Final Report:

Improving Drug Safety

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1. Structured Abstract (Select for Elements).

Purpose: To refine and implement a pharmacy alert system (PAS) that uses linked data from the Pharmacy Information System (PIMS) and the Laboratory Information System (LIMS) to identify and warn pharmacists of possible errors in a) drug selection and dosing for patients with chronic renal insufficiency (Renal Intervention); b) lab monitoring of patients receiving high-risk drugs (Lab Monitoring Intervention); and c) drug selection for elderly patients (Medication Safety in the Elderly Intervention).

Scope: All eligible KPCO members (N=~400,000) were randomized to either intervention or control for each intervention, as appropriate.

Methods: Eligible patients were identified using condition, prescribing, and age information available in the pharmacy information system.

Results: The Renal Dosing project initiated in 2003 achieved a 53% reduction in inappropriate dosing errors for CKD patients, sustained through 2005. The High-Risk Drug Lab Monitoring project initiated in 2003 achieved a 14% improvement in lab monitoring. For the Medication Safety in the Elderly project, 543 (1.8%) intervention group patients age 65 or older were newly dispensed prescriptions for study medications compared with 644 (2.2%) patients in the usual care group ($p=0.002$). All these improvements were statistically significant at the $p<0.05$ level.

Key Words: Medication safety, pharmacy, decision support, alert systems, error reduction

2. Purpose (Objectives of Study)

Specific Aims of this Project

1. To refine and implement a pharmacy alert system (PAS) that uses linked data from the Pharmacy Information System (PIMS) and the Laboratory Information System (LIMS) to identify and warn pharmacists of possible errors in:

a. Drug selection and dosing for patients with chronic renal insufficiency **(Renal Intervention)**

b. Lab monitoring of patients receiving high-risk drugs **(Lab Monitoring Intervention)**

c. Drug selection for elderly patients **(Medication Safety in the Elderly Intervention)**

d. Drug selection for pregnant patients **(Pregnancy Intervention)**

The Pregnancy Intervention was launched and terminated early due to unacceptably high false-positive alert rates and low numbers of actual errors.

2. To conduct three separate randomized, controlled trials to assess the impact of the PAS intervention on the rate of medication errors for patients that 1) have chronic renal insufficiency, 2) receive high-risk drugs requiring lab monitoring, or 3) are 65 years old or older receiving inappropriate medications. All eligible KPCO members will be randomized to a study group (intervention) or control group (usual care).

3. To evaluate the possible public health impact and potential for translation and generalizablity of the PAS interventions using the “RE-AIM” framework of Reach, Effectiveness, Adoption, Implementation, and Maintenance.

4. To develop a dissemination guide that will be made be available to other practice sites interested in implementing the same or similar interventions. This dissemination guide will include a detailed description of the PAS as well as barriers identified in the implementation process and approaches to overcome these barriers.

This project refined and experimentally evaluated a novel Pharmacy Alert System that intercepted medication errors after a prescription has been written but before a pharmacist dispenses the drug. We conducted three separate randomized, controlled trials to evaluate the impact of the intervention on the occurrence of medication errors for 1) 19,000 patients with chronic kidney disease, 2) 21,000 patients who receive high-risk drugs requiring laboratory monitoring, and 3) 59,700 patients age 65 years and older. Randomization at the patient level will assign participants to either a “usual care” group or an “intervention” group. The primary outcome of the study will be the occurrence of medication errors. We also evaluated the intervention’s potential for translation and generalizability using the RE-AIM framework of reach, effectiveness, adoption, implementation, and maintenance.

3. Scope (Background, Context, Settings, Participants, Incidence, Prevalence)

Overview of Strategies to Decrease Medication Errors

Medication errors can occur at any of several points in the process of medication use, including drug ordering, dispensing, drug administration, and/or drug therapy monitoring for efficacy or toxicity. Strategies to decrease medication errors have been proposed that target each of these points in the medication use process (Bates et al 1996). Although the methodological quality of the research is variable, error reduction strategies with some degree of evidence supporting their impact include barcoded medication packaging, unit-dose medication distribution, bedside-scanning technology, computerized prescriber order entry (CPOE), linking laboratory and pharmacy systems, including a pharmacist on physician's patient rounds, Clinical Decision Support Systems (CDSS), reviewing medication orders, interdisciplinary drug therapy protocols, and using information technology (e.g., to assist with dosage calculations, improve communication, assist with monitoring) (Kaushal et al 2003, Kohn 2001, Bates et al 1998, Bates et al 1999, Johnston et al 1994, Hunt et al 1998, Evans et al 1998, Durieux et al 2000, Teich et al 2000, Walton et al 1999, Bates and Gawande 2003, Bates et al 1996). Any strategy employed alone, however, cannot eliminate medication errors (Ballentine et al 2003).

