

## Effects of Ambulatory-Care Pharmacist Consultation on Mortality and Hospitalization

Yong Yuan, PhD; Joel W. Hay, PhD; and Jeffrey S. McCombs, PhD

**Objective:** To determine the effect of 3 alternative models of ambulatory-care pharmacist consultation on patient survival and hospitalization.

**Study Design:** Patients were randomly chosen adult Kaiser Permanente (KP) Southern California enrollees with at least 1 prescription in the base year. The demonstration lasted 23 months. Using time-dependent proportional hazards estimation, survival and hospitalization were examined across 5 patient risk groups.

**Interventions:** The pharmacy interventions were (1) consultation about new or changed prescriptions as mandated by 1992 state and federal regulations (State model), (2) consultation focused on selected high-risk ambulatory care patients (KP model), and (3) pre-1992 standard care (Control model).

**Results:** In the 6 service areas in which only 1 of the models was implemented, both the KP (relative risk [RR] = 0.295,  $P < .001$ ) and State (RR = 0.338,  $P < .001$ ) models significantly reduced emergency hospital admissions over 2 years compared with the Control model when measured across all risk groups. The State model also was associated with fewer urgent and emergency admissions (RR = 0.854,  $P < .001$ ). In the randomized treatment sample of 5499 patients, the KP model was associated with lower total mortality per new prescription filled (RR = 0.921,  $P < .01$ ), and significantly lower hospitalization and mortality in high-risk patient groups.

**Conclusions:** Intensive outpatient pharmacist consultation targeting high-risk patients would improve survival and decrease hospitalization rates. Broader nontargeted consultation would reduce hospitalizations, but was not associated with lower mortality within the 2-year intervention.

(*Am J Manag Care* 2003;9:45-56)

adverse drug reactions still constitute the sixth leading cause of death in the United States (mean = 106 000, 95% confidence interval [CI] = 76 000-137 000).

A recent study reported that drug-related morbidity and mortality resulting from medication error cost the United States an estimated \$177.4 billion in 2000. Since 1995, the estimated costs associated with drug-related problems have more than doubled.<sup>2</sup> Medication nonadherence may be responsible for almost 10% of all hospital admissions and a significant fraction of nursing home admissions.<sup>3</sup> Estimates of the economic costs of noncompliance amount to approximately 20 million lost working days per year.<sup>3</sup> In addition, approximately 140 million prescriptions remain unfilled every year.<sup>4</sup>

These studies of the impact of drug misadventures suggest that pharmacists have tremendous opportunity to affect ambulatory patient outcomes, including survival and hospitalization. Not surprisingly, several studies have shown that increased provision of pharmacist consultations and other pharmaceutical care services in outpatient settings provides a unique opportunity to impact patient outcomes such as quality of life, patient satisfaction, and the use and cost of healthcare services.<sup>5-11</sup> Increased pharmacist consultation services can be

Drug-related morbidity and mortality are significant problems in the United States. A meta-analysis of 39 prospective studies found adverse drug reactions to be the fourth-ranking cause of death in the United States, after heart disease, cancer, and stroke.<sup>1</sup> Even if this study's lower confidence limit of 76 000 fatalities is used,

From Global Epidemiology Outcomes Research, Bristol-Myers Squibb, Princeton, NJ (YY); and the Department of Pharmaceutical Economics and Policy, University of Southern California, Los Angeles, Calif (JWH, JSM). YY was in the Department of Pharmaceutical Economics and Policy, University of Southern California, when this research began.

This research was presented in part at the International Society for Pharmacoeconomics and Outcomes Research 4th Annual Meeting, May 20-22, 1999, Arlington, VA.

Address correspondence to: Joel W. Hay, PhD, Department of Pharmaceutical Economics and Policy, University of Southern California, USC CHP 140, 1540 E Alcazar Street, Los Angeles CA 90089-9004. E-mail: jhay@usc.edu.

an effective way to combat drug-related morbidity and mortality and to resolve the problems that threaten patient adherence to medication regimens.<sup>11</sup> However, there is little rigorous research regarding the impact of ambulatory care pharmacists on patient mortality and hospitalization. In previous pharmaceutical services outcome studies, only Hawkins et al<sup>12</sup> mentioned mortality differences.

