-prescribed QT prolonging medications and renally cleared QT prolonging antiarrhythmic agents to estimate the number of medication errors associated with these agents.	HMO Research Network

Study of the Quality Cycle of Therapeutic Development	In collaboration with the American College of Cardiology and the American Heart Association, evaluate the continual process by which clinical research is developed into clinical practice guidelines and then quality indicators to measure performance that ultimately impacts outcome (the Quality Cycle).	American College of Cardiology, American Heart Association
Impact of the American Heart Association/American College of Cardiology/European Society of Cardiology guidelines for treatment of atrial fibrillation on prescribing patterns of antiarrhythmic agents.	Evaluate the impact of the American Heart Association/American College of Cardiology/European Society of Cardiology guidelines for the treatment of atrial fibrillation on real world use of antiarrhythmic agents.	Food and Drug Administration, IMS Health
PILOT-EBM (Patient focused Intervention to improve long term adherence to evidenced based medications.	Develop and test a system in which clinical pharmacists, community pharmacists, local physicians, and hospital physicians work together to improve patients' adherence to evidence-based therapies for heart failure and secondary prevention of coronary artery disease.	American Pharmacists Association Foundation (APhA), North Carolina Association of Pharmacists
Demonstration project of the utility of using pharmacy benefits manager data to evaluate ambulatory adherence to evidence-based therapies.	A pilot study to evaluate the utility of using pharmacy benefits manager data to determine outpatient adherence to evidence-based therapies for coronary artery disease	Medco Health Solutions
Financial evaluation of strategies to improve secondary prevention of coronary artery disease: PILOT-EBM substudy	Assess the financial impact of selected interventions to improve adherence to evidence-based therapies from the perspective of hospitals, health plans, healthcare providers, and patients.	
Consultation with the Coalition for Affordable Quality Healthcare (CAQH) on their Cardiovascular Quality Initiative.	Collaborate with CAQH in developing a national initiative to evaluate long term use of beta-blockers in patients with previous MI.	Coalition for Affordable Quality Healthcare
Evaluation of the use of life-saving cardiovascular therapies in the Duke databank for cardiovascular disease: treatments for coronary artery disease.	Evaluate the prevalence of use, predictors of use, and consequences of use of all evidence-based therapies individually and in combination in patients with coronary artery disease within the Duke databank for cardiovascular disease.	
Evaluation of the use of life-saving cardiovascular therapies in the Duke Databank for Cardiovascular Disease: treatments for heart failure.	Evaluate the prevalence of use, predictors of use, and consequences of use of all evidence-based therapies in individual and in combination in patients with heart failure within the	

	Duke Databank for Cardiovascular Disease.	
Use of Duke CERTs web site to disseminate information about cardiovascular therapies.	Develop and maintain a web site that provides patients and providers with educational information and resources on therapies for cardiovascular disease.	
Incremental Cost-Effectiveness of long-Term Clopidogrel Therapy following PCI	Explore the economic implications of widespread adoption of evidence-based therapies for secondary prevention of coronary artery disease and heart failure from multiple perspectives.	
Observational study of outcomes associated with placement of coronary stents --a substudy of a large clinical trial.	Evaluate long-term outcomes in patients who receive stents in a large clinical trial in which the choice to place a stent and the selection of the stent type are left to the treating physicians; a planned analysis of bare vs. coated stents will be performed.	Center for Devices and Radiological Health, Center for Drug Evaluation and Research
Observational study of outcomes associated with coronary stents: Duke Databank for Cardiovascular Disease.	Evaluate "real-world" use of stents and their associated long-term outcomes; if adequate numbers of coated stents are placed, a comparison of outcomes with bare and coated stents will be conducted.	Center for Devices and Radiological Health, Center for Drug Evaluation and Research
Improved dissemination to clinicians of Medwatch Alerts, FDA Advisories, and decisions of the Cardiorenal Advisory Committee.	Work with FDA and ACC to develop and evaluate a method by which critical information on cardiovascular drugs and devices is effectively disseminated to clinicians.	Food and Drug Administration, American College of Cardiology
Evaluation of the receipt of medication guides and mandatory patient package inserts and patient comprehension of key educational messages in these materials.	In a real world setting, evaluate the distribution of medication guides and mandatory patient package inserts and evaluate patients' understanding of key educational messages.	Center for Drug Evaluation and Research, Medco & Co., Inc.
Evaluation of patient comprehension of key educational messages in medication guides and mandatory patient package inserts: laboratory assessment.	Conduct cognitive experiments to determine how well patients understand and remember key information contained within mandated patient education materials for select medications.	Duke Department of Psychology, Center for Drug Evaluation and Research
Fellowship training program.	Work with the Duke Clinical Research Institute and Duke University Medical Center to ensure continued provision of a well rounded training for cardiology fellows interested in clinical research.	Duke University Health System, Duke Clinical Research Institute
Post-approval cost of safety for	Estimate the post-approval cost of safety	PhRMA

pharmaceuticals.	for pharmaceuticals including the costs of case handling, summa ry report production, safety surveillance, epidemiology, infrastructure, strategic input, and safety-related marketing support.	
Heart failure inpatient registry.	Registry of all inpatients at Duke with heart failure that contains data on clinical history, demographics, medications, and treatment patterns.	
RB Chart	Collection of data on all patients participating in the Duke outpatient heart failure program for quality improvement.	

To Top

HMO Research Network		
Project Name	**Project Description**	**Partners**
Antibiotic use in children.	Retrospective cohort study using automated record linkage to determine rates of pediatric antimicrobial use from and indications for therapy over time and across nine geographic regions.	Brigham and Women's Hospital, Fallon Community Health System, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Care, Harvard School of Medicine, Harvard School of Public Health, Health Partners, Henry Ford Health System, Kaiser Permanente of Colorado, Georgia, Northern California and Northwest
Use and effectiveness of cardiac medications in patients hospitalized with heart failure.	Retrospective cohort study using automated record linkage to evaluate variation in rates of cardiac medications dispensed following hospitalization for congestive heart failure. Evaluate the effect of cardiac medication use on risk of re-hospitalization during subsequent 12 months.	Brigham and Women's Hospital, Fallon Community Health System, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Care, Harvard School of Medicine, Harvard School of Public Health, Health Partners, Henry Ford Health System, Kaiser Permanente of Colorado, Georgia, Northern California and Northwest
Impact of changing co-payment requirements on use of anti-diabetic therapy.	Retrospective cohort study using automated record linkage to assess the impact of different co-payment requirements on diabetics' use of anti-diabetic therapy.	Brigham and Women's Hospital, Fallon Community Health System, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Care, Harvard School of Medicine, Harvard School of Public Health, Health Partners, Henry Ford Health System, Kaiser Permanente of Colorado, Georgia, Northern California and Northwest
CERTs Prescribing Safety Program: Overall Safety of Current Drug Use.	Assess the overall frequency of prescribing at variance with FDA 'black box' warnings or commonly	University of Pennsylvania