Computerized Prescriber Order Entry (CPOE) with Clinical Decision Support Systems (CDSS)

In the 2001 AHRQ evidence report on patient safety practices, one of the 12 practices rated most highly as a research area for patient safety was computerized prescriber order entry (CPOE) with computerized decision support systems (CDSS) to decrease medication errors and adverse events primarily due to the drug ordering process (2001 AHRQ Evidence report). Interventions at the point of drug ordering, such as CPOE, decrease prescription order and transcription errors involving drug doses not being available at the time of intended administration to hospitalized patients, drug dosing and frequency errors, administration route errors, drug substitution errors, and errors involving drug allergies (Bates et al 1998, Bates et al 1999). CPOE coupled with a CDSS can also be an effective tool to improve physician prescribing and was one of the proven patient safety processes endorsed by the IOM (To Err is Human 2000). For example, Teich and colleagues studied a CPOE and CDSS system in which, at the time the physician entered a drug order, the computer provided drug use guidelines, including alternative drugs, dosages, and frequencies (Teich et al 2000). For example, medication selection of a preferred histamine-2 blocker increased from 15.6% of all orders to 81.3% ($p<0.001$) with the system. The percentage of all drug doses that exceeded the recommended maximum dosage decreased from 2.1% to 0.6% ($p<0.001$). Several types of CDSS can be provided, including active suggestions, clinical prediction rules, decision

algorithms, or website links for information. CDSS not only can improve drug dosing but also can potentially improve clinician performance in quality assurance and can improve patient outcomes and prevent medication errors (Johnston et al 1994, Hunt et al 1998, Evans et al 1988, Durieux et al 2000, Walton R et al 1999, Shojania et al 1998).

Significance of Medication Errors in Renal Dysfunction, Laboratory Monitoring, and among Patients 65 years and older

Renal Dosing: This project alerted pharmacists to errors in prescribing for the 19,000 KPCO patients with chronic kidney disease, a condition in which medication doses frequently need to be adjusted based on kidney function.

High-Risk Drug Lab Monitoring: This project alerted pharmacists to errors in lab monitoring for the more than 10,000 KPCO members per year receiving prescriptions from a group of high-risk drugs. There were 20,000+ patients prescribed high-risk drugs that required lab monitoring.

Elderly: This project targeted the 59,680 health plan members age 65 and older. Pharmacists received alerts on all patients randomized to intervention who were newly prescribed a targeted medication.

Prescribing Errors in Patients with Chronic Renal Insufficiency

Recent estimates suggest that approximately 10 million Americans have renal dysfunction (Jones et al 1998, Clase 2001, Coresh 2001), including approximately 378,000 with end-stage renal disease (US Renal Data System 2002). Many drugs are eliminated from the body through the kidney, and patients with renal insufficiency are at risk of having these drugs accumulate, with resulting increases in risk of drug toxicity. Medication dose adjustments for these patients are important for safe drug use, optimal patient outcomes, and managing drug costs (Matsue 1997, Talbert 1994). Medication dosing guidelines for patients with chronic renal insufficiency are available from several sources (Frye 2002, Aronoff et al 1999, Kappell 2002). Adherence to renal dosing guidelines in hospital and long-term care settings is suboptimal, with studies determining that between 20% and 67% of evaluated prescriptions contain errors, usually either excessive drug dosages or prescription of contraindicated drugs (Wong 1998, Kai-Ting 2001, Cantu 1992, Papaioannou 2000). Use of clinical pharmacy services and computer-assisted dosing improves renal dosing guideline adherence in the inpatient setting (Delaney 1995, Preston 1995, Peterson 1991, Golightly 1993, Rind et al 1994, McMullin et al 1997, Goldberg 1991, Falconnier 2001, Chertow et al 2001). Although the majority of patients with renal insufficiency receive medical care and medications in the ambulatory environment, very few published data exist to evaluate adherence to renal dosing guidelines or associated clinical outcomes. Whether computer-assisted dosing and the services of clinical pharmacists can improve renal drug dosing in

ambulatory care has not been evaluated. Our project was designed to fill these knowledge gaps.