The role of the pharmacist in the outpatient setting is changing from the traditional role of dispensing products to providing drug consultation, education and monitoring services. The redirection of the pharmacy profession's role was highlighted by several laws passed in the United States requiring pharmacists to provide consultation to patients. The federal 1990 Omnibus Budget Reconciliation Act requires a pharmacist's consultation for Medicaid patients when dispensing medication.<sup>13</sup> In addition, several states, including California, have implemented mandatory patient counseling.<sup>14</sup> In California, pharmacy practice laws instituted in November 1992 require pharmacists to counsel patients with new or changed prescriptions without regard to the type of medication dispensed or the individual characteristics of the patient.

Health insurance plans and government programs are reluctant to fully implement pharmaceutical consultation services for ambulatory patients without reliable data regarding the effect of these services on healthcare costs and patient outcomes. In addition, the shifting of risk from payer to provider in the HMO environment has placed physicians and other healthcare providers under increasing pressure to provide medical services that optimize patient outcomes in a cost-effective manner. It has become essential to comprehensively evaluate the effects of pharmacist consultation services on patient outcomes and costs because mandatory consultation for every new or changed prescription adds costly additional pharmacist time per prescription.

To evaluate these issues, the Kaiser Permanente (KP) Medical Care Program of the Southern California region and the University of Southern California (USC) School of Pharmacy jointly designed and implemented a study to evaluate the costs and outcomes of 3 different models of providing pharmacist consultation to ambulatory-care patients. The full study design has been detailed previously.<sup>15,16</sup>

The results of the pharmacist consultation study regarding satisfaction with pharmacy services, use and cost of healthcare services, and quality of life

have been reported elsewhere.<sup>5-7</sup> However, previous reports did not evaluate the survival effects of these pharmacist consultation models. This study is the first research attempt to rigorously examine and quantify these effects. This paper evaluates whether pharmacist consultation intervention models have a favorable effect on 2 time-related outcomes: mortality and hospitalization.

---

## METHODS

### Design of the Pharmacist Consultation Models

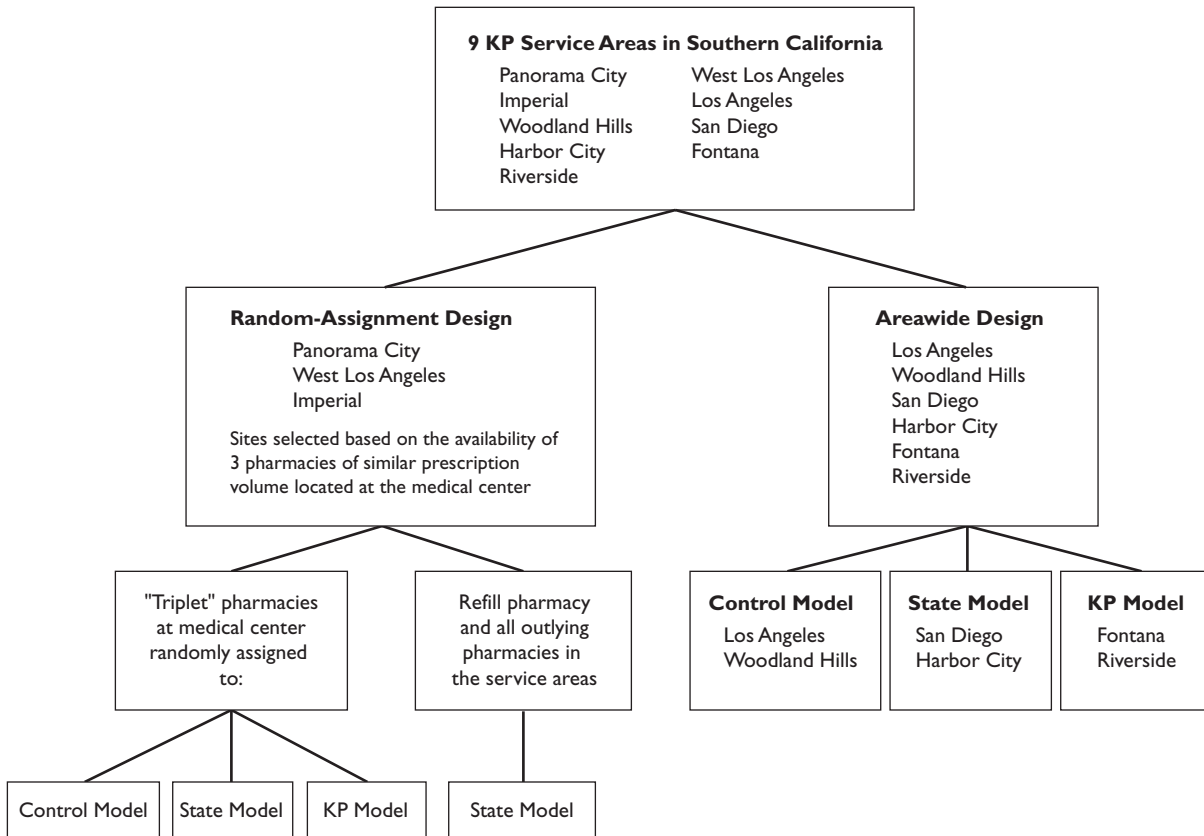
The KP/USC Patient Consultation Study was designed to investigate the effects of 3 pharmacist consultation models on a broad range of outcome measures:<sup>5-7,15,16</sup>