	accepted clinical guidelines.	
CERTs Prescribing Safety Program: Safety of Prescribing to Children.	Determine the frequency of serious medication errors among children; develop an approach to child-specific interventions for reducing serious medication errors.	
CERTs Prescribing Safety Program: Errors in Laboratory Monitoring Associated with Drug Use.	Study to describe and assess appropriateness of laboratory monitoring in patients on medication for which monitoring is recommended.	
CERTs Prescribing Safety Program: Assessing Patient Preferences for Notification of Prescribing Error.	Study to evaluate patient preferences about disclosure of medication errors, through questions about hypothetical error scenarios based on real life problems.	
CERTs Prescribing Safety Program: Clinician Education Program to Improve Prescribing Safety.	A group-randomized clinical trial assessing the impact of academic detailing on medication error rates.	
CERTs Prescribing Safety Program: Automated Order-Entry Computer Programs to Improve Prescribing Safety.	Two separate group-randomized clinical trials to assess impact of different forms of order-entry alerts on inappropriate prescribing in ambulatory setting. One trial is coupled with educational interventions directed toward pharmacists and patients.	
Prescribing Safely During Pregnancy.	Assess drug use before and during pregnancy in a large population of women in eight different health systems and geographic regions. A principal goal is to assess the frequency of prenatal exposure to drugs that may injure the fetus.	
Incidence of drug-induced liver injury (R01DK062322-01)	Retrospective cohort study of drug-associated hospitalization for liver injury.	
Tuberculosis surveillance program		UnitedHealthcare , Centers for Disease Control and Prevention, Vanderbilt University Medical Center
Study of use of antibiotics, resistance and cost-effectiveness	5 year, community-based study	Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Massachusetts Department of Public Health, Massachusetts Division of Medical Assistance

Prevalence and strategies for appropriate prescription medication dosing for children. (AHRQ task order).	Retrospective cohort comparing error rates from pharmacy claims with medical records and electronic medical records. Also will compare error rates at site with electronic medical records to 2 sites without EMR.	Group Health Cooperative, Fallon Community Health System, Kaiser Permanente Northwest
Estimating the incidence and prevalence of inflammatory bowel disease (IBD) and variation in prevalence and health care utilization for IBD.	Determine the population-based incidence and prevalence of IBD within a large national cohort and estimate national and regional statistics for the United States. It will analyze regional variations in pharmacy and health care utilization patterns.	Fallon Community Health Plan, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Care, HealthPartners, Henry Ford Health System, Kaiser Permanente of Colorado, Georgia, Northern California and Northwest, Centers for Disease Control Foundation, Crohn's & Colitis Foundation of America
HRT Initiation and cessation following results from the Women's Health Initiative. (U19CA79689-supplement).	Analysis of HRT use at five managed care organizations before and after release of results of WHI.	CRN, Fallon Community Health Plan, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Care, HealthPartners, Kaiser Permanente Colorado, NIH/National Cancer Institute
CERTs Prescribing Safety Program: Rates of potentially inappropriate medication use among elderly persons enrolled in managed care plans in the United States: 2000-2001.	Retrospective study of the frequency of 33 medications dispensed to elderly patients. (Medications identified in the Beers criteria, as modified in Aahn et al, [1] as potentially inappropriate for persons age 65+)	
Assessment of maternal effects and infant outcomes in women exposed to medications during pregnancy.	Assess risks of drug use during pregnancy of pregnant women in five HMOs by examining major congenital malformations among infants born to women exposed to certain medications and women that are not.	
An epidemiologic program for the study of the safety and utilization of Lotronex in the United States.	A retrospective cohort study that includes a nested case-control study will use automated claims and medical records from nine HMOs to assess the utilization and safety of Lotronex, a drug used to treat irritable bowel syndrome among women with predominant bowel syndrome of diarrhea. A cohort study will be conducted to determine incidence rates of events. A nested case-control study will be conducted to determine risk factors.	GlaxoSmithKline
Enhanced identification of adverse drug reactions.	A retrospective analysis evaluating a total population of ~11 million from 1999 through early 2004. In conjunction with the FDA staff	Brigham and Women's Hospital, Harvard Pilgrim Health Care, Harvard School of Public Health, Kaiser Permanente Colorado, Georgia,

	approximately 15 new molecular entities (NMEs) will be selected for evaluation. Outcomes of interest to assess will focus on those contained in the new FDA list of Designated Medical Events (Dames). A retrospective analysis evaluating a total population of ~11 million from 1999 through early 2004. In conjunction with the FDA staff approximately 15 new molecular entities (NMES) will be selected for evaluation. Outcomes of interest to assess will focus on those contained in the new FDA list of Designated Medical Events (DMEs). We will analyze the data as it would have become available with the passage of time by partitioning the data set into 3-month intervals.	Northern California and Northwest , Food & Drug Administration
Improving adherence to preventive therapy after acute myocardial infarction through patient and provider interventions.	Assess the persistence of beta blocker use for post-AMI patients following a direct to patient intervention designed to increase rates of evidence-based long-term use of medications (beta blockers, lipid lowering agents, aspirin and ACE inhibitors) that increase survival following AMI. Describe patient and system characteristics associated with differences in impact of the intervention.	Duke University Medical Center, American Heart Association
Improving drug safety: linking lab and pharmacy data.	To refine and implement pharmacy alert system that uses linked data from the Pharmacy Information System and the Laboratory Information System at (KPCO) to identify and warn pharmacists of possible errors in: pregnant patients, with renal insufficiency, patients receiving high-risk drugs.	Agency for Healthcare Research and Quality
CERTs Prescribing Safety Program: Errors in prescribing of QT interval prolonging drugs.	An evaluation of the co-prescription of QT-prolonging medications, and of appropriateness of dosing of renally cleared, QT-prolonging antiarrhythmic agents.	Duke University Medical Center
CERTs Prescribing Safety Program: Multiple Medication Use	Describe the incidence of potentially clinically significant co-prescribing interacting drugs.	