Errors in Laboratory Monitoring

Laboratory parameters, such as liver function tests or blood counts, should be monitored before and during therapy for many drugs with known organ toxicity. Appropriate laboratory monitoring can reduce the risk of adverse events. The importance of laboratory monitoring is reflected in black box warnings in product labeling or in clinical guidelines for drugs such as carbamazepine, azathioprine, and amiodarone (Beach 1998, Hande 1986, Schoenenberger 1995). Research on adherence to laboratory monitoring recommendations has only been conducted for selected drugs, such as liver function testing for statin drugs and thiazolidinediones and serum creatinine monitoring for metformin (Roblin 1994, Graham 2001, Emslie-Smith 2001, Abookire 2001, Schoenenberger 1995, Tegeder 1999, Selby 1999, Calabrese 2002, Graham 2001). In these evaluations, monitoring recommendations were not followed for a high percentage of patients (27% to >50%) and/or the drug dosage was not reduced despite evidence from laboratory monitoring suggesting that dosage reduction was necessary.

Medication Safety in the Elderly

Prior studies estimated the prevalence of prescribing potentially inappropriate medications to elderly individuals to be 12% to 40%. (Zhan et al 2001, Raji et al 2003, Mort et al 2000, Wilcox et al 1994, Pitkala et al 2002, Mott et al 2000, Hanlon et al 2000). Using data from the 1996 Medical Expenditure Panel Survey, one study determined that 21.3% of community-dwelling elderly patients in the United States received at least one of 33 potentially inappropriate medications and that 2.6% of these patients received at least one of 11 medications that an expert consensus panel considered “should generally be avoided’’(Zhan et al 2001, Beers et al 1997).

Prescribing Errors during Pregnancy

The use of medications during pregnancy has been recognized to pose risks to mother and fetus ever since the thalidomide tragedy (Kajii 1973). The US Food and Drug Administration (FDA) subsequently developed a pregnancy risk classification system to assist prescribers in determining the level of risk associated with use of specific drugs during pregnancy (Appendix A). Pregnancy Category D includes those drugs for which there is positive evidence of human fetal risk, but benefits from use in pregnant women may be acceptable despite the risk. Pregnancy Category X includes those drugs for which animal or human studies document fetal abnormalities and the risk of use of the drug in pregnancy clearly outweighs any possible benefit. Examples of drugs in this category include etretinate, diethylstilbestrol, and misoprostol (Appendix B).

Authorities have long argued for limiting medication prescribing during pregnancy, but studies document continuing prescription drug use in pregnant women (Olesen et al 1999, Lacroix 2000, Andrade et al 2003, Rubin et al 1993, Brocklebank et al 1978, Piper et al 1987, Buitendijk and Bracken 1991, Piper et al 1988). Two studies from Europe have raised concerns regarding potential risky prescribing practices in pregnant patients. In a study of nearly 16,000 pregnant women in Denmark, Olesen and colleagues reported that the proportion of women who received at least one drug during pregnancy with "proven or anticipated harmful fetal effects" based on the Swedish classification system was 18% (Classification of medicinal products, 1993). One percent of these women received five or more prescriptions within these categories during pregnancy (Olesen et al 1999). In the second study, Lacroix et al examined the original prescriptions issued throughout the pregnancy of 1000 women in France in 1996 (Lacroix 2000). Seventy-nine percent of women were exposed to drugs for which there is no human or animal data available about safety of use during pregnancy. Fifty-nine percent of women were prescribed a drug from US FDA Pregnancy Category D. One point six percent of women in the Lacroix study received one or more prescriptions for drugs in Pregnancy Category X. The Pregnancy Intervention was terminated early due to unacceptably high false-positive alert rates and low numbers of actual errors.

Setting

The PAS intervention intercepts medication errors after a prescription has been written but before a pharmacist dispenses the drug. We conducted a randomized, controlled, population-based, effectiveness trial involving all Kaiser Permanente Colorado patients.

All projects were population based – conducted in all KPCO clinics and all KPCO pharmacies, and including all eligible KPCO members in the Denver-Boulder market. The KPCO Denver-Boulder market includes over 400,000 patients, which was over 90% of the KPCO membership. Over 550 physicians provide medical services for these patients at 16 separate medical offices that are spread geographically across the metropolitan area. Sixteen of the pharmacies were located in the ambulatory medical offices, one was located in the outpatient area of Exempla St. Joseph Hospital, one pharmacy served primarily patients who live in long-term care facilities, and one pharmacy processed prescriptions for patients who preferred to have their medications delivered by mail. Over 96% of KPCO patients have a pharmacy benefit that allows them to obtain medications for a modest prescription copayment. Internal KPCO data indicate that virtually all members with discounted pharmacy benefits obtain their medications through KPCO pharmacies.

All KPCO members were randomized to either intervention or control for each intervention. All KPCO members with the targeted characteristics that increase the risk of medication error or patient harm were included (e.g., all chronic kidney disease patients are included in the Renal Dosing project).

