The Impact of Studies Funded Under Outcomes of Pharmaceutical Outcomes Research

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A. Introduction

In a report entitled *The Outcome of Outcomes Research at AHCPR*, Tunis and Stryer[1] defined the types of impact that outcomes research can have on further research, on policy making, on clinical practice, and on patient outcomes. While recognizing that it is important to fund research that is likely to have an impact in these areas, the authors also stressed the significant challenges faced in connecting specific research efforts with their effects. The process of change in program, policy, and clinical practice is complex and subject to many external influences. Thus, it is difficult to trace changes in health care practice and outcomes to a particular study or set of studies that may have contributed to them.

The present report is part of a project that provides research and editorial support to assess the impact of 18 pharmaceutical research studies funded during the 1990s by the Center for Outcomes and Effectiveness Research (COER) at the Agency for Healthcare Research and Quality (AHRQ). These research studies varied in scope but addressed the following key areas of interest: data and analytic methods involved in the study of drug therapy effectiveness, factors affecting the appropriateness of drug prescribing, the role of the patient in drug therapy effectiveness, and economic analysis and the effects of changes in the health care environment.

The first part of the Outcomes of Pharmaceutical Outcomes Research project involved development of an updated list of publications generated by these research projects, entitled *Outcomes of Pharmaceutical Therapy (OPT) Program Update, November 2000*.[2] A subsequent phase of work involved analysis of these publications in terms of their contribution to knowledge about health care outcomes, their policy relevance, and their levels of impact as defined by Tunis and Stryer[1]. In addition, some Principal Investigators (PIs) were contacted for the purpose of learning about examples of project impacts that may not be reflected in published literature; 10 interviews were conducted with Principal Investigators and with users of research results. Analysis for several projects is still underway, and additional publications will be forthcoming, along with findings and related impacts on other research, policy, practice and outcomes.

In reviewing the report it is important to understand how Tunis and Stryer[1] define impact levels. Their definition reflects the process by which basic findings in outcomes and effectiveness

research are linked over time in increasingly concrete impacts on the health of patients as illustrated in the table below:

Levels of Impact Resulting from Outcomes Studies[1]
Level I – Impact on Further Research. This level includes effects of research studies that do not represent a direct change in policy or practice. This includes new tools and methods for research, instruments and techniques to assist clinical decision-making and studies that identify areas in which scientific knowledge is absent but needed. Level I impacts are also provided when studies describe findings that are inconsistent with current clinical paradigms and stimulate rethinking and questioning within a clinical specialty.
Level II – Impact on Policies. A policy or program is created as a direct result of the research, e.g. the information is used by health plans, public programs such as Medicaid, professional organizations, legislative bodies, regulators, and/or accrediting organizations.
Level III – Impact on Clinical Practice. The research results in a change in what clinicians or patients do, or in changes in a pattern of care. These changes may be demonstrated in a limited study population as a result of a specific intervention, or they may be trends identified outside a formal research context.
Level IV – Impact on Health Outcomes. This includes actual impact on health outcomes including those that are clinical, economic, related to quality of life, or related to satisfaction. They may be demonstrated in a limited study population as a result of a specific intervention, or beyond and outside of a formal research context.

The following section of this report summarizes the types of impact demonstrated by the 18 COER-funded studies. In addition, this section illustrates the degree to which these studies address current important policy issues, key DHHS target populations, and diseases and conditions that are important to the Nation's health. Section C provides an overview of each project and presents specific findings from one or more studies or research publications within the project that are relevant to further research or that have had an impact on policies, clinical care or outcomes.

B. Summary of Studies' Impact and Relevance in Today's Policy Environment

1. Impact on Research

The research projects funded by COER reflect the breadth and depth of pharmaceutical-related issues faced in health care delivery in the United States today. Some focus on the role of the pharmacist, some on the use of information technology, and others on prescribing patterns among physicians. Yet others look at the role of patients in managing drug regimens and how to effectively elicit information from patients to improve treatment and outcomes.

Taken together, these projects have generated a significant impact on the research base that is necessary to address the complex and evolving range of questions related to drug use and drug policy. As Table 1 in the Appendix shows, these projects have contributed important primary research (Level I) in a number of key areas, including:

- Treatment effectiveness
- Cost and economics of health care
- Tools for patient management
- Research tools and translating research for clinical care
- Special needs of target populations
- Public health and prevention, and chronic and persistent disease.

2. Impact on Policies, Clinical Practice, and Health Care Outcomes

Eight of the projects have demonstrated direct influence on the policies (Level II) of one or more organizations, including managed care organizations, State Medicaid programs, clinical associations, quality accreditation commissions, private insurance programs, integrated delivery systems and/or Federal agencies. Further, despite the challenges that Tunis and Stryer[1] cite about linking research to impact Levels III (clinical practice) and IV (health care outcomes), at least four funded studies have demonstrated effects at one or both of these levels. These projects are identified in Table 2.

3. Focus on Target Populations and Key Diseases and Conditions

It is also important to note that taken together these projects address a range of population groups that are important because they represent key public financing programs (e.g., the elderly for Medicare, the poor for Medicaid, and children for SCHIP) or because they represent racial or ethnic subgroups of the population that are of significance because of health care and other disparities (e.g., African Americans, Hispanics, Native Americans). Eleven projects address issues related to key populations, as presented in Table 3.

Most of the projects also focus on diseases and/or conditions of significant public health interest, including those that are highly prevalent, chronic and/or costly (Table 4), such as HIV/AIDS, asthma, and heart disease.

4. Relevance to Current Policy Issues

Another illustration of the relevance of this body of work can be seen by comparing the issues it addresses to topics of current health policy interest. The rise in health care premiums and costs, and particularly pharmacy costs, and the current debate about a Medicare prescription drug benefit are among the top issues in U.S. domestic policy today.

Representative of this policy focus was a high-profile meeting convened by the Office of the Assistant Secretary for Planning and Evaluation (OASPE) on Pharmaceutical Pricing Practices, Utilization and Costs on August 8-9, 2000 in Washington, D.C. Conference background materials and presentations addressed topics ranging from drug effectiveness and outcomes, to drug use by key target populations, to pricing and cost. Comparing the themes and issues raised in the conference with the research funded by COER reveals the ongoing relevance of much of the research to critical questions that we continue to face or that have become increasingly important. Table 5 illustrates key issues raised during the conference and identifies the COER-funded projects that address those issues.

C. Key Impacts and Findings by Project

This section provides an overview of each of the 18 COER OPT projects, along with a description of the project's impact by type, or level, of impact.

Within Level I (impact on further research) findings are presented within the following categories, as appropriate:

- Treatment effectiveness
- Cost and economics
- Tools for patient management
- Research tools and translating research for clinical care practice
- Special needs of target populations
- Public health and prevention, and chronic and persistent diseases and conditions.

These summaries are based on review of study-related publications, as well as interviews with some principal investigators and users of the research results.

1. Comparative Outcomes of Ambulatory Pharmaceutical Agents

Principal Investigator: Joseph Lau, M.D.
Grant Number: HS07782
Project Period: March 1993 – February 1997

Overview

This project advanced the analytical tools available to translate the results of randomized controlled trials (RCT) into clinically useful information. In addition, the project applied these tools to a broad range of key clinical conditions (e.g., renal disease, AIDS, hypertension, serious infection). Research efforts related to this project resulted in:

- New information being incorporated into clinical guidelines for chronic kidney disease patients
- Information supporting the development of new diagnostic approaches related to acute sinusitis
- Information supporting alternative treatment patterns for serious infections.

Methodologically, the project also advanced the science of meta-analysis, in particular, enhancing the value of relatively small, randomized, controlled trials.

The project developed a computer-based automatic process called Real-Time Meta-Analysis System (RTMAS). This process organizes, routinely updates, and displays RCTs and meta-analyses of pharmaceuticals in a simple and easy to understand matrix format. This significantly reduces the time required to conduct a systematic review and/or meta-analysis of the effectiveness or comparative effectiveness of therapeutic agents. A major contribution of the project is in the methodological improvement of meta-analysis with the development of control rate meta-regression.

Research related to this project resulted in 38 articles to date, including seven articles in the *Annals of Internal Medicine*, five in the *Journal of Clinical Epidemiology*, two in *The British Medical Journal*, and one in the *Journal of the American Medical Association*.

Impact on Clinical Practice (Level III)

- Hospitalization and Infection: A meta-analysis conducted with the RTMAS confirmed that a single dose of aminoglycosides is as effective as and is less toxic than the standard multiple doses. A topic ripe for investigation, this study was one of the earliest of a number of studies in the field that confirmed this finding. According to the Project PI, anecdotal evidence suggests a definite shift in treatment patterns towards an increase in single-dose treatment as a result of this finding.
  The meta-analysis compared a once-daily regimen versus the standard practice of multiple daily doses of aminoglycoside for serious infections. No significant difference was found in efficacy between the strategies in patients with serious infections, and there was a reduced risk of nephrotoxicity with the once-daily regimen. "Once-daily dosing can reduce the cost of administration and the toxicity of aminoglycoside in the inpatient setting. In addition, the once-daily dosing regimen could result in increased "ambulatory" use of these potent antibiotics instead of current practice of primarily

inpatient use. The adoption of this approach has the potential for lowering costs for patients by obviating or shortening their lengths of hospitalization"[3].

Impact on Policies (Level II)

As further described below, work conducted under this project was influential in the development of guidelines for chronic kidney disease, recommendations for the management of acute sinusitis, a framework used by researchers in reporting RCT results, and syntheses of research on congestive heart failure and hypertension.

- National Kidney Foundation's Evidence-based Guidelines: Work conducted under this project related to non-diabetic renal disease provided important contributions to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K-DOQI). K-DOQI is expanding into chronic kidney disease and looking at management of lipid abnormality in chronic kidney disease patients, and the management of hypertension in chronic kidney disease patients[4].

- Evidence-based Practice Center Report on the Management of Acute Sinusitis: This project's work related to antibiotics for sinusitis was integral to the recommendations made in an Evidence-based Practice Center report on the management of acute sinusitis[4].

- Clinical Trials Checklist: A checklist was developed, proposed and refined by the Working Group on Recommendations for the Reporting of Clinical Trials in the Biomedical Literature. It may be used to help improve the reporting of clinical trials by: serving as a framework for authors in submitting reports on clinical trials to journals; being used as a quick reference tool in planning reports to facilitate greater uniformity and completeness; serving as a teaching tool; and offering more effective peer review[5].

- Systematic Reviews by Cochrane Collaboration Collaborative Review Groups: The study potentially addresses Level II through its impact on key change agents in the field of evidence-based medicine and clinical research: "The RTMAS approach… has proven to be well-received." It was presented to key organizations, including the Society for Clinical Trials, the Cochrane Collaboration, and the American Statistical Association. The registries of congestive heart failure clinical trials and hypertension RCTs were contributed to the Cochrane Collaboration Collaborative Review Groups on these topics. Further, the project's various disease- and drug-specific meta-analyses have the potential to influence changes in clinical practice and patient outcomes in areas including treatment of hypertension, HIV/AIDS, and serious infections and in the use of aspirin[6,7].

Impact on Further Research (Level I)

Both the RTMAS model itself, as well as applications of the model, have resulted in significant findings furthering research in a wide range of areas.