To Top

University of Pennsylvania School of Medicine		
Project Name	**Project Description**	**Partners**
Reducing the use of antibiotics for acute bronchitis in outpatients.	Observational cohort study.	University of Pennsylvania Health System/University of Pennsylvania Medical Center, Pharmacia & Upjohn
Effect of formulary changes on the resistance patterns of E. coli and klebsiella.	Observational cohort study. Case-control study.	University of Pennsylvania Health System/Presbyterian Medical Center, National Institutes of Health
Expanding the use of meta-analysis to study rare side effects of antibiotics.	Computer simulations of various data analytic approaches to these analyses.	
Adherence to non-nucleoside reverse transcriptase inhibitors in HIV.	Observational cohort study.	Bristol-Myers Squibb Company Worldwide
Refill adherence with antiretroviral therapy and outcomes in human immunodeficiency virus (HIV).	Prospective cohort study.	Department of Veterans Affairs/National Institutes of Health, Agouron Pharmaceuticals, GlaxoSmithKline
Research sponsorship and the statistical power to detect adverse effects of newly approved drugs.	Cross-sectional analysis of published post-marketing epidemiologic studies of ADEs attributable to new drugs receiving FDA approval during an eight-year period.	
Risk factors for drug-resistant pneumococcal pneumonia.	Case-control study.	NIH/National Institute of Allergy and Infectious Diseases
Expansion of curriculum on therapeutics in medical school.	Curriculum development, implementation, evaluation.	
Pharmacoepidemiology Fellowship Training Program.	Educational-training program in pharmacoepidemiology.	University of Pennsylvania Health System/University of Pennsylvania Medical Center, National Institutes of Health, American Heart Association, Aventis Pharmaceuticals, Berlex, Genetech, Ortho-McNeil Pharmaceutical, Inc., Pfizer , Inc., Whitehall-Robins, Wyeth-Ahearst
Medication errors as causes of preventable acute renal failure in the inpatient setting. Project 3 of "Improving Patient Safety through Reduction in Errors in the Medication Use Process."	A hospital-based case-control study nested in a dynamic cohort of patients receiving aminoglycoside antibiotics.	Agency for Healthcare Research and Quality
Natural history of coagulase-	Retrospective cohortstudy.	University of Pennsylvania Health

negative Staphylococci catheter-associated bloodstream infections.		System/University of Pennsylvania Medical Center
The impact of bioterrorism on antimicrobial prescribing.	Time series design, a series of cross sectional studies over a 2-year study period.	University of Pennsylvania Health System (4 hospitals)
Medication errors: The role of transition to inpatient.	Retrospective chart and pharmacy record review.	University of Pennsylvania Health System/University of Pennsylvania Medical Center
Epidemiology of quinolone resistance in Escherichia coli.	Prospective cohort study.	Centers for Disease Control and Prevention
Variation in provider use of antimicrobial drugs.	Linking survey data about physician attitudes and national database information about actual prescribing patterns.	Department of Veterans Affairs/Research/Health Services Research and Development
Medication errors leading to hospitalization among the elderly through reduction in errors in the medication use process.	A prospective cohort study enrolling members of the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE).	Agency for Healthcare Research and Quality, Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE)
Viral Load 20-500 observational study.	Observational cohort study.	
Risk factors for candidemia in critically ill children.	A nested case control study in a population of critically ill children.	
A patient intervention to reduce antibiotic overuse.	Evidence-based and formative research methods to develop a new computerized educational intervention with regard to antibiotic overuse.	Pennsylvania Department of Public Health
Transplant surgeons' perceived risks of intraoperative virus transmission use of prophylactic interventions, and willingness to provide organs for infected patients.	Mailed questionnaire to study transplant surgeons' views and practices with regard to transmission risks for HBV, HCB, and HIV, fear of infection, utilization of prophylactic strategies, and willingness to provide organs to patients infected with these 3 viruses.	
Systematic review of antibiotic combination vs. monotherapy in the treatment of Pseudomonas bacteremia.	Comprehensive review and evaluation of literature.	
The effect of inaccurate communications during antimicrobial management telephone interactions.	Retrospective cohort study to determine the association between inaccurate communication of patient data and inappropriate antimicrobial medications by practitioners in a pre-approved antimicrobial management program.	

Quinolone resistance in nosocomial urinary infections.	Investigate risk factors for FQ resistance for individual pathogens as well as for gram-positive and gram-negative pathogens as distinct groups.	National Institutes of Health
Institute of Medicine Committee on Smallpox Vaccination Program Implementation ("smallpox committee")	Dr. Strom chairs a multidisciplinary committee for the IOM, which in turn is funded by CDC, to provide CDC with advice regarding its implementation of the President's smallpox vaccine program.	
Small area variation in levels of pneumococcal drug susceptibility.	Investigation of the validity of using hospital level susceptibility data to determine regional susceptibility patterns.	NIH/National Institute of Allergy and Infectious Diseases
Educational contributions related to use of antibiotics.	Preparation of edited book and book chapters relating to hospital epidemiology and prevention of nosocomial infections.	
Colonization and resistance of Streptococcus salivarius in the oropharynx of individuals with acne.	The purposes of this proposal are multifold: 1) to estimate the percentage of young adults with acne who are colonized by Streptococcus salivarius in their oro-pharynx; 2) to estimate the percentage of young adults with acne who are colonized by Streptococcus salivarius in their oro-pharynx who are on antibiotics for their acne and who are not on antibiotics for their acne; 3) to measure the percent resistance of these organisms to different antibiotics; and 4) to simply determine if these organisms produce BLIS.	
Virologic effectiveness of antiretroviral therapy in Botswana's National Program.	Virologic effectiveness of antiretroviral therapy in Botswana's National Program.	Penn Center for AIDS Research
Association between antibiotic use and relapse of inflammatory bowel disease.	This study examines the relationship between use of antibiotics and exacerbations of IBD. The study uses data from GPRD.	
Introduction to the FDA Drug Safety and Risk Management Advisory Committee.	In order to optimize the use of drugs, the FDA established an advisory committee in 2002 to assist in assuring that the benefits of drugs outweigh their risks. The committee advises the Commissioner of Food and Drugs with regard to the safety, efficacy, abuse potential, risk management, risk communication, and quantitative evaluation of spontaneous reports of	Food and Drug Administration