All these projects promoted the KPCO principle of “physician support” by (1) removing unnecessary work from within the office visit and (2) creating redundancy of safeguards for tasks frequently overlooked during the office visit. Staff pharmacists working in standard clinical settings under usual circumstances delivered the interventions. Each of the three projects was rigorously evaluated for at least 1 year to determine if it was successful. If the evaluation showed that the intervention reduced medication errors, the project was continued and expanded to include all members. The primary outcome measure for all interventions was the occurrence of medication errors, defined as the dispensing or monitoring of medications that deviates from accepted clinical guidelines.

The overall design was the same for the three projects. All our projects used a unique, KPCO-developed Pharmacy Alert System (PAS) to intercept medication errors after the prescription is ordered but before it is dispensed. The PAS combines data from the electronic medical record and clinical databases with screening functions of the pharmacy information system to identify and alert pharmacists to potential errors. In the PAS projects, prescriptions are screened for potential errors using guideline-driven decision rules. When potential errors are detected, alerts are triggered. The pharmacist cannot dispense these prescriptions without active intervention. The pharmacist confirms an alert’s validity and consults decision support guides that assist the pharmacist in resolving possible errors in collaboration with the prescriber. Pharmacists use scripted conversations to explain to patients the reason for the alerts and the rationale for medication changes in a manner that supports the physician-patient relationship. Factors previously shown to positively impact care processes and patient outcomes were incorporated into the PAS intervention (i.e., use of practice guidelines, opinion leaders, and audit and feedback).

Sponsors of the interventions were found throughout KPCO. They included labor and management leaders from the Pharmacy Department, the Clinical Research Unit, Regional Patient Safety, Physician Regional Department Chiefs, and, most importantly, the KPCO professional staff pharmacists. The projects were collaboratively developed with labor and management leaders from the Pharmacy Department, the Clinical Research Unit, Colorado Permanente Medical Group leadership, and the Kaiser Foundation Health Plan of Colorado leadership.

The interventions related to several of our Departmental, Medical Center, and Regional Patient Safety priorities. Specifically, KPCO Patient Safety priorities directly related to this program included (1) identifying and analyzing near-misses and errors; (2) identifying and analyzing potential risks of harm; (3) examining systems issues that contribute to near-misses or errors; (4) examining alternative patient safety strategies; (5) selecting and implementing patient safety strategies, including system changes; and (6) monitoring these interventions to ensure that the program was effective in reducing harm.

Most medication error reduction strategies have focused on the inpatient setting. Our projects are unique because they are focused on the point of dispensing. These projects successfully used “point of dispensing” alerts in the pharmacy to reduce medication errors at KPCO. In the era of the electronic medical record (EMR) and the potential for alerts at the “point of prescribing,” one might question the future value of “point of dispensing” alerts in the pharmacy. There are several important reasons why “point of dispensing” alerts are vital in the new EMR environment: (1) A review of the medical literature suggests that EMR-based prescribing alerts are frequently overridden by physicians (EMR alerts have been shown to be overridden up to 80% of the time in some studies). (2) The success rates reported with EMR-based prescriber alerts are typically lower than what we observed with our pharmacy-based interventions. (3) No software-based alert can match the professional judgment of a pharmacist reviewing an automated alert. (4) Our alerts do not interrupt physician workflow unless the alert has first been validated by a pharmacist. Alerting the pharmacist frees the physician to focus on other patient needs while providing high reliability to specific medication dispensing processes. (5) All these projects support our physicians in keeping our patients safe without placing the sole responsibility for medication safety within the confines of an office visit. Finally, even regions that want to start with an EMR-based medication safety program can benefit by incorporating the alerts we developed into their EMR.

4. Methods (Study Design, Data Sources/Collection, Interventions, Measures, Limitations)

The data collection and analysis process was similar for all projects. Medication errors were the primary outcome measure for assessing the success and sustainability of all four projects. To determine whether a medication error had occurred, all medications dispensed were reviewed by a clinical pharmacist blinded to whether the patient was in the invention or usual care group. The proportion of medication errors was determined by dividing the number of patients who did not receive the recommended adjustment or monitoring specific to the project (numerator) by the number of patients who received the targeted drugs (denominator). The same analytic approach was used to assess whether the proportion of medication errors differed between the intervention and usual care groups: Chi-square analysis was used to determine whether the proportion of medication errors in the intervention group differed from the proportion of medication errors in the usual care group. We then repeated the statistical analyses using multivariable regression models to adjust for any differences in the characteristics of patients in the intervention and usual care groups. The results of these regression analyses were similar to the primary analyses.