Research Tools and Translating Research for Clinical Care

- Meta-analysis: As mentioned above, the RTMAS offers a methodological improvement of meta-analysis through the development of control rate meta-regression. This latter methodological innovation was supported in a well-recognized study on the discrepancies between meta-analysis and a large RCT. Another methodological area explored was the comparison of meta-analysis of large studies versus meta-analysis of small studies; the results of smaller studies are usually compatible with the results of large studies, but discrepancies do occur even when diversity across studies is

considered. Examining sources of heterogeneity between the results of large and smaller trials provides information that may not be conveyed by estimates of average treatment effect. Further, the investigators identified the need to "to re-examine the idea that we should not start a randomized control trial unless sufficient patients are available to avoid reasonable Type I and II errors. Meta-analyses will come to the rescue, provided trials continue to be published at the present rate"[4].

The project addresses Impact Level I in that RTMAS provides a unique and powerful way of visualizing the availability of evidence. The ability to dynamically generate evidence tables by answering a series of questions makes it more efficient to conduct systematic reviews. From a collection of studies of various designs, RTMAS could readily determine the quantity of various levels of evidence available for synthesis and decide whether certain questions can be answered[4].

- Bringing Practice Up to Speed with Research: Comparison of the results of RCTs with clinical expert recommendations reveal that these recommendations are not often synchronized with accumulating evidence. The rational use of therapeutic drugs can be achieved only through the routine use of meta-analysis on high-quality clinical data. This implies that: clinical trials related to the same topic should be viewed as a continuum of experience; meta-analyses should be revised regularly; and a method of regularly updating and reporting findings to individual physicians and investigators should be developed. Proposed steps to pursue include: ensure all clinical trials follow an agreed-upon scientific format; set up a mechanism for registering all clinical trials undertaken; ensure that all registered clinical trials with some outcome data are included in ongoing cumulative meta-analyses; ensure that experts trained both in the specialties of interest and in clinical trials monitor databases of earlier noted recommendations, and agree on information to go to health practitioners; and institute regular physical and knowledge examinations for physicians[6].

Treatment Effectiveness

- ACE Inhibitors and the Progression of Non-diabetic Renal Disease: This study found that Angiotensin-converting enzyme (ACE) inhibitors are more effective than other anti-hypertensive agents in reducing the development of end-stage non-diabetic renal disease, and they do not increase mortality[8].

- Diabetes and Non-diabetic Renal Disease: Pooling the results of 10 studies in two meta-analyses showed that dietary protein restriction effectively slows the progression of both diabetic and non-diabetic renal diseases. These results provide sufficient justification to recommend dietary protein restriction for well-informed patients with chronic renal disease and renal insufficiency[9].

- Antibiotics for Acute Sinusitis: This study found that amoxycillin and folate inhibitors are essentially as effective as more expensive antibiotics for the initial treatment of uncomplicated acute sinusitis. Small differences in efficacy may exist but are unlikely to be clinically important[10].

- HIV Infection: Sulfamethoxazole-trimethoprim is the superior regimen, and low doses could improve tolerance without losing effectiveness for primary prophylaxis. Low doses of dapsone reduce toxic effects, but at the expense of some loss of efficacy. RCTs may underestimate the case-fatality of *Pneumocystis carinii* pneumonia (PCP) in the community where surveillance is less rigorous and diagnosis is often delayed. In addition to preventing PCP, oral regimens were shown to reduce the incidence of toxoplasmosis by an on-treatment analysis[11].

- HIV Infection: For patients with AIDS and expected survival greater than 3.8 years, low dose trimethoprim-sulfamethoxazole (TS) is better than standard dose TS as the first choice agent for

preventing PCP. As patients with AIDS live longer, the routine use of low dose TS will be more than adequate for patients at risk for PCP[12].

- HIV Infection: Mortality rates are halved by combinations involving protease inhibitors or lamivudine, at least in the short term. Switching to or adding didanosine, zalcitabine or stavudine in patients on long-term azidovudine results only in modest risk reductions in disease progression. Changes in therapy can delay disease progression and improve survival in antiretroviral-experienced patients and may be relatively more effective in earlier stages[13].

- Hypertension in the Elderly: One study assessed the effect of anti-hypertensive drug treatment on mortality and morbidity in elderly patients and found that treatment of hypertension in this population produces a significant benefit in total mortality and cardiovascular morbidity and mortality[14].

Public Health and Prevention, and Chronic and Persistent Disease

- Gastrointestinal and Hepatic Diseases: This analysis finds that

> "RCTs are so necessary to evaluate the small incremental changes in the treatment of gastrointestinal and hepatic diseases evolving out of basic research that their future potential is enormous. As the suggested improvements in treatment become smaller, and the use of a no-active-treatment group less ethically acceptable, individual trials will seldom be large enough. Cumulative meta-analyses will be increasingly important as one contributor to the decision needing to be made in a timely fashion as to whether a new treatment is better, worse or the same as the standards. Acute viral hepatitis is so variable in its course that RCTs will be crucial to the proper evaluation of the many new antiviral agents coming out of the laboratory in the next few years."[7]

The study provides suggestions for future research directions, including selective RCTs that focus on specific treatment issues e.g., "the presently popular proximal or selected vagotomy for peptic ulcer is not entirely satisfactory and many attempts at improvement can be expected…Also, the five methods of treating bleeding peptic ulcers through the endoscope need to be compared in well-controlled studies"[7].

2. Computer-based Prospective Drug Utilization Review

Principal Investigator: William M. Tierney, M.D.
Grant Number: HS07763
Project Period: July 1993 – January 1997

Overview

In this project, the investigators incorporated treatment guidelines into a computer-based system in a large institutional setting where all test and prescription ordering must be carried out on computer stations. The randomized controlled trial was conducted to demonstrate the impact of this system on treatment patterns, prescriptions, and patient-centered outcomes, but concluded without positive result. However, the research resulted in significant lessons about:

- Pharmacist work patterns
- The importance of patient-reported symptom information
- Providing computer-based information to physicians so that it is effective in influencing decisionmaking
- Using computerized patient databases to identify patients most in need of intervention.

The project helped to fuel research in other areas such as aging and palliative care. In addition, the project resulted in the adoption of new policies and procedures for the large integrated delivery system in which the study was conducted. This health services delivery system continues to attract attention for its innovations in system-wide and centralized computerization for clinical care.

Impact on Further Research (Level I)

Cost and Economics of Health Care

- Using Electronic Medical Records to Predict Mortality: The purpose of this study was "to identify high-risk patients with heart disease by using data stored in an electronic medical record system to predict six-year mortality." The study found that routine clinical data generated during ordinary clinical encounters and stored in patients' electronic medical records "are capable of predicting mortality among patients with heart disease. This could allow increasingly scarce health care resources to be focused on those at highest mortality risk…. Unlike most previous studies which often included only referred patients, inpatients, or patients with specific types of [disease, treatment or tests], we studied all primary care patients with any evidence (correct or not) of ischemic or congestive heart disease"[15].

Tools for Patient Management

- Computerizing Practice Guidelines: The final report for this project, as well as other project-related publications, highlight some critical lessons about when and how guidelines can most effectively be incorporated into electronic systems from the provider's perspective. The final report describes the necessary conditions for success in computerizing practice guidelines: "The guidelines must be accepted as the local standard of practice by clinicians…computer prompts must be timely and use data that are already available electronically…and computerized guidelines should have measurable

effects." The study also concludes that "changing from a paper-based outpatient prescription system to a microcomputer-based prescription-writing system had profound effects on the types of activities carried out by pharmacists in a hospital-based outpatient pharmacy." The report notes "that delivering real-time drug utilization review (DUR)-based treatment suggestions to outpatient pharmacists had dramatic and salutatory effects on their [pharmacists'] work patterns, increasing opportunities for them to advise patients, consult with providers, and solve problems." With respect to physicians, the report also concludes "that the favorableness of respondents' opinions of the inpatient workstations declined as the level of training increased, a trend that was independent of computer literacy. Increasing computer use by physicians would probably require modification of the educational and socialization process rather than mere reliance on increasing computer literacy"[16].

A related article finds that the Agency for Health Care Policy and Research Heart Failure Guidelines as written cannot be automated in existing electronic medical record systems. The author proposes the following recommendations to improve future versions of these and other clinical practice guidelines: Write all guidelines in a simple "if-then-else" format; make algorithm logic hinge on explicitly defined values of accepted clinical parameters; expect that local translation of guidelines will be necessary and help guide that process; include rules about errors of commission and omission, and don't ignore common co-morbid conditions; balance the costs of diagnosis and treatment (not only in terms of dollars) and consider the likelihood that individual patients will benefit from the guidelines' recommendations; and evaluate the resulting guidelines using real patients and representatives of all those who will use them[17].

- Electronic Guideline-based Treatment Suggestions for Pharmacists: The component of the project that looked at pharmacist work patterns found favorable results: "The results of this study indicate that a dramatic, favorable change in work patterns occurred when pharmacists were provided with an electronic display of guideline-based, patient-specific treatment suggestions. Specifically, pharmacists who had access to treatment suggestions spent less of their time preparing and filling prescriptions and more of their time functioning in an advisory role with patients, physicians, and nurses. Moreover, more of the pharmacists' time was spent solving problems…. The delivery of patient-specific information to pharmacists at the time of dispensing significantly and favorably influenced pharmacist work patterns by increasing opportunities for pharmacists to advise, consult and solve problems"[18].

  Researchers also learned about the barriers pharmacists face in talking with patients, which is important for prospective utilization review. Patients often do not like to interact with pharmacists in the drug store. Further, pharmacists may feel intimidated dealing with physicians, and prefer the less threatening e-mail response system[19].

- The Importance of Symptom Information, and Quality-of life Measures: The DUR project revealed that it may be helpful to provide physicians with additional information for decision making as long as the information is provided in such a way that physicians can apply the information to each patient individually, rather than being forced to categorize patients according to a predetermined definition of disease. The study highlighted the importance of providing physicians with symptom information. Because of this, the researchers have sought to find ways of measuring symptomatic information. They explored ways of assessing clinically important changes associated with quality of life. For example, in one analysis they determined that the standard error of measurement (SEM) closely approximates minimal clinical important difference standards (MCID) for key dimensions of common health-related quality-of-life instruments[20,21].

- Association of Electronic Prescription Records with Compliance: How well does electronic data on prescriptions indicate actual client use? This study examines whether the medication possession ratio

(MPR) values computed from electronic prescription records at an internal medicine practice were associated with medication compliance as reported by patients for the past month using a validated questionnaire. "We conclude that our patients receive sufficient quantities of their medications, but MPR estimates vary widely. Older patients have higher medication availability. Patient responses to selected questions from validated compliance questions are associated with the MPR but differ by disease"[22].

Translating Research to Influence Practice

- Multidimensional Work Sampling Among Pharmacists: This study found a multidimensional work sampling methodology to be a valuable tool in gathering quantitative information about the use of human resources in the delivery of care. The study measured the baseline effect of implementing expert system technology on pharmacist work activities in a large outpatient hospital pharmacy. "Though our baseline data indicate that our pharmacists spend the largest portion of their time working alone…technologic and process changes within the pharmacy should increase opportunities for educating patients about their drugs and consulting with physicians about drug therapy." However, the "quick code" concept must be evaluated further. Codes provide pharmacists with a simple and efficient way to record frequently occurring tasks but the disadvantage is "the risk that pharmacists may gravitate towards these single-entry codes when another 3-entry combination might provide a more accurate description of what they were doing when signaled"[23].