	drugs and other substances.	
Risk factors for mediastinitis following cardiac surgery in children.	Primary aim is to identify risk factors for the development of mediastinitis in children undergoing cardiac surgery.	GlaxoSmithKline, Society for Healthcare Epidemiology of America
Evaluation of the THIN database.	Empirically assess the quality of data from medical practices that were not previously included in the GPRD but have been added to the new THIN database. This project is a series of case-control studies examining well established epidemiological associations within the THIN database. The case-control studies will be performed separately in those patients who were previously included in the GPRD and those who are present only in the THIN database.	EPIC
GI bleeding following quinolone use among warfarin users.	To determine the relative risk of gastrointestinal bleeding events among elderly patients on warfarin 14 days following a first antibiotic prescription for a quinolone antibiotic compared to amoxicillin, erythromycin, or trimethoprim/sulfamethoxazole (TMZ).	
Literacy, misperceptions and adherence in HIV.	Determine the prevalence of medication misperceptions in individuals on antiretroviral therapy and whether these misperceptions are associated with lower rates of adherence. It will also determine if low medical literacy is associated with having these misperceptions.	
Study of adverse events associated with prolonged antibiotic use - FDA task order phase.	To determine the incidence of different types of adverse events for patients on prolonged (> 30 days) antimicrobial drug therapy and compare these incidences across different types of antimicrobial drugs and different patient groups, adjusting for indications for therapy.	Center for Health Care Policy and Evaluation, HMO Research Network
Impact of antibiotic use for acne on subsequent upper respiratory infections.	Investigate whether excess colonization of the oropharynx by group A streptococcus (GAS), and organism associated with upper respiratory tract infections, results in medical illness. We therefore propose to evaluate this issue using a large medical database.	
Epidemiology of ESBL-producing bloodstream	Identify risk factors for bloodstream infection caused by extended-spectrum	

infections in hospitalized children.	beta-lactamase (ESBL) -producing escherichia coli and klebsiella species (ESBL-EK) in children; to identify risk factors for adverse outcomes in children with these bloodstream infections; to determine patterns of transmission and spread of ESBL-EK in hospitalized children.	
Pilot study of "Managed Problem Solving" to reduce medication non-adherence in HIV.	1) determine the feasibility/barriers to implementing a Managed Problem Solving intervention and 2) describe the magnitude of adherence in subjects undergoing the Managed Problem Solving intervention. The intervention approaches multiple potential barriers that may affect adherence.	
Identifying physician attitudes and beliefs promoting antibiotic overuse in the elderly.	Identify the attitudes and practice patterns among physicians associated with increased rates of antibiotics prescribing for older adults with acute respiratory infections.	Pennsylvania PACE Program, Pennsylvania PACE Program, Robert Wood Johnson Foundation
Improving antibiotic use in acute care treatment (The IMPAACT Trial).	Test a combined physician and patient educational intervention to reduce antibiotic overprescribing for patients with acute respiratory tract infections treated in hospital emergency departments.	VA, AHRQ
Patient-level meta-analysis vs. aggregate-level meta-analysis for the investigation of subgroup effects.	1) To compare patient-level and group-level analyses of subgroup effects, asking whether the group-level analyses give the correct result (i.e., whether they agree with the patient-level analyses of the same data). 2) We will perform simulation studies to determine what conditions make it likely or unlikely that an aggregate-level analysis can reproduce the results of a patient-level analysis (the reference or gold standard).	
Prospective meta-analysis and other applications of principles of experimental design.	To develop guidelines for the conduct of prospective meta-analyses, i.e., meta-analyses planned prior to having any knowledge of the results of the studies to be included. This is a method to avoid potential biases in the selection of topics or trials in the performance of a meta-analysis.	Clinical Trials Centre (CTC) of the University of Sydney in Australia,
Availability of safety and efficacy data from supplement manufacturers.	Aim 1. To determine the proportion of manufacturers of dietary supplements for colonic health that have tested the	

	efficacy of their product. Aim 2. To determine the proportion of manufacturers of dietary supplements for colonic health that have tested the safety of their product. Aim 3. To determine what information manufacturers of dietary supplements will provide to allopathic health care professionals inquiring about efficacy, safety, and standardization of production of products used by their patients.	
Re-emergence of gram-negative primary bloodstream infections.	1) To identify longitudinal trends in gram-negative primary bloodstream infections; 2) To determine if trends differ across hospital locations or across particular species of gram negative pathogens.	
A computerized patient intervention to reduce antibiotic overuse.	Using a simple computer game, a modification of "Space Invaders," this project will evaluate the usability and initial efficacy of this intervention in teaching children ages 6 to 16 when it is appropriate to request and/or use antibiotics. The aims of the project are to implement the intervention according to the design specifications developed during the pilot study, evaluate the usability of the intervention, and evaluate the feasibility of deploying the intervention in the lay community.	
Risk of Infectious Complications in Nosocomial Pneumonia [K23 project]	1) describe the epidemiology of clinical superinfection in HAP patients in the ICU, and 3) determine the impact of superinfection on in-hospital mortality in these patients. ICU patients with HAP will be enrolled into a prospective cohort. Exposures to be examined include duration and spectra of antibiotic use and severity of illness as measured by Apache II score.	NIH/NIAID
Test Characteristics of Pperi-Rectal and Rectal Swab Compared to Stool Sample for Deterection of Fluoroquinolone-Resistant Escherichia coli in the Gastrointestinal Tract	To determine the sensitivity and specificity of perirectal and rectal swab techniques, when compared to the gold standard of stoool culture. Cross sectional study of subjects enrolled in a alrger prospective cohort study of quinolone resistant E. coli.	Centers for Disease Contol