Renal Intervention

Subjects. We identified eligible subjects using the following inclusion/exclusion criteria: KPCO members with evidence of chronic renal insufficiency, defined as those with a documented creatinine clearance (CrCl) <50 mL/min on two or more occasions separated by at least 3 months, were included (K/DOQI guidelines 2002). Please note that there is some controversy regarding the exact CrCl cutoff that defines renal insufficiency, and some classification systems would consider patients with CrCl in the range of 50-60 mL/min to have renal insufficiency. However, we chose CrCl <50 mL/min as our cutoff, because all common classification systems define a patient with this level of renal function as having renal insufficiency (K/DOQI 2002). CrCl measures can be directly measured or calculated using the Cockcroft Gault formula (Appendix E) (Cockcroft Gault, 1976). Although there are several techniques available to estimate renal function, we chose the Cockcroft Gault estimation, because it is a standard method used to adjust medication doses. The Cockcroft Gault equation uses five data elements (age, gender, weight, height, and serum creatinine), commonly available for KPCO patients, to calculate CrCl. We determined that over 85% of KPCO adult members have sufficient data elements available to estimate CrCl. We identified over 19,000 eligible KPCO members with a documented CrCl <50 mL/min on two or more occasions separated by at least 3 months who were not currently receiving dialysis treatment.

We excluded the following patients from the renal intervention: 1) patients with a CrCl $\geq$50, 2) patients receiving chronic dialysis treatment, and 3) patients with insufficient data elements available to calculate CrCl (e.g., no serum creatinine).

We excluded patients receiving chronic dialysis treatment, because dosing decisions for these patients cannot be made merely on the basis of CrCl but also must consider the timing and other factors related to dialysis. Because the vast majority of children have not had serum creatinine measured, we can only estimate CrCl for only about 5% of children (<18 years of age). However, we are not excluding children, because it is important to assess the feasibility and effectiveness of the intervention on children as well as adults.

Monitoring Intervention

Subjects. Based on data from calendar year 2002, we anticipated having over 20,000 eligible subjects to participate in the monitoring intervention. The study subjects for this intervention were the subset of KPCO members who received one or more critical drugs requiring baseline or scheduled lab monitoring. Patients who did not obtain their medications at KPCO pharmacies were excluded.

Content of Intervention. Like the renal intervention, the monitoring intervention was multifaceted and was composed of integrated system, clinician, and patient components.

System Component

Using the established electronic interface, we transferred data on the results of lab tests commonly used in monitoring high-risk drugs from LIMS to PIMS. PIMS then screened for possible errors in lab monitoring with each new prescription by comparing the tests that had been performed against those that are recommended for that specific medication. The screening for lab monitoring errors was facilitated by a set of guideline-driven decision rules for baseline and scheduled lab monitoring that had been developed by our research team and had already been programmed into the PIMS.

If PIMS detected a possible error in lab monitoring, then a medication alert was issued, but, unlike the renal intervention, the prescription label was produced, and the medication was dispensed. In our pilot work on lab monitoring, we learned that patients often obtain recommended lab monitoring for high-risk drugs later on the same day or in the days shortly after picking up their medications. Therefore, in cases with possible errors in lab monitoring, we felt that it was more appropriate to allow the medication to be dispensed and to follow the case and intervene if recommended monitoring was not completed within a week of dispensing the medication.

Elderly Intervention

Subjects. We identified eligible patients using age information available in the pharmacy information system. Subjects were KPCO members who were 65 years of age or older or who reached age 65 during the study period. Conditions that may interact negatively with certain medications were identified through diagnostic codes, and this information was then sent to PIMS.

System component. Screening for medication errors among elderly patients was facilitated by a set of guideline-driven decision rules that were developed by our research team and programmed into the PIMS system.