Special Needs of Target Populations

- The Relationship of Race and Age to Primary Care: This study found that "African American patients had fewer outpatient encounters, including primary care visits, emergency department visits, urgent care visits, or pharmacy visits for medication refills. Among males, African Americans had greater emergency department use than white patients." The study also found that younger African Americans have a rate of hospitalization that is three to six times greater than 30- to 35-year olds, with the greatest risk for African American males. The authors conclude that inadequate primary care among inner city adolescents and African Americans with asthma results in costly and morbid hospitalizations[16].

3. Improving Outcomes in Elderly NSAID Users

Principal Investigator: Wayne A. Ray, Ph.D., M.S.
Grant Number: HS07768
Project Period: July 1993 – July 1998

Overview

This project addressed the use of non-steroidal anti-inflammatories (NSAIDs) for osteoarthritis in the elderly population. The project:

- Resulted in published guidelines for the management of osteoarthritis, including preferred drug treatment
- Demonstrated the value of prior authorization in reducing costs for NSAIDs, which have similar efficacy but substantial variation in cost
- Provided guidance in the use of administrative data for research purposes.

Impact on Policies (Level II)

Guidelines for medical management of osteoarthritis of the hip and of the knee were published in *Arthritis and Rheumatism*[24], and in *Archives of Family Medicine*[25].

- Guidelines and Management for Osteoarthritis: The objective of several publications in leading clinical journals was to guide primary care physicians in their approach to patients with osteoarthritis and other disorders causing musculoskeletal pain. In most patients, acetaminophen is preferable to NSAIDs as a first-choice agent because of its lower toxicity. If NSAIDs are used they should be prescribed initially in lower doses. Ibuprofen may be the preferred initial NSAID[24,25].

Impact on Further Research (Level I)

Studies associated with this project identified the significant cost savings that can result from prior authorization features of drug utilization review. It also illustrated the advantages and challenges of using administrative data (e.g., Medicaid data) for research purposes.

Cost and Economics

- The Cost of NSAID Use: This project conducted a cost-identification, retrospective cohort study among Tennessee Medicaid enrollees age 65 years or older that quantified utilization of and costs for medical care for treatment of gastrointestinal disease attributable to non-steroidal anti-inflammatory drug (NSAID) use. NSAID use in elderly patients was associated with substantial excess costs and utilization of medical care for gastrointestinal disorders. The study found that prior-authorization requirements may be highly cost effective with regard to expenditures for NSAIDs, drugs that have very similar efficacy and safety but substantial variation in cost. Expenditures decreased by 53 percent for estimated savings of $12.8 million. The reduction in expenditures resulted from the increased use of generic NSAIDs as well as from a 19 percent decrease in overall NSAID use. There was no concomitant increase in Medicaid expenditures for other medical care. Regular users of non-generic NSAIDs had similar reductions in NSAID expenditures and use, with no increase in expenditures for other medical care[26,27].

Translating Research to Influence Practice

- Use of Administrative Data: "If used properly, administrative databases are a valuable resource for retrospective evaluations….However, the usefulness of these databases can be limited by data quality, the absence of a control group, the lack of data elements that correspond to important outcomes, and problems in accounting for differences in case mix. Including more data elements in administrative databases is an obvious approach to improving their suitability for use in research. Ultimately, greater emphasis needs to be placed on concurrent, planned evaluation of policy and program changes through either randomized controlled trials or prospective cohort analyses"[28].

4. Outcomes Associated with Therapy for Otitis Media

Principal Investigator:	Stephen Berman, M.D.
Grant Number:	HS07816
Project Period:	July 1993 – June 1997

Overview

This study focused on the comparative cost-effectiveness of various antibiotic treatments of otitis media (OM). The investigators used the Colorado State Medicaid database to identify exposure and outcomes. Information related to this work has been used by a variety of organizations in development of policies and educational programs. In addition, the study identified important issues for further research in the area of diagnosis and treatment of the condition.

Impact on Policies (Level II)

Dr. Berman has worked with the Colorado State Department of Health to develop guidelines for Colorado Medicaid. He has also worked with the American Medical Association on a program to evaluate outcomes of otitis media that will be pilot tested in Utah. He has developed an Internet-based interactive Web site to teach current guidelines on the treatment of OM. The site and a companion workshop are sponsored by the American Academy of Pediatrics. Dr. Berman reports working with a number of managed care companies to develop guidelines but impact has not been quantified. Finally, Health Plan Employer Data and Information Set (HEDIS) measures include the use of amoxicillin or trimethoprim/sulfamethoxazole (TMP/SMX) as initial therapy for otitis media[29].

Concern about the development of resistant strains of bacteria have led a number of key public health policy and delivery organizations, such as the Centers for Disease Control, State health departments, and HMOs, to become interested in this research, because otitis media is one of the primary conditions for which antibiotics are prescribed. Researchers involved with the project noted that it is important that public agencies continue to support medical outcomes studies that provide a balanced perspective on such things as the use of limited spectrum versus broad spectrum antibiotics when appropriate, including for otitis media.

Impact on Further Research (Level I)

The findings of this project not only suggest that physicians over-prescribed antibiotics, and often failed to obtain appropriate audiology testing, but also show that the more expensive antibiotics were not associated with better outcomes.

Treatment Effectiveness

- Otitis Media: This study provides information on variations in prescribing patterns by specialty of physician and by treatment setting, as well as cost and outcomes data associated with different drug treatments. Physicians over-prescribed antibiotics, often failed to obtain appropriate audiology testing, and referred one in five of the children who had ventilating tubes prior to the recommended time of 3 months. While there was a wide variation in the selection of antibiotics to treat otitis, the more expensive antibiotics were not associated with better outcomes. Further, differences exist between family physicians and pediatricians in practice patterns related to managing persistent and recurrent otitis media. Family physicians would refer children for ventilating tube surgery three times more often than pediatricians when an asymptomatic middle ear effusion is present. The study also notes that to provide population-based information there is a need to measure the volatility of enrollment in an insured population before calculating rates of utilization[30,31,32].

Cost and Economics

- The Cost of Antibiotics for Treating Otitis Media: Thirty percent of children treated for new-onset otitis media in Colorado's fee-for-service Medicaid program received expensive antibiotic therapy, rather than less costly, equally efficacious products. More expensive antibiotics accounted for approximately 77 percent of the dollars spent for medications to treat otitis media in this population, but were not associated with better outcomes. Per child with otitis, expenditures were higher for males than for females, and higher for Caucasian children compared to Hispanic children or African American children[33].

- The Implications of the Cost of Otitis Media Treatment for Future Vaccination: This analysis developed information about otitis media-related medical expenditures to help evaluate the cost-effectiveness of vaccines being developed for respiratory pathogens that cause otitis media. It used data on medical visits, pharmaceuticals and surgical procedures for 87,057 children 13 years of age or younger who were continuously enrolled in Colorado's fee-for-service Medicaid program during 1992. Findings showed that expenditures for visits are the largest expenditure component, therefore case management guidelines should emphasize reducing unnecessary visits by improving physician training in pneumatic otoscopy and by scheduling follow-up visits for asymptomatic children 3 to 4 weeks after diagnosis rather than 10 to 14 days. Further, because 40 percent of expenditures are incurred between 1 and 3 years of age, vaccines designed to reduce the incidence of otitis media are most likely to be cost-effective if they can be administered before the child's first birthday[34].

Tools for Patient Management

- The Effect of Continuous Medicaid Enrollment and Having an Assigned PCP: This analysis looked at the likelihood of a Medicaid child enrollee having a primary care physician (PCP) if they were continuously enrolled in Medicaid as compared to discontinuously enrolled. It also looked at the relationship between having a primary care physician and emergency room use for otitis media. Children and continuously enrolled in Medicaid throughout the entire year were more than four times as likely to always or sometimes have a PCP compared with children who were discontinuously enrolled. Further, the likelihood of ever using the emergency department for an otitis media-related visit was increased by 26 percent when a child sometimes had a PCP, and increased by 50 percent when a child never had a PCP. Finally, the likelihood of ever filling an antibiotic for otitis media was reduced by 23 percent and 34 percent respectively when a child sometimes or never had a PCP compared with always having a PCP[35].

5. Outcomes of Compliance with an AMI Guideline

Principal Investigator: Stephen B. Soumerai, M.D.
Grant Number: HS07631
Project Period: December 1993 – November 1996

Overview

This project confirmed that beta-blocker therapy reduces mortality and cardiac hospitalizations of myocardial infarction (MI) patients over the age of 75, a group accounting for 80 percent of all heart attack deaths. The project resulted in the first of several peer-reviewed articles that provided real-world confirmation of clinical trial evidence for the benefit of these agents. It has contributed to changes in clinical practice and outcomes, as well as the implementation of related policies and procedures among key national organizations.

Impact on Clinical Practice and Outcomes (Levels III & IV)

There is evidence that both clinical practice and outcomes have changed as a result of this and related studies[29].

- A followup study of opinion leaders found that an intervention to improve quality of care for heart attack patients increased appropriate use of beta-blockers and aspirin by 31 percent.[36]

- The Cooperative Cardiovascular Project (CCP) included the appropriate use of beta-blockers among its efforts to improve care of Medicare heart attack patients. Aspirin use, use of re-perfusion, and counseling for smoking cessation were also targeted. In its four-State pilot program, prescription of beta-blockers at discharge improved from 47 to 68 percent. Absolute mortality was 0.9 percent less in pilot States than in non-pilot States during the followup period[37]. The Health Care Financing Administration (HCFA) estimates that 200 deaths were prevented. If the national CCP effort produces comparable results, about 3,000 fewer Medicare patients hospitalized with heart attacks will die.

Impact on Policies (Level II)

This work is associated with the adoption of policies and programs by key change agents including the National Committee for Quality Assurance (NCQA), the American Medical Association (AMA), and major health maintenance organizations (HMOs)[29].

- Based on the result of this study, NCQA amended its Health Plan Employer Data and Information Set (HEDIS) measures by requesting all HMOs nationwide report beta-blocker use among this age population after diagnosis of MI.

- United HealthCare has included this measure in a national profiling project of its 262,000 physicians.

- The AMA has identified appropriate use of this medication as an achievable aim for improved quality of care for older Americans.

- The AMA, in conjunction with the American Academy of Family Physicians, the American College of Cardiology, and the American College of Physicians-American Society of Internal Medicine, issued a Quality Care Alert regarding the benefits and underuse of beta-blockers post MI.

Impact on Further Research (Level I)

This study was covered extensively in the lay press, including AP, AP Worldstream, UPI and the *Boston Globe*. A follow-up study demonstrated that beta-blockers are underutilized in frail and disabled elderly patients and that the benefits of beta-blockers extend to this population. The Soumerai study was also part of the basis for the General Accounting Office report, "Heart Attack Survivors Treated by Cardiologists More Likely to Take Recommended Drugs"[29]. In addition, publications in leading journals, including *The New England Journal of Medicine* and the *Journal of the American Medical Association*, described the various findings of this research.

Treatment Effectiveness

- Calcium Channel Blockers and AMI: A retrospective cohort study which used linked New Jersey Medicare and Medicaid drug claims data found that the use of long-acting dihydropyridine calcium channel blockers after acute myocardial infarction (AMI) was associated with substantially lower rates of re-hospitalization and death compared with use of their short-acting counterparts[38].

- Beta-blockers and AMI: This study found that only 21 percent of eligible New Jersey Medicare beneficiaries who survived an acute myocardial infarction (AMI) receive beta blocker therapy following the heart attack. Calcium channel blockers were used almost three times as often despite a lack of evidence that they decreased mortality. Those patients on beta-blockers were re-hospitalized 22 percent less often and their mortality rate was 43 percent lower than non-recipients. Eligible patients receiving calcium channel blockers instead of beta-blockers doubled their risk of death[39].