*The State Model of Pharmacist Consultation (State Model).* The State model reflects the changes in California pharmacy practice laws instituted in November 1992 that require pharmacists to briefly counsel all patients with new or changed outpatient prescriptions at the time the medication is dispensed. These regulations specify that the following drug information topics should be discussed with the patient during the consultation: when and how to take the drugs, how to store the drugs, potential treatment interactions, and the specific side effects that might be experienced.

*The Kaiser Permanente Model of Pharmacist Consultation (KP Model).* The KP model was developed to focus the same manpower resources into more comprehensive pharmacist consultations and other elements of pharmaceutical care for selected high-risk, ambulatory-care patients.<sup>15,16</sup> The definition of "high risk" was based on use of drugs with a narrow therapeutic index (carbamazepine, digoxin, phenobarbital, phenytoin, procainamide, quinidine, theophylline and warfarin), use of drugs with a significant incidence of adverse drug reactions (antidiabetic agents, benzodiazepines,  $\beta$ -blockers, calcium channel blockers, and metered-dose inhalers), or concomitant use of 5 or more medications of any type. These patients were identified by the pharmacist with Kaiser's online real-time computerized drug information system.

*Control Model.* Both the State and KP models of pharmacist consultation were compared with a Control model that reflected how pharmacists practiced under the pre-1992 state pharmacy regulations, which required consultations only when the patient requested consultation or the pharmacist determined that consultation or other actions were necessary.

Figure 1. Research Design



KP indicates Kaiser-Permanente.

The California State Board of Pharmacy granted the required waivers for the study, recognizing that the results could be used to refine the newly instituted patient consultation regulations, especially for patients at low risk for poor drug therapy outcomes. The USC Institutional Review Board approved the project. The study was initiated in November 1992 and was fully operational by April 1993. The demonstration project ran for a total of 23 months. More than 100 Kaiser Permanente outpatient pharmacies took part in the demonstration project.

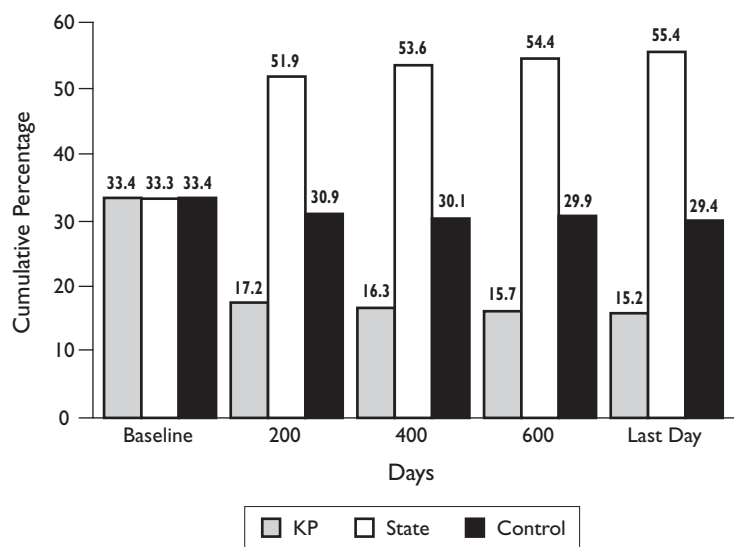
**Research Design**

The research project consisted of 2 separate, but parallel, demonstration designs (Figure 1). Kaiser Permanente of Southern California is divided into service areas, each associated with a major KP medical center. Three of these medical centers were selected to be included in a “random-assignment” design because each of these medical centers