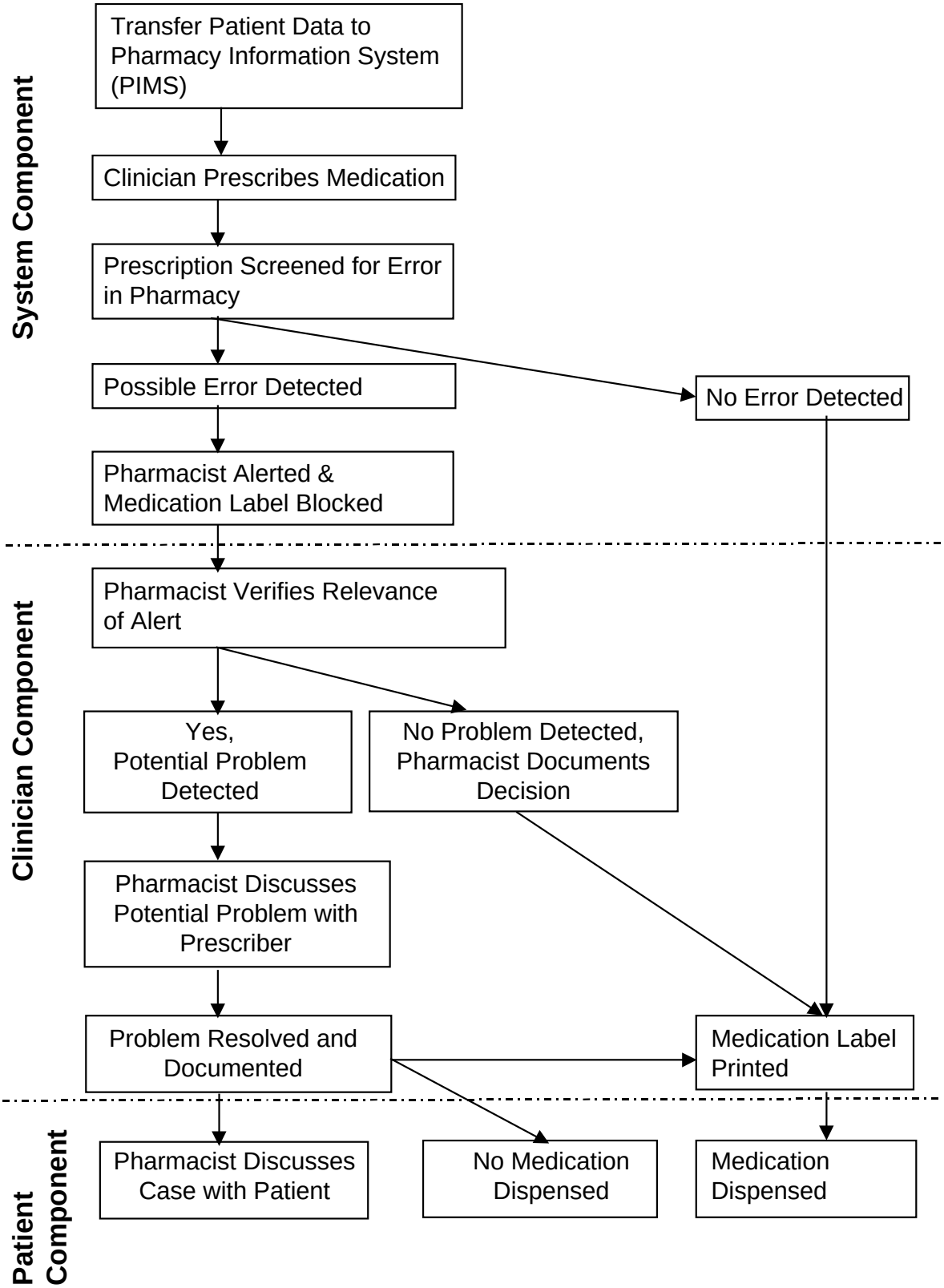
As with the renal intervention, if PIMS detected a possible error, a medication alert was issued, the prescription label was not produced, and the medication could not be dispensed without active intervention by the pharmacist.

Clinician Components. The steps of the clinician component for the Elderly Intervention were similar to those for the Renal Intervention. The intervention was delivered in one of the following previously approved ways: First, the pharmacist confirmed that the patient was elderly and had been given an index prescription for a drug that could be unsafe in the elderly or could interact negatively with an existing condition. After confirming the accuracy of the alert, the pharmacist reviewed the "Elderly PAS Guide." The pharmacist then contacted the prescribing clinician or clinical pharmacy specialist to discuss the case, and they together developed a plan to resolve the issue. Once the problem was resolved, the pharmacist resubmitted the prescription if a new medication was needed and documented the prescribing decision and rationale in the PIMS census note. Once the census note was documented, the alert was turned off and a medication label was printed.

Patient Component. The pharmacist was provided with standardized scripts to use in discussing with patients both the reasons for the alert and the rationale for any changes to the prescription.