Special Needs of Target Populations

- Beta-blockers and Elderly That Have Had AMI: Although the beneficial effects of beta-blockers post-MI were found to extend to the elderly (not normally included in RCTs), rates of use were very low in a study of New Jersey Medicare enrollees[39].

6. Outcomes of Pharmaceutical Therapy for HIV Disease

Principal Investigator: Richard D. Moore, M.D.
Grant Number: HS07809
Project Period: February 1993 – January 1998

Overview

This project served the multiple purposes of: 1) developing a comprehensive longitudinal database of human immunodeficiency virus (HIV)-infected individuals cared for in an urban setting; 2) examining the effectiveness of antiretroviral and antimicrobial therapies in preventing progression of HIV disease and its complications; 3) determining the association of surrogate laboratory markers with clinical outcomes; 4) delineating the frequency and consistency of prescription drug use; and 5) identifying the sociodemographic and clinical patient characteristics associated with consistent use of and response to drug therapy.

The project has contributed to significant changes in treatment for HIV/AIDS patients. Further, project-related data and information have been used by a variety of clinical, policy, and regulatory organizations. The project has not only furthered research in the field through a broad range of studies, but it has established a powerful data resource to fuel ongoing research efforts.

Impact on Clinical Practice and Outcomes (Levels III & IV)

The majority of the research associated with this project focused on clinical outcomes associated with different drug and other treatment regimens. A study conducted within this project, one of three studies in the field that were published around the same time, made the important finding that "combination therapy is superior to monotherapy with regard to measures of viral load and immune suppression"[40]. This finding has resulted in major changes in treatment of the disease.

The dissemination of HIV/AIDS-related research, including research conducted under this project, has been amplified through the efforts of a variety of clinical and policy organizations (see policies below). There has been rapid change in treatment protocols, and clinicians in the field may anticipate and monitor developments more regularly than in many other specialties. For this reason it may be particularly difficult to associate changes in treatment and outcome with specific research efforts. Nevertheless, this project has addressed many key questions related to treatment issues for HIV/AIDS. Some examples are provided below.

- *Pneumocystis Carnii* Pneumonia (PCP): An assessment of the long-term safety of adjunctive corticosteroids in the treatment of PCP found that adjunctive corticosteroids do not increase mortality or the risk of most common HIV-associated complications[41].

- Bacterial Infection and AIDS: This study provides evidence that neutropenia raises the risk of bacterial infections in patients with advanced immunodeficiency from HIV infection. "Neutropenia appears to be an independent risk factor for acquiring bacterial infection in patients with HIV infection." The study cites the need to assess the cost-effectiveness of interventions to prevent neutropenia in advanced HIV disease[42]. Subsequent findings suggested that the associated risks were not great, suggesting that available high cost drug treatment was not necessarily optimal[43].

- Opportunistic Disease and HIV Infection: The study determined that the development of opportunistic disease is a risk factor for survival that is independent of cell count (CD4) and possibly viral load. This underscores the need for continued prophylaxis for opportunistic illness even if the CD4 count improves on new antiretroviral therapies. The study concludes that "these data support the hypothesis that opportunistic diseases enhance HIV pathogenesis and further underscore the importance of prophylaxis"[44].

Impact on Policies (Level II)

Project-related data and findings have been presented and used by a wide variety of Federal, State, private and voluntary organizations, including the Food and Drug Administration (FDA), The Health Resources and Services Administration's HIV/AIDS Bureau (HRSA's HAB), the Health Care Financing Administration (HCFA), Maryland's Department of Health and Mental Hygiene, the Infectious Disease Society of America, the HIV Quality Care Association, and several pharmaceutical companies. Project-related publications have been among those reviewed by several groups involved in developing treatment guides for HIV/AIDS with respect to anti-retroviral use and the prevention and treatment of opportunistic disease[43,45].

The kinds of policies that project-related data have helped to address include those related to drug toxicity (FDA), those related to financing policy (Maryland Medicaid), those related to service delivery (HRSA and HAB), and those related to guideline development. For example:

- Pharmaceutical companies have followed project results. Findings by the project related to neutropenia (low white cell count) prevent over-utilization of a high cost drug.

- The Maryland Department of Health and Mental Hygiene reviewed project-related data in the development of its AIDS capitation program in 1996-97.

- HRSA followed data on cost implications related to the use of antiretroviral medication.

Impact on Further Research (Level I)

This project has a had similarly broad impact on research in multiple areas as described below.

Treatment Effectiveness

- HIV and Drug Therapy Adverse Events: This study found that adverse effects from antiretroviral drugs and PCP prophylaxis that interrupt therapy are relatively common, although serious events requiring hospitalization are rare; adverse event rates increase progressively with decline of CD4+ count; gender and race modify risk of adverse events for some drugs[46].

- Zidovudine (ZDV) Regimen for HIV: This study found no difference between ZDV-experienced and ZDV-naïve patients. Results suggest that earlier clinical studies demonstrating a diminished response to d4T in ZDV-experienced patients may not generalize to the current clinical practice setting. In contrast to previous trials, most patients in this study also received a protease inhibitor. The debate over sequencing of nucleoside reverse transcriptase inhibitors (NRTIs) may be less relevant when they are combined with protease inhibitors. Longer term followup data from ongoing clinical trials will help to clarify this issue further[47].

- Natural History of Opportunistic Disease in HIV Patients: This study documented trends in HIV disease important for resource and treatment planning. In patients studied, incidences of secondary PCP, cryptococcal meningitis and herpes zoster (all frequently complications of HIV infection) declined in the previous 5 years and occurred at more advanced immunosuppression than in the past. The study finds that continued efforts are needed to develop effective strategies for preventing opportunistic disease in very advanced HIV infection[46].

Cost and Economics

- Protease Inhibitors and the Cost of HIV: This study found that although protease inhibitor-containing antiretroviral regimens were being used by only about half of Maryland's Medicaid-insured patients with HIV infection, when they were used there were significantly lower hospital inpatient and community care costs, as well as lower costs associated with the treatment of opportunistic diseases. Even with the concurrent increase in their pharmacy costs, total health care costs were stable or slightly lower for these patients[48]. The costs savings benefit was primarily associated with patients with the most advanced disease[43].

- Incorporation of Cost in Project Database: The database associated with this project allows researchers to quantify the cost of clinical care provision for HIV infection. About 60 percent of patients in the database are insured by Medical Assistance. For these patients the project linked claims and clinical data which are extremely detailed and include both charges and payments for all individual inpatient, outpatient, home health, pharmacy and long-term care resources. "We have quantified how costs increase with advancing HIV disease. Among those with relatively early HIV disease, the cost is approximately $1,000 per month, but rises to $2,500 per month when CD4 counts decline below 50 cells/mm and becomes as high as $4,000 per month in the last six months before death. We have also modeled the cost-effectiveness of combination antiretroviral therapy with a protease inhibitor, finding a remarkably low rate of $10K per year of life saved when these drugs are used compared to monotherapy"[45].

- Combination Therapy for HIV Infection: This study found that combination drug therapy, while costlier from a pharmaceutical perspective, yields increased lifespan of three years. Pharmaceutical costs are likely to be offset by savings in other health costs. Also, combination therapy is superior to monotherapy with regard to measures of viral load and immune suppression. The study calls for subsequent studies with longer term longitudinal clinical followup. It also references a change in the New Zealand government's drug subsidization agency's policy to approve funding for antiretroviral combination therapy[40].

- Cost to Medicaid of Immunosuppression in HIV: This study sought to determine the relative costs that a Medicaid program will likely incur in providing payment for an HIV-infected patient population. The average costs to Medicaid for treating this urban clinic's poor patients increase more than twofold as CD4+ count declines from greater than 500 cells/mm^3 to less than 50 cells/mm^3. The use of inpatient care has declined from as high as 80 percent of overall costs since estimates five years ago. "These data should provide a useful comparative benchmark of the cost of health care for Medicaid-insured HIV-infected patients as we enter a new era of treatment using combination antiretroviral therapies"[49].

- Trends in Inpatient Costs for HIV: This study evaluates the evolution of patterns of inpatient hospital care in Maryland for HIV-infected individuals, and compares Maryland data with those of a national survey. It found that both the number and proportion of hospital discharges increased almost threefold between 1988 and 1992. It also noted the changing demography of HIV (an increasing

proportion of hospitalized women). The study found significant decreases in lengths of stay and financial charges that are independent of demographic factors and clinical stage of disease[50].

- Prophylaxis and Resource Use in PCP: Patients who developed PCP despite prophylaxis had a better outcome and used fewer resources than patients not receiving preventive therapy. The study emphasizes the impact of PCP prophylaxis on the morbidity, mortality and economics of HIV health care. It found that, although the choice of prophylactic regimens is an important consideration, access to primary health care, early detection of HIV infection, and compliance with appropriate preventive therapy are ultimately as important or more important in decreasing morbidity, mortality, and costs associated with PCP and AIDS[51].

Translating Research to Influence Practice

- HIV Infection and Dependency: This study corroborated findings that patients with dependencies in activities of daily living (ADLs) face higher mortality rates. The study indicated that further investigation is needed to determine how dependencies in ADLs and instrumental activities of daily living (IADLs) relate to survival: "Knowledge of the type of dependencies a patient has may assist in targeting interventions to address specific needs…. What is most interesting about our findings is the extent to which the dependencies reported in our population are those essential to independent living"[52].

Special Needs of Target Populations

- Racial Differences in Drug Therapy for HIV: This study found racial disparities in the receipt of medication to prevent PCP among patients with HIV disease. It found that blacks were significantly less likely than non-Hispanic Caucasian Americans to receive antiretroviral drug therapy and prophylactic drug therapy against PCP[53].

- Factors Associated with HIV Disease: Among patients with HIV infection who received medical care from a single urban center, there were no differences in disease progression or survival associated with gender, race, injection drug use, or socioeconomic status. The study determined that clinical outcomes as measured by progression to AIDS and survival are similar in: a) whites and non-whites; and b) those of higher versus lower socioeconomic status if access to and receipt of care for HIV infection is similar. The study contradicts previous studies' findings of differences in disease progression based on demographics. Data suggest that *access* to medical care is a more important predictor of survival than differences between the sexes, racial or ethnic groups, or other groups (e.g., users/nonusers of injection drugs). "This was an important finding since some earlier studies had suggested that there were differences in clinical outcome by gender, by race, and by drug use behavior. Importantly, our analysis was able to adjust for a large number of clinical, demographic and economic variables"[54].

Public Health and Prevention, Chronic and Persistent Diseases and Conditions

- Access to Care for HIV Patients: The goal of this study was to identify demographic, behavioral, and clinical features that correlate to failure to suppress viral load outside of clinical trial setting. The study found that unselected patients who begin highly active antiretroviral therapy (HAART) in a

clinical setting achieve viral suppression substantially less frequently than do patients in controlled clinical trials. Missed clinic visits were the most important risk factor for failure to suppress HIV-1 RNA levels. Women and patients taking ritonavir were at increased risk for adverse drug interactions. Studies are needed to identify interventions that maximize the performance of HAART in inner-city clinics. Association between increased age and higher rates of viral suppression must be confirmed and its underlying factors must be further delineated in future studies. Differences between men and women in body mass, metabolic rates or hormonal effects may play a role and warrant study in future investigations of new antiretroviral agents. Future studies of antiretroviral agents should address sex differences of HAART in real-world practice, and should address sex differences in pharmacodynamics and adverse drug reactions[55].