To Top

University of Alabama at Birmingham

Project Name	Project Description	Partners
Glucocorticoid cost modeling.	To model the probability and costs of glucocorticoid adverse events over a two year period.	Agency for Healthcare Research and Quality
Secondary prevention of fractures due to osteoporosis.	Design and evaluate a multi-modal provider change technique to improve management of patients who have already sustained a fracture due to osteoporosis.	Duke University Medical Center
A group-randomized trial to improve prevention and treatment of glucocorticoid-induced osteoporosis.	Examine the impact of a multi-modal physician intervention on prevention and treatment of glucocorticoid-induced osteoporosis among participants in a large national cohort.	NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases, Aetna US Healthcare, US Quality Algorithms (USQA)
Determinants of NSAID continuation and discontinuation.	Survey a representative sample of chronic NSAID users from a managed care organization.	Academic Medicine and Managed Care Forum, Un itedHealthcare
Pharmacogenomics of methotrexate in rheumatoid arthritis.	Examine genetic polymorphisms that are hypothesized to predict susceptibility to RA, clinical response of early RA to methotrexate, and RA toxicity.	NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases, Amgen (formerly Immunex)
Engalitcheff Arthritis Outcomes Initiative.	Issue RFA for up to five grants for four years each in the area of arthritis therapeutics.	Arthritis Foundation Maryland Chapter
Comprehensive Linked Data Collection of Biologic Pharmaceuticals and Medical Events	To conduct analyses on adverse events of marketed biologics.	Center for Health Care Policy and Evaluation, UnitedHealth Group
Risk Assessment and Risk Communication for Biological Agents in Rheumatoid Arthritis	Evaluate risk of specific adverse events associated with biological agents occurring in RA, examine the impact of federal and industry efforts at risk communication of a perceived heightened susceptibility to TB, and to identify patient and provider characteristics that determine receipt of biological therapies in RA patients.	Duke University Medical Center, Center for Biologics Evaluation and Research, Center for Health Care Policy and Evaluation, UnitedHealth Group
NSAID patient safety and education.	A 4-year project to test the effectiveness of a maximally intensive, minimally intrusive intervention promoting safe prescribing of NSAIDs in the outpatient setting.	

Determining the cost effectiveness of an intervention to increase screening and treatment of glucocorticoid-induced osteoporosis.	GIOP intervention to determine the cost-effectiveness and benefits to patients and physicians.	NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases
Developing tailored patient educational messages to promote appropriate receipt of Total Joint Replacement (TJR).	Develop educational interventions that might help patients make informed decisions concerning Total Joint Replacement.	Agency for Healthcare Research and Quality, NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases
Alabama Arthritis Practice-based Continuing Medical Education (CME) and Research Network - Improving the safe and effective use of hormone replacement and anti-osteoporotic therapy.	Education intervention targeted to primary care physicians, responsible for the majority of care of postmenopausal women, that is designed to improve their evidence-based practice in this area.	Agency for Healthcare Research and Quality, Alabama Continuing Medical Education Research Network
Carpal Tunnel Syndrome (CTS) medical guideline adherence and outcomes.	Examine adherence patterns and predictors to evidence-based quality indicators producing information useful in paving the way for development of future research opportunities in targeted interventions for CTS.	
Continuing Education Osteoporosis Website expansion to include registered dieticians.	Update an osteoporosis professional website for pharmacists for registered dietitians.	

To Top

University of North Carolina at Chapel Hill		
Project Name	**Project Description**	**Partners**
Evidence-based tools to assess pediatric population.	Literature review and grading of evidence on instruments.	RTI Health Solutions
Model pediatric therapeutic drug monitoring service to improve patient outcomes.	Teaching caregivers how to incorporate drug monitoring into care.	Cincinnati Children's Hospital
MedMARx: Improving care through analysis of pediatric medication error data.	Identify priority areas for practice improvement.	United States Pharmacopeial Convention, Inc. (USP)
Surveillance and registries for pediatric hepatotoxicity using Medicaid data.	Identify priority areas for practice improvement.	North Carolina Medicaid AccessCare, Inc.,
Safety and efficacy of continuous subcutaneous blood glucose monitoring systems in the management of type 1 diabetes mellitus in children.	Providing better and more detailed data for diabetes management.	Medtronic, Inc./Diabetes Management Subsidiary MiniMed, Inc.

Postmarketing surveillance of drugs in emergency department pediatric patients.	Establishing feasibility of using ED databases to track adverse drug events.	Food and Drug Administration, South Carolina Office of Research and Statistics (SCORS), Carolina Medical Review
Impact of antibiotic resistance on the management of childhood infections: a community evidence-based approach. I-UTI	Aiding practitioners in understanding and preventing resistance.	
Impact of antibiotic resistance on the management of childhood infections: a community evidence-based approach. 3-antibiotic resistance surveillance.	Aiding practitioners in understanding and preventing resistance.	
Impact of antibiotic resistance on the management of childhood infections: a community evidence-based approach. 5 - education project.	Aiding practitioners in understanding and preventing resistance.	
Systematic review to the bedside: changing the management of bronchiolitis in nonacademic emergency departments.	Using evidence base to support practice change.	Duke University Medical Center
Medication/vaccine safety studies using the GPRD.	Exposing young researchers and clinicians to valuable data.	RTI-International
Protection of human research subjects, with particular reference to pediatric studies.	General introduction for pediatric researchers to the protections essential to the conduct of ethical human subjects research with the latest information on federal policy governing such research, and the Institutional Review Boards who are responsible for overseeing it, as well as, the unique challenges and constraints associated with children as research subjects.	University of North Carolina-Chapel Hill, Committee on Protection of Rights of Human Subjects
Developing an innovation community for children's healthcare improvement.		North Carolina Center for Children's Healthcare Improvement, American Academy of Pediatrics

To Top

Vanderbilt University Medical Center		
Project Name	**Project Description**	**Partners**
COX2 NSAIDs and CHD: TennCare	Retrospective cohort.	

COX2 NSAIDs and CHD: Kaiser	Retrospective cohort.	
Fetal exposure Category X drugs.	Cross sectional.	
Use of high-dose rofecoxib.	Cross sectional.	
Enrollment gaps and asthma exacerbation.	Retrospective cohort.	Agency for Healthcare Research and Quality
Fetal effects of antimicrobials likely to be used in bioterrorism.	Cohort study of use of antimicrobials likely to be used in bioterrorism in pregnant women, with the outcomes being birth defects.	Food and Drug Administration, TennCare/Medicaid
Effects of NSAIDs on lung cancer risk in patients with chronic obstructive pulmonary disease (COPD).	Determine if NSAIDs protect against lung cancer in COPD patients by conducting a cohort study in TennCare/Medicaid. NCI Special Projects of Research grant (SPOR).	NIH/National Cancer Institute
COX2 NSAIDs and serious coronary heart disease.	Retrospective cohort.	
Drug-drug interactions and sudden cardiac death.	Retrospective cohort study of use of interacting medications and sudden cardiac death.	FDA, NIH, Tennessee Bureau of TennCare, Tennessee Department of Health, Janssen Pharmaceutica
Secular trends of increasing antipsychotic use in children.	Descriptive study of secular trends of antipsychotic use and their indications in children.	
Racial differences in antidepressant treatment preceding suicide.	Descriptive study of use of medications preceding suicide.	