Measures

The indicators of safety measured in the project were medication errors, defined as the dispensing or monitoring of medications that deviated from accepted clinical guidelines. The indicators of safety were measured in the following manner: (1) To determine whether a medication error had occurred, all medications dispensed were reviewed by a clinical pharmacist blinded to whether the patient was in the intervention or usual care group. (2) For each patient safety project, an assessment of medication errors was made on a quarterly basis for a minimum of 1 year so that we could get a stable estimate of the intervention's impact. (3) Evaluation beyond a year was done for the Renal Dosing and Elderly projects to assess long-term sustainability.
We assessed each project's effectiveness by comparing the rate of medication errors in the intervention and usual care groups. In the High-Risk Drug Lab Monitoring project, we compared rates of laboratory monitoring consistent with recommendations. In the Renal Dosing project, we compared rates of dispensing prescriptions that were not adjusted for level of renal function. In the Elderly Intervention, we compared rates of dispensing of inappropriate medications for people age 65 years and older.


System Component
Transfer Patient Data to Pharmacy Information System (PIMS)
Clinician Prescribes Medication
Prescription Screened for Error in Pharmacy
Possible Error Detected
No Error Detected
Pharmacist Alerted & Medication Label Blocked
Clinician Component
Pharmacist Verifies Relevance of Alert
Yes, Potential Problem Detected
No Problem Detected, Pharmacist Documents Decision
Pharmacist Discusses Potential Problem with Prescriber
Problem Resolved and Documented
Medication Label Printed
Patient Component
Pharmacist Discusses Case with Patient
No Medication Dispensed
Medication Dispensed

Limitations

1. *Potential limitation:* The pharmacists maybe overloaded with alerts from for three different types of medication errors. In the real world, alert systems will be screening for many more than just three types of errors (for instance, some systems screen for drug-drug interactions; drug-lab checks; and drug selection and dosing in children, the elderly, pregnancy, renal dysfunction, hepatic dysfunction). If alerts for just three types of errors overwhelm the pharmacists, this would be very important to learn. *Reality:* The total volume of alerts from the three interventions did not overwhelm the pharmacists.

2. *Potential limitation:* This study is being conducted at a group-model HMO, so the results may not be generalizable to other settings. *Reality:* This pharmacy-based intervention should be generalizable to any organizations that can link their pharmacy and lab data, something that more and more organizations can accomplish. For instance, in Denver, the two largest health systems, the Veterans Administration and the Denver Health Hospital and Community Clinic system, are both able to link their lab and pharmacy data. It is also worth noting that this intervention will be more generalizable than interventions that rely on the use of an electronic medical record.

3. *Potential limitation:* The pharmacists provide the experimental intervention to control patients. *Reality:* As we stated above in the design section, we believe the likelihood of contamination was low. For instance, for the pharmacist to provide the Renal Intervention for a control patient in the absence of an alert, they first would need to recognize that the medication was one of a long list requiring renal dosage adjustment. Second, the pharmacists would need to obtain all relevant clinical information to calculate creatinine clearance (age, gender, serum creatinine, and weight). Third, the pharmacist would then need to calculate the creatinine clearance by hand. Finally, the pharmacist would then need to determine the appropriate dose and contact the prescribing clinician if a change was needed. A similar level of effort would be necessary for the pharmacist to provide the other interventions to control patients. We believe that it is highly unlikely that the pharmacist will be able to complete these tasks for control patients in a setting in which they are expected to fill dozens of prescriptions per day.

5. Results (Principal Findings, Outcomes, Discussion, Conclusions, Significance, Implications)

This study addressed medication errors, an important patient safety problem. The study sought to reduce medication errors for three high-risk groups: CKD patients, those taking high-risk drugs, and the elderly. The project advanced scientific knowledge in the field of patient safety. First, most medication error prevention programs have been studied in the inpatient setting. We implemented and evaluated an intervention to reduce medication errors in the ambulatory care setting. Second, although most medication error reduction strategies have focused on the point of prescribing, our interventions targeted the point of dispensing. Third, this project put into practice the concept of transferring patient-specific clinical data to pharmacists to use for error detection. Finally, we conducted a population-based effectiveness study that includes all eligible KPCO members and all KPCO pharmacies. The study assessed the true effectiveness (as opposed to efficacy) of the intervention, because pharmacists working in standard clinical settings and under usual circumstances delivered the error reduction program. As a result, the study provided a realistic estimate of intervention effects in other settings.

All three projects resulted in a measurable decrease in medication errors. The Renal Dosing project initiated in 2003 achieved a 53% reduction in inappropriate dosing errors for CKD patients, sustained through 2005. The High-Risk Drug Lab Monitoring project was initiated in 2003 and achieved 13% and 14% improvements in lab monitoring. The Medication Safety in the Elderly project started in 2005 found that, in 1 year, 543 (1.8%) intervention group patients age 65 and older were newly dispensed prescriptions for targeted medications compared with 644 (2.2%) patients in the usual care group ($p=.002$). All these improvements described in this paragraph were statistically significant at the $p<0.05$ level. The Pregnancy Intervention was terminated early due to unacceptably high false-positive alert rates and low numbers of actual errors.