- HIV in Injection Drug Users (IDUs): The goal of this study was to assess antiretroviral therapy (ART) in HIV-infected IDUs. The study findings support anecdotal evidence suggesting that HIV+ IDUs are not receiving optimal care, and make recommendations for expanding simultaneous treatment services for HIV infection and substance abuse (and other interventions, e.g., housing) to enhance response to ART. "If some of the identified barriers to care can be resolved, appropriate use of combination therapy could be expanded"[56].

7. Patient Outcomes Associated with Antidepressant Drugs

Principal Investigator:	Judith M. Garrard, Ph.D.
Grant Number:	HS07772
Project Period:	March 1993 – February 1998

Overview

This study looked at the association between different indicators for depression among community-dwelling elderly who were members of a managed care plan (Health Partners) in Minnesota between 1992 and 1994. Building on prior findings in the field about the under-detection of depression, this project yielded important insights into the diagnosis of depression among the elderly. In addition to contributing to further research in the field, the results of the project were used within the participating managed care plan to generate discussion among its clinicians about diagnosis and treatment patterns and potential obstacles to diagnosis among the elderly members of the plan[57].

Impact on Policies (Level II)

Information resulting from this project was shared with Health Partners' geriatric providers, and focus groups were conducted to explore issues related to diagnosis and treatment. The focus groups revealed interesting observations related to the study's findings that persons with "minor depression" experience significantly lower quality of life measures compared to those who are asymptomatic. Providers reported they are reluctant to share a minor diagnosis with the patient or put it in the medical record, because they feel the patient will feel stigmatized; often they will not conduct systematic testing, but will talk to the patient instead; words such as "depression" are considered to be particularly negative and "loaded" by the elderly and therefore physicians find it hard to communicate about this diagnosis.

Health plan staff reported a generally increased awareness among clinical staff about diagnosis and treatment of depression among the elderly. Plan administrators found it valuable to learn that minor depression has significant cost implications. This study also provided support for a related initiative to staff primary care clinics with mental health professionals. It also generated discussion about the most effective tools for patient screening.

In addition, Health Partner staff working with the Women's Health Task Force of the American Association of Health Plans, are involved in a related initiative to look at what health plans are doing programmatically related to the detection and treatment of depression.

Impact on Further Research (Level I)

The findings of studies associated with this project resulted in important information about different approaches to detecting depression, and about key issues in the diagnosis of depression in the elderly that could be used to influence practice.

Tools for Patient Management

- The Significance of Minor Depression: The project found that minor depression may play a stronger role in the health-related quality of life of community-dwelling elderly people than previously

suspected. Controlling for other factors, elderly people living in the community who reported symptoms of either minor depression or serious depression had significantly worse health-related quality of life than those who were asymptomatic. Differences between the asymptomatic and minor depression groups were statistically significant on all eight health-related quality-of-life measures. In contrast, mean differences between those with minor versus serious depression were statistically significant on only three of the eight measures[58].

- Self-report versus Clinical Detection: This study found that: a) approximately half of the community-based elderly people with self-reported feelings of depression were not detected as possibly depressed by their health providers based on documentation in the health care records; b) physician detection of depression appears to increase with the severity of patients' self-reported indications of depression; c) elderly women tend to have higher rates of clinical detection of depression than men; d) the two groups at highest risk for under-detection of depression were men between the ages of 65-74 and men 85 years and older; and e) despite the increasing rates of clinical detection of depression by severity of the test score, approximately one fifth of women and over a third of the men with the most severe indications of self-reported depression were not recognized as possibly depressed by their physicians[59].

- The Effect of Depression on Self-rated Physical Health: This study tested whether the association between self-rated physical health and clinically defined illness differs for persons who are not depressed compared with persons with minor or serious depression. Self-rated physical health was associated with both minor and serious depression, independent of clinically defined illness; minor depression was no longer significant when self-reported pain and physical function were added to the model. A significant negative correlation between self-rated physical health and clinically defined illness was observed for minor and no depression, but no correlation was seen for serious depression. These results emphasize that for persons with serious depression, self-rated health provides a less accurate picture of clinically defined illness at both ends of the spectrum. Also, a diagnosis of minor depression should not forestall investigation of inconsistencies between patient report and clinical evidence[60].

8. Patient Outcomes with Antibiotic Therapy for Lyme Disease

Principal Investigator:	G. Thomas Strickland, M.D., Ph.D.
Grant Number:	HS07813
Project Period:	March 1993 – February 1998

Overview

By prospectively following up with patients reported to the Maryland Lyme Disease Registry, the project was designed to address the comparative effectiveness of different antibiotic regimens in treating Lyme disease (LD). Delmarva Health Plan, which participated as a partner in the research, has used information from the study in educating health plan physicians about over-diagnosis and over-treatment of the disease. The project raised important questions about what definition of LD should be used in estimating impact on prevention and public health budgets, in contrast to definitions that may be appropriate for surveillance purposes. This information was of considerable interest to pharmaceutical companies marketing vaccines for the disease.

The project is of interest beyond the particular disease it addresses because it is a case example of a condition where clinical guidelines for testing and treatment conflict significantly with the fears and desires of patients, resulting in pressure on physicians to over-diagnose and over-treat, with potentially significant implications for excess costs.

Finally, although not yet published, the research has found significantly greater long-term morbidity among adults that have had LD compared with a matched comparison of those that did not have the disease. Analysis of project results is still in progress[61].

Impact on Policies and Clinical Practice (Levels II and III)

Delmarva Health Plan has experienced declines in the use of expensive antibiotics and overtreatment of tick bites by health plan physicians during the period in which it provided educational materials and presentations to health plan physicians about the results of this research. Education consisted of announcements in the Delmarva Health Plan Provider Bulletin, and presentations (e.g., through Grand Rounds) at local hospitals by project researchers. The plan's May 2000 Provider Bulletin included a Lyme Disease Update, which among other things reported that:

> Management of tick bites has proven a source of confusion. In general, only a few percent of tick bites will result in infection in endemic areas, and there is ample evidence that prolonged attachment (more than a day at least) is necessary for infection, although rare exceptions exist. The recommendation for tick bite management is generally to carefully observe for signs and symptoms of infection although it may be prudent to consider prophylactic antibiotic therapy for those individuals in endemic areas who have had prolonged tick attachment. *There is almost no place for serologic testing of patients with tick bites without symptoms of Lyme disease* (emphasis added)[62,63].

Impact on Further Research (Level I)

Treatment Effectiveness

- Antibiotic Treatment of Lyme Disease (LD): This report provides an analysis of antibiotic therapy for LD in Maryland. It found that patients presenting with erythema migrans (EM) alone were more likely to receive one course of antibiotic than those with extracutaneous manifestations, with or without EM. It also established average length of treatment with different antibiotics. The study further found that, although "almost half of the patients did not meet the national surveillance case definition for LD, these patients were diagnosed and treated for LD by their primary care physicians." The article suggests including such cases in calculations of total cost of LD and cost-effectiveness of new LD vaccines[64].

  Another report from the study establishes that oral doxycycline, tetracycline and amoxicillin were the most frequently prescribed antibiotics in LD treatment. Most (71 percent) therapeutic courses lasted 2-3 weeks, and there is evidence of over-diagnosis of LD. This report notes that physicians are generally following choices, dosages and duration most frequently recommended in the literature. Given this and the over-diagnosis/treatment of patients with Lyme disease-like symptoms, this study "shows that efforts to educate physicians should be directed more towards the diagnosis rather than the treatment of Lyme disease"[64].

  A related discussion of the study suggests the need to provide practicing physicians in the State with guidelines for ordering screening serologic tests and encouragement to obtain Western blot confirmation before treating serologically positive patients with atypical findings of LD[64]. The most important component of the project, the outcomes of patients with Lyme disease as influenced by their initial symptoms, antibiotic regimens and a host of other independent variables, has not been published yet[65].

Cost and Economics

- Antibiotic Therapy for Lyme Disease: The objective of the study was to assess the pattern of use of serologic testing and antibiotic therapy for tick bites and LD, and associated charges for management in the endemic area. Expert recommendations discourage the routine use of antibiotic therapy for prophylaxis of LD following tick bites, but the extent to which physicians in endemic areas have adopted these recommendations is not known. The study found that most patients consulting physicians for tick bites received prophylactic antibiotic therapy of unproven efficacy and underwent unnecessary, costly serologic testing. Despite almost universal use in this study, serologic testing for LD did not appear to influence treatment of patients diagnosed as having LD[66].

- Serologic Testing for Lyme Disease: This study analyzed testing on patients with Lyme disease (LD) reported to Maryland's Department of Health and Mental Hygiene from 1992 through 1995. The most commonly performed test, an enzyme immunoassay (EIA), lacks sensitivity in detecting (certain) antibodies in the earliest stages of the disease, and costs about $72 per test. The use of the Western immunoblot (WB) test, which costs about $106, constitutes 10 percent of the LD serologic tests performed on Maryland residents. The study found that the use of serologic tests in managing patients suspected of having LD or tick bite exposures in Maryland is increasing in both number and cost. "The 30,000 tests for LD performed annually on Maryland residents at a cost of over $2 million in direct medical costs must be added to the public health burden of LD in this State." Data from this study and other sources show that physicians in Maryland are using LD serology more often in patient management. They often used EIAs to follow patients after treatment, an inappropriate practice that provides misleading information, increases the proportion of positive EIAs, and increases the overall cost of testing for LD. Also, some physicians have used EIAs and WBs

simultaneously while screening for LD. This increases the cost and reduces the proportion of positive WBs. Neither of these practices is considered a cost-effective use of serology in managing LD. The researchers found that, "it might be cost-effective to base clinical management decisions on results of EIA for patients who have characteristic clinical findings of LD (e.g., facial palsy, arthritis of the knee in children), using the second test only in patients with positive or equivocal EIA results and less typical manifestations of LD." Further, "…we join the California investigators [the only other study of economic impact of LD serology] in urging primary care physicians to resist using LD serology in this inefficient manner"[67].

Special Needs of Target Populations

- Rates of Lyme Disease Among African Americans: This study found that African Americans are not less likely to get Lyme disease than Caucasians. The rash (and thus the acute infection) is less frequently recognized in dark-skinned individuals. African Americans therefore have a higher risk for chronic manifestations of Lyme disease, e.g., Lyme arthritis[68].

9. Pharmaceutical Care and Pediatric Asthma Outcomes

Principal Investigator: Andreas S. Stergachis, Ph.D.
Grant Number: HS07834
Project Period: March 1993 – February 1997

Overview

This was a community-based, randomized controlled trial to demonstrate the effectiveness and cost-effectiveness of a pharmacist intervention program to enhance the outcomes of asthma care in children. While the final result failed to support the program's effectiveness, the study's findings provide information relevant to efforts to develop reimbursement to pharmacists for cognitive services.

Impact on Further Research (Level I)

Translating Research to Influence Practice

- Patient Counseling by Pharmacists: This pharmaceutical care evaluation of asthma in kids (PEAK) found no significant effect on health or health systems use outcomes of those using a pharmaceutical care intervention designed to be offered by pharmacists within the context of community-based practice. However, the study identified factors that should be addressed in future research in this area. For example, the report notes that the intervention may not have been powerful enough to significantly affect pharmacists' behaviors, the study measures may not have been sensitive to the assessment of the effects of interventions, and/or the pharmacists may have had low compliance with the study protocol due, in part, to patient- and practice-related barriers.