Completed Projects

Last Projects Update 12.13.04

Arizona | Duke | HMO Research Network | Penn | UAB | UNC | Vanderbilt

University of Arizona Health Sciences Center		
Project Name	**Project Description**	**Partners**
National medication errors survey of third-year medical students, internal medicine clerkship, and residency programs.	Survey of needs and development of educational programs.	Food and Drug Administration
Advance PCS data mining for drug interactions.	Advance PCS database evaluation, for potentially serious combinations of co-prescribed medications.	AdvancePCS
Fourth-year medical school course on therapeutics.	Didactic, small group, individual teaching and assessment.	Food and Drug Administration
Genetic predictors of drug-induced QT interval prolongation.	Clinical protocol.	NIH/National Institute of General Medical Sciences, Pharmacogenetics Network

To Top

Duke University Medical Center		
Project Name	**Project Description**	**Partners**
Retrospective evaluation of aspirin use in patients with coronary artery disease.	Determine prevalence of aspirin use, predictors of aspirin use, and consequences of aspirin use from the Duke Databank for Cardiovascular Disease.	
Evaluation of reasons reported for aspirin non-use in patients with coronary artery disease.	Determine reasons for aspirin non-use through a patient survey.	
Evaluation of beta-blocker use and non-use in patients with heart failure.	Validate beta-blocker use status and determine reasons for non-use through a patient survey.	
Evaluation of the national market uptake of dofetilide.	Evaluate prescribing trends of all antiarrhythmic agents from the time dofetilide was marketed through 2001.	Center for Drug Evaluation and Research
Evaluation of the dofetilide risk management program at Duke University Medical Center: practitioner perceptions.	Determine practitioner perceptions of the dofetilide risk management program and agreement with dosing and monitoring recommendations.	
Evaluation of physicians'	Evaluate physicians' knowledge of the QT interval	

understanding of the QT interval and medications that may alter it.	and medications, diseases, and drug combinations that may alter the QT interval.	
Evaluation of the dofetilide risk management program at Duke University Medical Center: adherence to guidelines.	Compare adherence to dosing and monitoring recommendations for dofetilide and sotalol at Duke University Medical Center.	
Educational module on QT prolonging medications.	Using results from the Pharmacy Benefits Manager analysis, the national prescribing pattern analysis, and the QT surveys, develop an Internet-based educational module for health care providers on the QT interval to help minimize risk associated with use of QT prolonging medications.	American Heart Association
Determine critical postmarket surveillance questions and explore novel solutions for cardiovascular devices.	In conjunction with the American College of Cardiology, the Center for Devices and Radiological Health of FDA, the Society of Thoracic Surgery and AdvaMed, the largest device trade organization, a workshop was held. The premise for this workshop was that, while many devices offer great promise for millions of cardiovascular patients, a comprehensive picture of the safety and effectiveness of these treatments often emerge only when careful pre-market investigation is followed by focused post-market surveillance.	Center for Devices and Radiological Health, Advanced Medical Technology Association, American College of Cardiology, Society of Thoracic Surgeons
Postmarket surveillance of transmyocardial revascularization.	In collaboration with FDA and the Society for Thoracic Surgeons, conduct a post-marketing surveillance program of Transmyocardial Revascularization (TMR) used alone or in combination with coronary artery bypass graft surgery (CABG).	Center for Devices and Radiological Health, Society of Thoracic Surgeons
Effect of beta-blockers in heart failure patients: a meta-analysis.	Conduct a meta-analysis of previously published trials evaluating the use of beta-blockers in patients with heart failure.	
Economic implications of changes in treatment strategies for patients with cardiovascular disease.	Examine the cost-effectiveness of treating heart failure patients with beta-blockers from different perspectives: society, hospital, Medicare and physician. Determine whether cost effectiveness of beta-blocker therapy is sensitive to variations in key clinical and economic variables.	
Evaluation of antiarrhythmic drug use patterns from 1995 to 2000.	Determine national prescribing patterns and trends for antiarrhythmic agents from 1995 through 2000.	Center for Drug Evaluation and Research
Evaluation of the prescribing of concomitant QT prolonging medications.	Using a Pharmacy Benefits Manager (PBM) database, evaluate various combinations of different QT prolonging medications and QT prolonging medications with other medications that affect the pharmacokinetics of the QT	AdvancePCS, University of Arizona Health Sciences Center

	prolonging medications.	
Evaluation of the Duke CERTs QT educational module.	Evaluate the ability of an Internet-based educational program on the QT interval to provide a test population of health care practitioners with usable, easy to understand, and clinically relevant guidance on measuring and monitoring the QT interval to reduce the risk of torsades de pointes.	Duke's Educational Media Services
Cost effectiveness of drug-eluting stents compared with conventional stents.	Perform an economic analysis of coated stents and conventional stents within the Duke Health System.	

To Top

HMO Research Network		
Project Name	**Project Description**	**Partners**
Asthma drug use.	Retrospective cohort study using automated record linkage to assess patterns of use of asthma drug therapy over time and across nine geographic regions.	Brigham and Women's Hospital, Fallon Community Health System, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Care, Harvard School of Medicine, Harvard School of Public Health, Health Partners, Henry Ford Health System, Kaiser Permanente of Colorado, Georgia, Northern California and Northwest
Development of algorithms for identification of patients with Churg-Strauss syndrome.	Retrospective cohort study to determine feasibility of developing an algorithm for efficient identification of Churg-Strauss syndrome in large, unselected populations. If so, then epidemiologic study will be done, focusing on asthma drugs for etiology.	Brigham and Women's Hospital, Fallon Community Health System, Group Health Cooperative of Puget Sound, Harvard Pilgrim Health Care, Harvard School of Medicine, Harvard School of Public Health, Health Partners, Henry Ford Health System, Kaiser Permanente of Colorado, Georgia, Northern California and Northwest
Systematic review of drug interventions in managed care.	Review of published and unpublished reports of drug-related interventions conducted in managed care organizations. Focuses on interventions that have undergone formal evaluation using either randomized comparison or other quasi-experimental designs.	
Create a web-based resource summarizing effective drug-related interventions in managed care.	Review of published and unpublished reports of drug-related interventions conducted in managed care organizations. Focuses on interventions that have undergone formal evaluation using either randomized comparison or other quasi-experimental designs.	American Association of Health Plans