The Medication Safety in the Elderly project demonstrated the effectiveness of a computerized tool plus collaboration between healthcare professionals in decreasing potentially inappropriate medication dispensings in elderly patients. Coupling data available from information systems with the knowledge and skills of physicians and pharmacists can improve prescribing safety among patients age 65 or older. This study is the first randomized study testing an intervention to decrease potentially inappropriate medication prescribing in elderly patients in which the intervention occurs at the point of medication dispensing. The results demonstrate that linking patient age and drug prescribing information to identify potentially inappropriate prescribing among patients age 65 and older, providing that information to pharmacists, and then having pharmacists and physicians discuss safer medication alternatives was effective at decreasing the proportion of elderly patients receiving these medications.

The Improving Drug Safety project was part of a larger drug safety program that was submitted to and was a finalist for the David M. Lawrence Patient Safety Award, a national award amongst all Kaiser Permanente regions.

The results of these projects are sustainable. All these projects have been sustained through the period of this writing and have sustained reductions in medication errors beyond 1 year. Additional evidence of the sustainability of these projects is found in the fact that the projects are not static. In 2004, the Laboratory Monitoring intervention was modified to include some new drugs (e.g., antidepressant combinations, spironolactone), whereas some low-yield drugs were removed.

Measurement of reduction in medication errors is a surrogate marker of avoidance of adverse patient outcomes. It is not possible to directly evaluate the number of hospitalizations or deaths or the amount of patient suffering avoided. However, indirectly, it is evident that these interventions reduce hospitalizations, deaths, and patient suffering, because the proper and safe use of medications is enhanced and preventable medication errors are avoided. By avoiding such complications, we feel confident in stating that we avoid patient harm.

The implications of these projects for KPCO are improved patient safety and clinical outcomes and reduced costs due to fewer adverse medication-related events. The projects have facilitated enhanced dialogue and improved cooperation among pharmacists, physicians, laboratory personnel, call-center staff, and patients. All the interventions have become part of routine clinical practice in Colorado.

6. List of Publications and Products (Bibliography of Published Works and Electronic Resources from Study)

Published Papers:

Raebel MA, Charles J, Dugan JP, et al. Randomized Trial to Improve Prescribing Safety in Ambulatory Elderly Patients. J Am Geriatr Soc 2007; only available online as of 6/26/2007, to be published shortly.

Raebel MA, Chester EA, Newsom EE, et al. Randomized Trial to Improve Laboratory Safety Monitoring of Drug Therapy in Ambulatory Patients. *Pharmacother* 2006;26:619-26.

Raebel MA, Lyons EE, Bodily MA, et al. Improving Laboratory Monitoring at Initiation of Drug Therapy: A Randomized Trial. *Arch Intern Med* 2005;165:2395-2401.

Magid DJ, Estabrooks PA, Brand DW, et al. Translating Patient Safety Research into Clinical Practice. Advances in Patient Safety: From Research to Implementation. 2005 2 AHRQ Publication No. 050021, 1-4.

Papers in Press:

Raebel MA, Carroll NM, Kelleher JA, et al. Randomized Trial to Improve Prescribing Safety during Pregnancy. *J Am Med Inform Assoc* 2007 Apr 25; [Epub ahead of print] PMID: 17460126.

Posters:

Raebel MA, Carroll N, Chester EA, et al. Randomized Trial to Improve Prescribing During Pregnancy. 13th Annual HMO Research Network Conference, Portland, OR. March 20, 2007.

Chester B, Magid D, Raebel M, et al. Improving Medication Safety. Kaiser Permanente National Quality Conference. Monterey, CA. June 2005.

Magid DJ, Raebel MA, Bhardwaja B, et al. Improving Prescribing Safety in Patients with Chronic Kidney Disease: A Pharmacy-Based Intervention. 11th Annual HMO Research Network Conference. Santa Fe, NM. April 2005.

Raebel MA, Magid DM, Chester EA, et al. Translating Research into Practice in Real Time: Optimizing Laboratory Monitoring at Initiation of Drug Therapy. 9th Annual HMO Research Network Conference. Denver, CO. 2003.

In Process:

An abstract entitled “Imbedding Research in Practice to Improve Medication Safety” was recently accepted and Marsha Raebel is in the process of preparing a manuscript along the lines of the abstract for the AHRQ publication *Advances in Patient Safety: New Directions and Alternative Approaches.*

The manuscript on the Renal Intervention is in progress and should be submitted in 2007.