  In addition, study findings could have impact on the development of programs involving reimbursement to pharmacists for cognitive services under Medicaid, Medicare or other drug utilization review programs. Interviews with pharmacists identified the following patient- and pharmacy-centered barriers to the provision of pharmaceutical care.

  Patient-related barriers included:

  - Difficulty in scheduling appointments with patients was the main barrier.
  - Patients enrolled in the study were typically in school during the period of the day when pharmacists had time for appointments.
  - Patients frequently did not have access to transportation, or parents were unable to bring patients because of work schedule.
  - Patients and parents were skeptical of, or unfamiliar with pharmacists' role (relative to physicians).

  Pharmacy-related barriers included:

  - Prescription volume and lack of time to perform intervention and
  - Difficulty staffing and scheduling pharmacists to allow those participating in the PEAK program to prepare for and perform the intervention.

  Better management support and intervention was considered necessary to accommodate these factors[69].

10. Pharmaceutical Care: The Patient Role

Principal Investigator:	Betty A. Chewning, Ph.D., M.S.
Grant Number:	HS07773
Project Period:	March 1993 – February 1998

Overview

The purpose of this project was to look at the patient's perspective on the process and outcomes of arthritis drug regimen decisions. It considered: a) how patients' perceptions about quality of life, symptoms and medication benefits affect adherence to prescribed treatments and over-the counter self-care use; b) the effects of patient medication-taking behaviors on arthritis outcomes, including quality of life, clinical symptoms and health care utilization; and c) how patients' perceptions of quality of life vary with their clinical symptoms.

The project has revealed interesting findings related to the patient's role in decisionmaking and in providing information useful to ongoing treatment planning. The research suggests that the patient's role may be particularly important for diseases such as arthritis where patient-reported symptoms are a primary determinant of regimen (as opposed to blood sampling or blood pressure tests for diseases such as diabetes or hypertension). Analysis of project results are not yet complete and additional information about this finding as well as others will be forthcoming.

Impact on Further Research (Level I)

Information generated by this project has been presented at numerous meetings of national and international organizations, including events sponsored by the American Association of Pharmaceutical Scientists, the American Pharmaceutical Association, the American College of Clinical Pharmacy, the American Association of Colleges of Pharmacy, and the American Public Health Association.

Tools for Patient Management

- Comparison of Two Quality-of-life Measures for Arthritis: The study found that the two health quality-of-life measures reviewed add important information to that gathered by traditional clinical status measures. Some of this information unique to arthritis would be lost if the shorter, more widely used Medical Outcomes Study Shortform (SF-36) were administered instead of the Arthritis Impact Measurement Scale (AIMS2) subscales, as this sacrifices the chance for comparison across health/disease conditions[70].

- Role of Patient in Medication Management: The study found a high level of prescription and over-the-counter (OTC) medications taken as needed (PRN, according to patient judgement). "Approximately 37 percent of the rheumatoid arthritis patients and 43 percent of the osteoarthritis patients had a regiment that included a prescription or OTC drug to be taken PR….While health care is conceptualized typically as prescribed by a provider or as self-care, these data help to describe a more complex medication management role of patients. Especially for patients who have symptoms (such as pain) which they can monitor personally, PRN medication judgements become part of their daily care. The PRN category is interesting not only for what it implies about patient arthritis medication management roles, but equally important for what it suggests about physicians' roles in

relation to patients, acknowledging that patients are partners in deciding when certain medications are needed"[71].

In addition, the study found a high degree of change in medication regimens, including re-calibration of doses, changes in brand, and changes in drug. "Nearly half of the rheumatoid arthritis patients had their regimens change along the four dimensions across one year…more than half of the osteoarthritis patients showed changes in their regimens." This, along with the importance of patient-reported symptoms and patient assessment, suggests the need for paying greater attention to preparing patients as partners in decisionmaking. This also suggests a focus on developing tools and approaches to prepare, facilitate, and cue patients to provide the right information and data. The development of new techniques to facilitate patient documentation of drug side effects and other symptoms can be important to other diseases as well, such as cancer[71,72].

- Influences on Patient Choice of Drugs: The study found that side-effects are one of the most important factors influencing patient choice of drugs, while out-of-pocket costs influence adherence to a drug regimen. This indicates a need for better information about toxicity and side-effects on the one hand (which the study will also look at), and on the other hand, raises issues related to the importance of drug coverage[72].

11. Use of Record Linkage to Study Outcomes of Drug Therapy

Principal Investigator:	Richard Platt, M.D., M.S.
Grant Number:	HS07821
Project Period:	August 1993 – July 1998

Overview

By use of a new microelectronic technology, the project aimed to achieve four objectives with reference to hypertension medication compliance: developing a standard definition of adherence; validating other alternative methods of adherence assessment such as patient reports, pharmacy dispensing records or pill counts; evaluating the relationship between adherence and a target medical condition (blood pressure); and examining the predictors of adherence.

Impact on Further Research (Level I)

This study has led to AHRQ funded research in other related areas.

Tools for Patient Management

- Monitoring Patient Compliance with Drug Regimens: The study found that there is considerable overlap of monitored adherence across levels of patient-reported adherence. Nonetheless, patient-reported forgetfulness of doses was qualitatively informative and predictive of adherence to dose number and timing. Patient-reported non-adherence when coupled with measures of drug effect or levels may be useful in guiding therapeutic decisions.

  Factors associated with adherence included: younger age, increased number of children in household, lower vitality on the Medical Outcomes Study Short Form (SF-36), tendency to forget, and side effects of medication. To varying degrees these factors may be modifiable or addressable. Adherence is lower for timing than for number of doses; where dose timing is important, electronic monitoring should be considered. The relationship between adherence and outcomes (e.g., blood pressure) needs to factor in minimum thresholds for effect, and long- versus short-acting nature of treatment[73,74].

12. A Health Status Measure to Evaluate Drug Therapy for PCP

Principal Investigator:	Albert W. Wu, M.D., M.P.H.
Grant Number:	HS07824
Project Period:	September 1993 – August 1995

Overview

As the first study in developing and using a health status measure in a clinical trial of an AIDS-related complication, this project was designed to demonstrate the reliability, validity, and usefulness of such a brief health status measure for acute *Pneumocystis carinii* pneumonia (PCP). Unlike traditional methodology studies in the field, this project added two new dimensions, namely, responsiveness and clinical utility, in the evaluation of health status measurement. By doing so, the project has enhanced the traditional validation approach that was based exclusively on reliability and validity of the instrument and set a new model for future studies in the field.

Impact on Further Research (Level I)

In addition to the application of new dimensions to health status measurement for this AIDS-related complication, this project influenced related publications that provide guidelines to researchers in understanding and selecting among quality-of-life measurement tools for different research purposes.

Treatment Effectiveness

- Differentiating Among Treatment Regimens Using Quality-of-life Measures: In one study that compared the tolerability and efficacy of three oral regimens for the treatment of patients with AIDS and *Pneumocystis carinii* pneumonia, it was found that the rates of dose-limiting toxicity, therapeutic failure, and survival did not differ across the three drugs. With respect to quality of life, at day seven the median increase in patient-reported health status scores was greatest for patients assigned to receive clindamycin-primaquine. This difference was particularly marked in comparison with patients receiving trimethoprim-sulfamethoxazole. By day 21, health status scores in all patients had improved further, and differences among the groups were less evident[75].

- Incorporating Quality of Life in Treatment Decisions for HIV/AIDS: This study included a descriptive assessment of different quality of life instruments to serve as a reference for investigators selecting an instrument for use. "Medical Outcomes Study (MOS) data have added importantly to understanding how treatments affect health. In some studies the Quality of Life (QOL) findings were discordant with the results suggested by other outcomes variables (e.g., cytomegalovirus retinitis retreatment trial: combination vs. monotherapy). Application of the measures results in a more comprehensive definition of the efficacy of treatment and a tangible description of the impact on patients' health. MOS measures have increased our understanding of how other factors affect the health of patients with HIV"[76].

13. Cognitive Impairment and Medication Appropriateness

Principal Investigator: Joseph T. Hanlon, Pharm.D.
Grant Number: HS07819
Project Period: March 1993 – May 1995

Overview

Built on a series of secondary data analyses using the longitudinal data from a representative sample of community-dwelling elderly, this project evaluated the relationship between cognitive status and medication use. Focused on two classes of commonly used medications in the elderly, the study demonstrated, in a dose-response fashion, that current benzodiazepine use is associated with memory impairment while nonsteroidal antiinflammatory drug (NSAID) use is not. The study also provided nonsteroidal antiinflammatory drug some clues to the pattern of medication use after the elderly develop cognitive impairment. In general, those elderly were less likely to use over-the-counter medications and analgesics than cognitively intact community-dwelling elderly.

Impact on Further Research (Level I)

This project provided information that can inform treatment planning for the elderly. In addition, it addressed issues that can be incorporated into educational programs for clinicians regarding the special needs of the elderly who are cognitively impaired, and those who are African American.

Special Needs of Target Populations

- Prescription Drug Use by Elderly Blacks: This longitudinal study of prescription and nonprescription drug use among community-residing elderly showed that the use of prescription drugs increases significantly with age. The study identified characteristics that predict change in the use of prescription and nonprescription drugs over a period of three years. Blacks were less likely than whites to become prescription drug users or to increase the number of prescription drugs used. This may reflect poorer communication between physicians (typically white) and their black patients, greater reliance of black patients on non-traditional methods (e.g., folk remedies, faith healing), or voluntary noncompliance, or, it may represent under-treatment or inappropriate treatment of disease. While cross-sectional studies consistently indicate that prescription drug use increases with age, the present data suggest that while age is an important predictor of use and increase in use, it is not as important as race or health status.

Public Health and Prevention, Chronic and Persistent Diseases and Conditions

- Cognitive Impairment in the Elderly: This study sought to determine whether medication use differs by cognitive status among community-dwelling elderly. This is of concern because medication is a common risk factor for cognitive impairment, and cognitive individuals may be over- or under-medicated, with each possibility having potential adverse outcomes. Given these issues and the growing number of drugs under investigation for treatment of dementia, documentation of the prescribing and self-medication patterns of cognitively impaired elderly is needed to guide health policy and future clinical research.

Cognitively impaired individuals were less likely to be users of prescription or over-the-counter medications than those who were cognitively intact. Those who were cognitively impaired were less likely to take analgesic medications, specifically NSAIDs, than those who were cognitively intact, but more likely to take central nervous system (CNS) medications. High use of CNS medications may reflect appropriate use of psychotropics, although comparative clinical trials have shown greater efficacy with selected alternative medicines as compared to benzodiazopine. Also, higher use of CNS medications may cause or exacerbate cognitive impairment[77].

In a related study of the medication use patterns among demented, cognitively impared and cognitively intact community-dwelling elderly people, researchers found an increasing level of cognitive dysfunction was associated with decreased use of OTC, cardiovascular and analgesic medications, and the use of fewer prescription medications[78].

14. Preference Assessment for Pharmaceutical Evaluation

Principal Investigator:	Alan Garber, M.D.
Grant Number:	HS07818
Project Period:	March 1993 – August 1996

Overview

The underlying economic principles for the preference assessment, which serves as the foundation for quality-of-life (QOL) measurement, are somewhat complicated. Aimed at increasing a subject's understanding of the preference assessment instrument and detecting inconsistencies in response, this project developed a computer-based multimedia presentation of health states and preference elicitation to provide support for the preference assessment process. The project demonstrated the validity, reliability, and usefulness of this multimedia presentation. In addition, the project also found that when a subject assigns a preference to a health state, that preference appears to be affected by the subject's current health state.