To Top

University of Pennsylvania School of Medicine		
Project Name	**Project Description**	**Partners**
Use of tetracycline for acne in an outpatient clinic: effects on antibiotic resistance patterns.	Primary data collection of a convenience sample of individuals with acne who are receiving tetracycline and a group who are not.	
Study the feasibility of using GPRD to study the epidemiology of drug-resistant pneumococcal pneumonia.	Evaluate the feasibility of using data from the General Practitioners Research Database–an electronic medical record within the UK.	Department of Veterans Affairs, General Practice Research Database/EPIC
Risk factors for infection due to fluoroquinolone-resistant escherichia coli and klebsiella pneumoniae.	Case-control study.	University of Pennsylvania Health System/Presbyterian Medical Center, Infectious Diseases Society of America, Roche Laboratories, Inc.
Adherence to protease inhibitors in HIV.	Observational cohort study.	Agouron Pharmaceuticals
Epidemiologic investigation of fluoroquinolone resistance in infections due to extended-spectrum-beta-lactamase (ESBL) producing escherichia coli and klebsiella pneumoniae (ESBL-EK).	Case-control study.	NIH/National Institute of Diabetes & Digestive & Kidney Diseases
Re-administration of antibiotics in patients with a history of beta-lactam allergy.	Retrospective cohort study.	General Practice Research Database/EPIC
Risk factors for drug-resistant urinary tract infections.	Case-control study.	Department of Veterans Affairs
Tensions between patient and public health values in generalists use of antibiotics.	Cross-sectional survey.	Robert Wood Johnson Foundation
Micro array technology in the detection of antimicrobial-resistant staphylococcal bloodstream infection.	Observational cohort study.	Nanogen Corporation
Vancomycin resistant enterococcal colonization in liver transplant candidates: Prevalence and risk factors.	Case control study.	
Colonization and resistance of Staphylococcus Aureus and Streptococcus pyogenes in the oropharynx of individuals without acne.	Cross-sectional study.	

Knowledge and attitudes regarding antimicrobial use among emergency department physicians in Pennsylvania following bioterrorism events.	A survey of emergency department physicians in Pennsylvania to investigate the knowledge and attitudes regarding antimicrobial use and bioterrorism response and preparedness.	Pennsylvania Department of Public Health
Extended-Spectrum ß-Lactamase-Producing Escherichia Coli and Klebsiella species: Risk Factors for Colonization and Impact of Antimicrobial Formulary Interventions on Colonization Prevalence.	Case-control study.	
Changes in Prevalence of Vancomycin-Resistant Enterococci (VRE) following Antimicrobial Formulary Interventions: Impact of Sequential Progressive Restrictions on Use of Vancomycin and 3rd-Generation Cephalosporins.	Before/after intervention study.	
Impact of a hospital-based antimicrobial management program on clinical and economic outcomes.	Retrospective observational cohort study.	Hospital of University of Pennsylvania
Chloramphenicol resistance in Vancomycin-resistant enterococcal (VRE) infections.	Case control study of risk factors for chloramphenicol resistance in VRE.	
Antimicrobial utilization in the emergency departments of academic medical centers: investigation of inappropriate use of fluoroquinolone antibiotics.	Prospective cohort study.	
Risk factors for multi-drug resistant Enterobacteriaceae in a neonatal intensive care unit.	Case-control study.	
Effectiveness of retrospective drug utilization review in Medicaid.	Frequency of problematic prescribing pre-and post-implementation of retrospective drug utilization review (RDUR) in a group of 6 Medicaid programs: pre-post comparisons of the rate of all-cause and cause-specific hospitalization in subjects with problematic prescribing.	Agency for Healthcare Research and Quality, NIH/National Institute on Aging, ProVantage Health Systems,Inc.,
Willingness to be vaccinated against smallpox: an assessment of hospital-based adult and pediatric emergency first responders.	A national cross-sectional survey of adult and pediatric hospital emergency department personnel located in large US cities, utilizing a self-administered anonymous questionnaire.	

HIV treatment interruption and immune function.	Randomized clinical trial.	
Institute of Medicine Committee to review the CDC anthrax vaccine safety and efficacy research program.	The Committee was convened to evaluate concerns raised about the safety and efficacy of AVA, including the suggested link between AVA vaccination and the illnesses experienced by some Gulf War veterans, and questions regarding the manufacture of the vaccine.	Centers for Disease Control and Prevention, Institute of Medicine
Predicting vaccine status and ED use in Medicaid newborns.		
Failure of oral antibiotics to prevent early bacteremia after hematopoietic stem cell transplantation.	Evaluate the incidence of bacteremia during the early post transplant period in pediatric stem cell transplant patients at The Children's Hospital of Philadelphia (CHOP); Evaluate the microbiologic profile and incidence of antimicrobial resistance of bloodstream infections; Evaluate risk factors associated with early bacteremia in this patient population.	

To Top

University of Alabama at Birmingham		
Project Name	**Project Description**	**Partners**
Preferences for fractures and other glucocorticoid-associated adverse effects among rheumatoid arthritis patients.	Determine rheumatoid arthritis patients' preferences, elicited by rating scale and time trade-off methods, for validated health-state scenarios depicting glucocorticoid adverse events.	NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases
Practice pattern variation in glucocorticoid-induced osteoporosis (GIOP).	Characterize glucocorticoid usage and patterns of osteoporosis-preventive therapies among a large national cohort.	Aetna US Healthcare, Medco Health Solutions., US Quality Algorithms (USQA)
Racial variations in osteoporosis management.	Determine the self-reported prevalence of osteoporosis risk factors and receipt of treatment in a large managed care population and determine racial variation in osteoporosis management, knowledge, and attitudes.	Medco Health Solutions, UnitedHealthcare of Alabama
Long-term safety and toxicity monitoring of non-steroidal anti-inflammatory drugs.	Identify potential drug-associated toxicities and monitoring practices of traditional and COX-2 specific NSAIDs in a large managed care population. Assess the influence of a multi-modal provider change technique on process of care.	NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases

Arthritis quality indicators development.	Define clinical markers of appropriate arthritis care through a systematic literature review.	Arthritis Foundation, UCLA/Rand Center for Adolescent Health Promotion
Medical errors in the management of gout.	Define gout medication errors/quality indicators via a comprehensive review of treatment guidelines and an expert panel.	University of Pennsylvania, Agency for Healthcare Research and Quality, General Practice Research Database (GPRD)
High risk arthritis survey.	Survey to target underserved populations in Alabama that are at high risk for developing arthritis and may be receiving lower standards of care.	Alabama Department of Public Health, Arthritis Foundation of Alabama Chapter
Outcomes of elderly onset rheumatoid arthritis.	Outcomes study to determine predictors of mortality and morbidity among an established cohort of patients with elderly onset rheumatoid arthritis.	American College of Rheumatology, Arthritis Foundation, Iowa Women's Health Study
Web site for arthritis patient education.	Develop and evaluate the feasibility and efficacy of an interactive, multi-media counseling intervention targeting arthritis-related behaviors.	Alabama Department of Public Health, Arthritis Foundation of Alabama Chapter, Medco Health Solutions
Improving primary care patient safety with handheld DSS.	Examine the barriers to implementation and the impact on patient safety of a suite of decision support programs available on a handheld computer (PDA).	Agency for Healthcare Research and Quality
Hydroxychloroquine lowers damage in systemic lupus erythematosus.	Hydroxychloroquine use to reduce the risk of systemic lupus erythematosus, lupus in minorities, nature versus nurture (LUMINA) cohort.	