Impact on Further Research (Level I)

Tools for Patient Management

- Multi-media Presentation to Assess Patient Preference: This study found that a multimedia (MM) presentation of multi-attribute health states helped respondents provide quality-adjustment weights for cost-utility analysis better than paper-based text presentations. "The results suggest that: 1) MM presentation results in better recall and recognition, indicating better transfer of information; 2) MM presentation appears to result in better definition of preferences (a smaller preference interval) and 3) recall and recognition testing of a health state description can identify material in the description that has an unintended impact on the respondents. In order to perform rating tasks on a health state, subjects must first have an accurate understanding of the health state being presented." The study found that multimedia presentation leads to greater recall and recognition memory of the health state than does a text-only presentation[79].

  Another article describes the software construction of IMPACT (Interactive Multimedia Preference Assessment Construction Tool). "Validation studies show that preference assessments performed using IMPACT have high test-retest reliability. Future work with IMPACT will focus on additional validation of the preference elicitation procedures implemented in the program. We are developing methods to assess the internal consistency of valuations across different methods and within a given method of preference assessment [as well as] developing interface designs that will allow us to apply these tests in an interactive fashion during computer interviews"[80].

- Patient Cost-utility and Preference Analysis: Although cost-utility analyses were designed to provide a common metric to compare competing health care interventions, the method of eliciting utilities and the population surveyed may so influence utility estimates that they make it difficult or impossible to compare the results of different studies. "We have shown that preferences depend on both the method of elicitation and the population surveyed." Further, this work suggests that future cost-utility analyses which attempt to elicit preferences for hypothetical health states from the general population should consider subjective rating of a respondent's own health status in determining representative population groups[81].

A related article described the effort to determine whether different procedures for establishing preferences for health states among various scaling models produced different results, and whether repeated testing led to a convergence of utility values towards a single true estimation: Do the effects of search procedures diminish with repeated testing or do they persist indefinitely? This project sought to ascertain numerical, patient-derived quality weights ("utility values") using: 1) the visual analog scale (VAS) rating quality of life with a given health condition on a linear scale of 1-100; 2) the time tradeoff (TTO), the amount of time in perfect health deemed equivalent to a longer period of time in poor health; and 3) the standard gamble(SG), which finds maximum risk of immediate death or some other adverse health condition that the subject would accept to avoid the health condition in question. The project found that "the search procedure (using either the TTO or the SG method) can influence utility values as much as does the rating task. The search procedure effects were surprisingly large. While it is well known that different scaling methods yield different results, our results suggest that the exact implementation of the utility-elicitation task is as important as the underlying conceptual valuation framework." There was no difference in utility values between VAS and SG. "The fact that subtle differences in procedures for utility elicitation result in large differences in estimated preferences suggests that estimated utility values, like other preferences, are constructed during the process of elicitation"[82].

15. Pharmaceutical Cost, Use and Outcome Among Insured Elderly

Principal Investigator:	Laura B. Gardner, M.D., Ph.D., M.P.H.
Grant Number:	HS08217
Project Period:	September 1993 – August 1996

Overview

The purpose of this study was to describe and analyze pharmaceutical and medical care utilization and costs for a group of older Americans over a period of time during which the patient's share of the cost of a prescription increased and changed several times. Whereas initially in 1988 enrollees were responsible for $5.00 of the charge of each prescription, this was increased to $8.00 for generics and $10.00 for brand name drugs in 1989, and again to $10.00 for generics and $15.00 for brand name in 1993. Then in 1994, the structure of the pharmaceutical benefit was radically modified so that the patient's co-payment became 50 percent of the allowed prescription charge, and capped at $50.00 per prescription. The study database was a group of 19,350 retirees of the Oregon Public Employees Retirement System (PERS) who were demographically representative of the general Medicare population. The database maximized its epidemiological potential by linking with Medicare claims data of those PERS individuals.

Impact on Policies (Level II)

This study had a direct impact on the Oregon Public Employees Retirement System (PERS) in demonstrating that the 50 percent co-pay was both a feasible and meaningful co-payment system. PERS has maintained this co-payment structure, in part because the study showed that it creates sufficient incentive for enrollees to consider generic drugs.

In addition, the study demonstrated the potential value of a database that links claims and clinical information. PERS has expanded the database so that International Classification of Disease (ICD-9) codes for visits can be linked to the drugs that are prescribed. This has allowed PERS to look at specific disease categories (e.g., osteoporosis) and the potential impact of concomitant and unrelated prescriptions.

Impact on Further Research (Level I)

The study is important in the context of policy discussions about a Medicare Prescription Drug benefit because it provides a case description of the relationship between utilization and a co-payment structure for a representative population.

Cost and Economics

- Pharmaceutical Costs Among Insured Elderly: The study found that none of the prescription co-payment options except the 50 percent prescription co-payment, affected utilization of and expenditures for pharmaceuticals and their generic substitutions. There was a dramatic shift to greater use of generics with the 50 percent co-payment structure, but no perceived negative impact on the quality of care provided—none of the co-payment options produced observable changes on subsequent use and expenditures of other Medicare services among those retirees[83].

Research Tools and Translating Research for Clinical Care

- Linked Databases and Total Health Services Use: This research involved linking multiple data sources to provide a picture that extended beyond drug use to total medical care use. Presentations at AHRQ and the Academy for Health Services Research (AHSR) led to positive acknowledgement of the level of sophistication of this large-scale time-series database that incorporated adjustments for bias[84].

16. Statistical Methods for Quality-of-Life Outcome Research

Principal Investigator:	Marcia Anne Testa, Ph.D.
Grant Number:	HS07767
Project Period:	March 1993 – February 1997

Overview

In this project the investigators: 1) evaluated and analyzed current and potential measurement and statistical techniques used in quality-of-life-related patient outcomes through a review of the literature; 2) refined existing analytical and statistical methodology so that it was appropriate for evaluation of pharmacologic therapies; and 3) developed data analysis demonstration projects within major analytical areas by applying selected methods to existing quality-of-life clinical trials databases of hypertension, diabetes, and human immunodeficiency virus.

Impact on Further Research (Level I)

This project illustrated through demonstration projects on key clinical conditions how quality-of-life data can provide substantive additional information that may alter treatment choices of individuals.

Treatment Effectiveness

- Benefits from Improved Glycemic Control in Patients with Type 2 Diabetes Mellitus: This analysis involved a double-blind, randomized, placebo-controlled parallel trial, which demonstrated that improved glycemic control of type 2 diabetes mellitus (DM) is associated with substantial short-term symptomatic, quality-of-life (QOL) and health economic benefits. These findings are among the first to link improved control of DM with self-reported productivity and ability to function at work. While baseline rates of employment, group productive capacity, health-related absenteeism, bed-days and days of restricted activity were similar for the placebo and active treatment group, by week 15, improved glycemic control for patients in the active therapy group was associated with greater improvement in overall work and disability outcomes compared with patients in the placebo group. Active therapy patients experienced higher retention of employment (97 percent versus 85 percent) and greater retained productive capacity (99 percent versus 87 percent) compared with the placebo group, even beyond what could be attributed simply to the difference in the dropout rate. Changes in absenteeism, bed-days and days of restricted activity also were statistically different between the two groups[85].

- Hypertension Treatment and Quality of Life: This study examined the differences in quality of life produced by 2 once-daily calcium channel blockers using different delivery systems: nifedipine gastrointestinal therapeutic system (GITS) and amlodipine. Results "suggest compound-specific effects on quality of life that may be due to differences in the delivery system. Nifedipine GITS is short-acting (2 hour half-life) and is delivered continuously over a 24 hour period, while amlodipine has a half-life of 40 hours, which may produce more sustained low-level effects. While a more beneficial profile was observed for nifedipine, amlodipine demonstrated positive effects on cognitive functioning"[86].

- Sensitivity of Quality-of-life Measures: "General measures of quality of life may be too crude and insensitive to capture the important gains in health outcomes due to new therapeutic interventions and

programs in diabetes. Quality-of-life evaluations for diabetes are at risk of favoring inferior programs with lower costs simply because gains or losses in health outcomes go undetected."

Specifically, this study demonstrated that current health state levels influence how patients value decrements and improvements in health. The health states rating clearly revealed that losses in function at relatively asymptomatic states have a greater negative utility than do losses at more severe states. It further notes that "our health states analysis demonstrated that people with mild-to-moderate diabetes substantially value smaller health improvements." The study makes the following recommendations: 1) enhance sensitivity of generic instruments rather than using disease-specific QOL instruments; 2) a QOL outcome measure must incorporate the subjective nature of preference by providing a comprehensive evaluation that focuses on patient self-perceptions of symptoms and health[87].

- Quality-of-life Measurement and Zidovudine Treatment: "Recent reports suggesting that the initiation of ziduvudine treatment when patients are asymptomatic provides no survival benefit have called into question the value of early intervention." This study explored whether integrating outcomes related to quality of life with traditional clinical end points may clarify this controversy. The study investigated quality-of-life considerations and found that, "even for the patient who valued the time after a severe adverse event four times more than the time after the progression of disease, the quality-of-life-adjusted time gained with 500mg of ziduvudine was less than one week during a period of 18 months." The study concludes that, "for asymptomatic patients treated with 500mg of zidovudine, a reduction in the quality of life due to severe side effects of therapy approximately equals the increase in the quality of life associated with a delay in the progression of HIV disease….These findings suggest that clinicians should attempt to incorporate patients' preferences into treatment recommendations, instead of making such decisions solely on the basis of the CD4+ cell count and published guidelines…. Future research may establish utility values that are based on patients' preferences, so that information on the quality of life can be integrated into traditional efficacy trials. In addition, a direct assessment of quality of life should be included in future clinical trials of treatment for HIV infection"[88].

Tools for Patient Management

- Measuring Quality of Life for AIDS-associated Wasting: This study reported findings from four focus groups conducted on patients with AIDS-associated wasting and highlights conceptual and measurement issues important for evaluating the therapeutic impact of pharmacological agents. "Generic measures of quality of life, while covering the appropriate domains, fail to provide the sensitivity and depth required to evaluate the major issues raised by the focus group participants with respect to the specific impact of HIV wasting on their lives…. Treatments for AIDS-associated wasting [i.e., involuntary loss of more than 10 percent of pre-morbid weight] have led to development of new treatments for enhancing weight gains…. However, the functional and quality-of-life impacts of these treatments have not been well studied…. It was clear that simply measuring increases in lean body mass or exercise endurance are inadequate metrics of improved health and quality of life for the evaluation of new therapeutic agents for AIDS-associated wasting…. Health outcomes should therefore focus not only on the biomedical parameters which signify therapeutic efficacy, but on [other] areas [including negative feelings about appearance, shame, embarrassment, social isolation, loss of appetite, loss of libido, grief, fear, loss of self-worth/self-esteem, hopelessness, cognitive dysfunction and difficulty sleeping] as well." Finally, "semi-structured focus groups of patients with specific conditions are a useful method for translating the best interests of the patient into therapeutic research and goals"[89].

Research Tools and Translating Research for Clinical Care

- Comparison of Randomized Clinical Trials and Primary Care Settings: The study examines whether discontinuation rates for anti-hyperlipidemic drugs in two health maintenance organizations (HMOs) differs from the discontinuation rates reported in clinical trials published from 1975 through 1993. "We evaluated the risks of discontinuation in patients enrolled in two HMOs and compared them with discontinuation rates for the same drugs reported in long-term clinical trials. "The risk of discontinuing anti-hyperlipidemic drugs in the two HMOs one year after the start of therapy ranged from 15 percent for lovastatin to 46 percent for niacin. For the bile acid sequestrants, gemfibrozil, and niacin, the risks observed in the HMOs were substantially higher than the summary estimates of discontinuation rates reported in randomized clinical trials." The study reports that the discontinuation rates in randomized clinical trials may not reflect the rates actually observed in primary care settings. The study also found that the principal reasons for discontinuation of drug therapy were adverse effects (18 percent), therapeutic ineffectiveness (10 percent), and noncompliance (2 percent)[90].

- Patient vs. Physician Report: This parallel randomized, double blind multi-center study found that, of the symptoms to which the typical patient confessed, only about one-quarter were also reported by the physician. By one measure, fewer than 7 percent on average also appeared in the physician's adverse event report. On average and across different prompted report processes, patients responded "yes" to adverse symptoms 50 percentage points more often than did their physicians. Differences are attributed to: "objectivity," "seriousness" of symptoms (such that physicians are more likely to report more serious symptoms than less serious ones), "clinical relevance," and "sensitivity" (reflecting the tendency to underreport embarrassing symptoms)[91].

17. Community-based Pharmaceutical Care: A Controlled Trial

Principal Investigator:	Morris Weinberger, Ph.D.
Grant Number:	HS09083
Project Period:	June 1996 – May 2000

Overview

The purpose of this study is to develop algorithms to facilitate pharmaceutical care for the treatment of asthma. A randomized controlled trial, with 460 patients in a pharmacy intervention group and two control groups, will be undertaken. The pharmacy intervention group will be provided with patient-specific clinical information displayed on their computer workstations when filling prescriptions. This study will take advantage of Indiana University's long-standing project to develop an electronic medical record. Patient records will be available to the pharmacist from six hospitals and 234 free-standing clinics. Pharmacy records will also be made available to these linked providers.

Findings and publications related to this study are forthcoming.

18. Impact of Prospective Drug Use Review on Health Outcomes

Principal Investigator:	Frank M. Ahern, Ph.D.
Grant Number:	HS09075
Project Period:	August 1996 – July 2000

Overview

The purpose of this study is to compare two different models of outpatient prospective drug utilization review (ProDUR) programs in the state of Pennsylvania, one of which allows active participation by a pharmacist in the process while the other does not. The study aims to: 1) conduct a descriptive epidemiological analysis of psychotropic drug use, prescribing patterns, and yield of ProDUR interventions, and compute estimates of drug-related outcome measures; and 2) to evaluate the independent effects of two different ProDUR procedures on health outcomes. The investigators will use data from the Program of All Inclusive Care for the Elderly (PACE) and Medicaid. Outcomes to be studied include hospitalization and utilization of other health-related resources.

Findings and publications related to this study are forthcoming.

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Appendices: Tables 1 –5

TABLE 1: Level I Impact on Research – new tools and methods for research, instruments and techniques to assist clinical decision-making, and studies that identify areas in which scientific knowledge is lacking.

PI Name (Project #)	***Treatment Effectiveness***	***Cost and Economics of Health Care***	***Research Tools and Translating Research for Clinical Care***	***Tools for Patient Management***	***Special Needs Target Popul***
Lau (7782)	X		X		
Tierney (7763)		X	X	X	X
Ray (7768)		X	X	X	
Berman (7816)	X	X			
Soumerai (7631)	X				X
Moore (7809)	X	X	X		X
Garrard (7772)				X	
Strickland (7813)	X	X			X
Stergachis (7834)	X				
Chewning (7773)				X	
Platt (7821)				X	
Wu (7824)	X				
Hanlon (7819)					X
Garber (7818)				X	
Gardner (8217)		X	X		
Testa (7767)	X		X	X	
Weinberger (9083)					
Ahern (9075)					

TABLE 2: Levels II – IV: Impact on Policies, Clinical Practice and Health Outcomes

Name	*Level II (Policies)*	*Level III (Clinical Practice)*	
Lau (7782)	▪ Evidence-based guidelines for non-diabetic renal disease (National Kidney Foundation's Kidney Disease Outcomes Quality Initiative). ▪ Clinical trials checklist (Working Group on Recommendations for the Reporting of Clinical Trials in the Biomedical Literature). ▪ Clinical trial registries resulting from this work were contributed to key collaborative review groups in the areas of congestive heart failure and hypertension.	▪ Shift in treatment patterns toward single-dose treatment with aminoglycosides for serious infection.	
Ray (7768)	▪ Guidelines for the management of osteoarthritis of the hip and knee.		
Berman (7816)	▪ Guidelines for Otitis Media for Colorado Medicaid. ▪ Program to evaluate OM outcomes (AMA). ▪ Interactive training Web site, and workshop (American Academy of Pediatrics). ▪ HEDIS measures (NCQA).		
Soumerai (7631)	▪ Policies on appropriate use of beta-blockers (NCQA, AMA, major HMOs).	▪ Increased rates of prescription of beta-blockers.	▪ Reducti associat
Moore (7809)	▪ HIV/AIDS-related policies (FDA, HRSA's HIV AIDS Bureau, Infectious Disease Society of America, the HIV Care Association and several pharmaceutical companies).	▪ Findings on the value of combination therapy relative to monotherapy resulted in significant shift in treatment patterns. ▪ Demonstrated the value of long-term safety of adjunctive corticosteroids. ▪ Increased treatment of opportunistic diseases.	▪ Change HIV/AI combin
Garrard (7772)	▪ Plan and provider awareness of cost and treatment issues associated with depression among the elderly (HealthPartners HMO).		

Strickland (7813)	▪ Health plan provider education and guidelines related to Lyme disease diagnosis, testing and treatment.	▪ Decline in rate of use of expensive antibiotics and over-treatment of tick bites in HMO (Delmarva Health Plan, MD).	
Gardner (8217)	▪ Study confirmed value of co-payment structure for prescription drug in a state health insurance program (Oregon Public Employees Retirement System), and demonstrated to the program the value of linking claims and clinical information to enhance quality and cost-effectiveness.		

TABLE 3: Target Populations

PI Name (Project #)	*Elderly*	*Low-income*	*Children*	*African American*	*Hispanic*
Lau (7782)	X				
Tierney (7763)				X	
Ray (7768)	X				
Berman (7816)		X	X		X
Soumerai (7631)	X				
Moore (7809)		X		X	
Garrard (7772)	X				
Strickland (7813)				X	
Stergachis (7834)			X		
Hanlon (7819)	X			X	
Gardner (8217)	X				
Ahern (9075)		X			

TABLE 4: Key Diseases and Conditions

PI Name (Project #)	*Asthma*	*Mental Health*	*HIV/AIDS*	*Arthritis*	*Heart Disease/ AMI*	*Diabetes*	*Otitis Media*
Lau (7782)			X		X	X	
Tierney (7763)	X				X		
Ray (7768)				X			
Berman (7816)							X
Soumerai (7631)					X		
Moore (7809)			X				
Garrard (7772)		X					
Strickland (7813)							
Stergachis (7834)	X						
Chewning (7773)				X			
Platt (7821)					X		
Wu (7824)			X				
Hanlon (7819)		X					
Testa (7767)			X		X	X	
Weinberger (9083)	X						
Ahern (9075)		X					

Table 5: Relevance of COER-funded OPT Projects to Current Policy Issues

Current Policy Issues Identified at OASPE Conference on *Pharmaceutical Pricing Practices, Utilization and Costs,* August, 2000 (Source: Conference Binder)		**COER OPT**
C. **D. High growth drugs**	**The drug categories that are expected to account for the most growth in future drug spending include those in the areas of:** ▪ The central nervous system (CNS) ▪ Cardiovascular and hypertension ▪ Respiratory ▪ Pain ▪ Gastroenterology[92].	Nine COER-funded projects invo these areas: ▪ CNS: Garrard, Tierney, I ▪ Cardiovascular and hype Soumerai, Testa, Tierne ▪ Respiratory: Stergachis, ▪ Pain: Ray, Chewning, H ▪ Gastroenterology: Lau, T
NSAIDs	Between 1996 and 1999 expenditures for the NSAID class, including Cox-2, increased by 50%. "Understanding the extent to which the appropriate medications are used by the population most at risk and in an effective manner is the next step in understanding the impact of prescription drugs on the health care system"[93].	Ray looked at the potential role o controlling NSAID use and cost versus non-generic brands. Ray for treatment of osteoarthritis inc acetominophen where appropriat
Drug effects in the elderly	There is poor information on drug effects in the elderly….With respect to chronic illness, there is evidence of under-prescribing[94].	Projects that addressed drug use include those by Lau, Soumerai, Hanlon. For example: ▪ Hanlon found that cogni less likely to be users of ▪ Soumerai found that alth of beta-blockers post-MI elderly, rates of use were enrollees.

Continued…

Table 5 Continued…

Current Policy Issues Identified at OASPE Conference on *Pharmaceutical Pricing Practices, Utilization and Costs,* August, 2000 (Source: Conference Binder*)		**COER OP**
Side effects and special populations	"The side effects of drugs must be considered more carefully…A well-documented example is of an older patient who complains of insomnia being given a long-acting benzodiazepine, then falls out of bed one morning and breaks a hip. " "Inadequate clinical trial information on use in special patient populations is an issue for potentially harmful medication….One difficulty in selecting appropriate drugs for the elderly has been the lack of randomized study data establishing minimum effectiveness guidelines….Without age-adjusted efficacy information, physicians are left to guess how best to use medicines in older patients" [94].	Soumerai and Ray looked at alte respect to side effects and safety Lau's meta-analysis work create small-size RCTs.
Physician training	"In cases where prescribers must be guided by experience rather than data, research shows that the more formal training physicians undergo the better"[94] .	Berman identified differences in patterns for otitis media by physi practice versus pediatrics), as we
Compliance	"The portion of patients who are given the right medication but take it the wrong way is believed to be…large….Definitive research here is lacking due to the complex features of individual prescriptions (e.g., dose, daily schedule and duration)"[94] .	Platt analyzed factors associated as well as the relative accuracy o approaches.

Continued…

Table 5 Continued…

Current Policy Issues Identified at OASPE Conference on *Pharmaceutical Pricing Practices, Utilization and Costs,* August, 2000 (Source: Conference Binder)		**COER Ol**
Disease management	"The implications of disease management programs are that better outcomes can reduce overall health care costs. However, PBMs typically do not have access to other health care cost information…[also] few evaluations of the effects of disease management programs were found in the literature" [95].	Stergachis identified factors like pharmacist-run disease manage Ray looked at the impact of cha cost of care.
Drug utilization review	"Concurrent drug utilization review (DUR) has been increasingly used by both HMO and employer clients of Pharmacy Benefit Service companies"[95].	Tierney identified factors impor of computerized guidelines and Stergachis identified factors im concurrent review and patient e Ray looked at the impact of pri Ahern's study will compare tw prospective drug utilization rev
The patient's role	"A…contributing factor is the pivotal role of the patient whose willingness and ability to follow the recommended regimen are rarely assessed and documented"[94].	Testa demonstrated that current how patients value decrements Chewning found that for arthrit need to prepare patients as partn changes in drug regimens and i related symptoms and side effe influence patients' choice of dr adherence. Garber explored approaches to their treatment preferences.