To Top

University of North Carolina at Chapel Hill		
Project Name	**Project Description**	**Partners**
NC Asthma Improvement Project.	A statewide educational effort to share knowledge about strategies for improving care of children with asthma--a three-hour interactive continuing medical education (CME) session and a learning collaborative within a NC AHEC region.	North Carolina Medicaid, North Carolina SCHIP, AccessCare, Inc., GlaxoSmithKline
Tailored implementation strategy for pediatric therapeutic guidelines.	Cross-sectional, multi-level assessment of CPG typology and tools for tailoring and adapting CPGs to different settings.	
Efficacy, safety, and pharmacokinetics of drugs in pediatric HIV.	High-pressure liquid chromatographic method to develop sensitive, specific, practical assay that could detect any of the four protease inhibitors most commonly used clinically (indinavir,	Cincinnati Children's Hospital, Columbus Children's Hospital

	ritonavir, saquinavir, and nelfinavir) in human plasma samples.	
Prevalence of Type II diabetes in childhood.	Measuring fasting blood glucose in frozen serum samples obtained in 1997 from 638 9th- and 10th-grade students to determine undiagnosed glucose intolerance.	
Prescribing patterns of psychotropic drugs for adolescents.	Retrospective analysis administrative database to address use of psychotropic drugs to treat depression and ADHD.	Center for Health Care Policy and Evaluation, UnitedHealth Group
CERTs Summer Institute: Using the Evidence on Therapeutics to Enhance Quality of Care.	Educational activity.	Institute for Health Care Improvement, National Initiative for Children's Healthcare Quality (NICHQ)
MedMARx monitoring and surveillance project.	Evaluation of in-patient error reporting system.	United States Pharmacopeial Convention, Inc. (USP)
Attention deficit-hyperactivity disorder (ADHD) project.	Design and test tool kits and process improvement strategies for practitioners to use in the diagnosis and management of attention deficit-hyperactivity disorder (ADHD).	National Initiative for Children's Healthcare Quality (NICHQ)
Pediatric adverse drug event and reaction reporting program.	Create a reporting process to improve the process of event reporting and patient care while maintaining confidentiality and the protection of information.	
Skeletal effects of oral replacement of vitamin D and calcium in adolescents with cystic fibrosis.	Assess the role of vitamin D and calcium in preventing osteopenia and osteoporosis using a controlled trial with one treatment arm and one control group, each with 30 adolescents who will receive a calcium supplement of 500 mg. per day.	
Prevalence of vitamin D-deficient rickets in minority infants.	Survey of NC pediatric primary care providers on attitudes toward vitamin D supplementation during breast-feeding; case evaluation of ethnicity of all rickets patients at two NC tertiary medical centers; proposal for state public health policy change.	Bowman Gray School of Medicine, Wake Forest Baptist Medical Center
Optimizing prescribing and treatment for otitis media.	To determine the impact of antibiotic prescribing at initial visit on the probability and frequency of AOM-related return visits among North Carolina (NC) Medicaid patients.	
Learning from Errors in Ambulatory Pediatric Settings (LEAP): A CERTs Supplemental Project.	Develop a web-based reporting tool for errors and near misses in pediatric ambulatory settings, identify the types of errors and near misses that are occurring in children.	American Academy of Pediatrics, Pediatric Research in Office Settings Network (PROS)
Effect of AAP guidelines on vitamin D supplementation	Improving provider behavior on vitamin supplementation.	North Carolina WIC, American Academy of Family

recommendations in practice.		Physicians, American Academy of Pediatrics
Evaluation of Synagis treatment for the prevention of RSV infection in children using Medicaid data.	Develop cost effectiveness methodology for NC Medicaid that includes relevant outcomes, costs; determine cost effectiveness of Synagis with an EGA of 32-35 weeks who have no co-morbidity and less than 2 risk factors; determine incidence of RSF and cost effectiveness in subgroup of children with congenital heart disease.	AccessCare, Inc., North Carolina Medicaid

To Top

Vanderbilt University Medical Center		
Project Name	**Project Description**	**Partners**
Antipsychotics and sudden death.	Retrospective cohort.	Jannsen Pharmaceuticals
NANSAIDs & CHD.	Retrospective inception cohort.	Food and Drug Administration
Prenatal erythromycin and pyloric stenosis.	Retrospective cohort.	Food and Drug Administration
NANSAIDs and cardioprotection.	Retrospective cohort.	
Thioridazine and sudden death.	Commentary.	
Early erythromycin and pyloric stenosis.	Nested case-control.	Food and Drug Administration
Benzodiazepine misclassification.	Methods study.	
Antidepressants and sudden death.	Retrospective cohort.	Jannsen Pharmaceuticals
Anti-lipid drugs and hip fracture.	Observational studies.	
Inception cohorts.	Methods study.	
Medical vs. surgical treatment GERD.	Retrospective cohort.	
Contraindicated use of cisapride.	Retrospective cohort.	HMO Research Network, Food and Drug Administration, UnitedHealthcare
Medication errors in home health.	Prevalence cohort.	John A. Hartford Foundation
Corticosteroids in childhood.	Prevalence cohort.	Food and Drug Administration
Cytoprotection in NANSAID users.	Prevalence cohort.	
ß-blocker therapy in AMI.	Observational study.	

Reducing NSAIDs: community.	Randomized control trial.	Agency for Healthcare Research and Quality
Reducing NSAIDs: nursing home.	Randomized control trial.	Agency for Healthcare Research and Quality
Medications home health: policy evaluation.	Randomized control trial.	John A. Hartford Foundation
Mental health carve-out and compliance among schizophrenics.	Observational studies.	NIH/National Institute of Mental Health
ACEI compliance in CHF.	Descriptive study of the proportion of heart failure patients prescribed ACEI who fill them.	