encompassed 3 outpatient pharmacies devoted primarily to filling new prescriptions. This “triplet” of pharmacies then was randomly assigned to provide 1 of the 3 models of pharmacist consultation, and the on-site refill pharmacy and all outlying pharmacies in the service area were assigned to provide the State model of consultation. Next, more than 6000 KP members residing in these 3 service areas were recruited and then randomly assigned to 1 of the 3 models (State, KP, or Control) of pharmacist consultation. Pharmacists were blinded to the identity of the randomly assigned patients to avoid possible bias. However, the blinding of pharmacists made it impossible to ensure that patients consistently used the pharmacy to which they were assigned.

Seventy-five percent of the randomly assigned patients completed the full 2 years of the demonstration. On average, 80% of randomly assigned patients filled at least 1 new prescription at a phar-

**Figure 2.** Percentage of New Prescriptions Filled at Alternative Pharmacy Models During the Demonstration Period (Random-Assignment Sample)



Percentages do not add up to 100% due to rounding.

KP indicates Kaiser-Permanente model; State, State model; and Control, Control model.

macy other than their assigned pharmacies during this period (Figure 2). Survey data were collected for all KP members enrolled in the random-assignment research design.<sup>15,16</sup>

To avoid the problems with intervention crossover inherent in the random-assignment design, a parallel areawide design was implemented that converted all pharmacies within the remaining 6 medical center service areas to 1 of the 3 models of care. In total, 233 470 Kaiser enrollees resided in geographic areas with the KP model pharmacies, 329 400 enrollees resided in areas with the State model pharmacies, and 296 850 enrollees resided in areas with the Control model pharmacies. Survey data also were collected for about 3900 study-eligible patients residing in these areas.<sup>15,16</sup>

The sample of nearly 3900 KP members for whom survey data were collected did not provide sufficient statistical power to detect small changes in relatively infrequent events such as hospitalizations or deaths. To improve the overall statistical power of the demonstration project, a 10% random sample of 37 750 KP members was selected from members residing in the 6 medical center service areas included in the areawide research design for

inclusion in the analysis of hospitalization outcomes. Each of these subjects filled at least 1 prescription in both the 1-year predemonstration period and the 23-month demonstration phase, and maintained study membership for the complete pre- and postintervention period (35 months).

#### Patient Risk Groups

The 3 alternative pharmacist consultation models focus on different target populations, and the intervention effects were expected to vary with the risk factors of the patient. Therefore, the research design prespecified 3 subsets of patients based on their medication profile at baseline for the purpose of stratifying the selection of patients for inclusion in the study. The subgroups were the polypharmacy and target medication population, the target-only population, and the low-risk population.<sup>15,16</sup>

*The Polypharmacy and Target Medication Population.* This population was defined as patients who filled at least 1 new prescription for a target medication and used 5 or more chronic medications during the baseline period. This subgroup of patients was supposed to receive services under both the State and KP models, but was expected to show more significant effects from the KP model of care because of its relatively intense focus on high-risk patients.

*The Target-Only Population.* This population consists of patients who filled a new prescription for 1 or more of the medications targeted for intervention in the KP model, but who did not fill 5 or more new prescriptions for chronic medications during the baseline period. The target drugs identified in the study were carbamazepine, theophylline, metered-dose inhalers, digoxin, quinidine, procainamide, antidiabetic agents, non-steroidal anti-inflammatory drugs, benzodiazepines,  $\beta$ -blockers, warfarin, and calcium channel blockers. This group also was expected to show more significant effects from the KP model of focused high-risk care.

*The Low-Risk Population.* This population consisted of patients who filled at least 1 prescription but did not use any target medication or take 5 or more chronic medications during the baseline period. It was expected that the effect of the KP model

of care would be minimal within this risk class of patients because of the low likelihood that these patients received any pharmaceutical intervention in the KP model pharmacy. However, the State model pharmacy should have had some impacts on these patients because they filled at least 1 new baseline prescription.

Two additional nonexclusive patient subgroups were specified post-hoc for individual analysis in addition to the 3 patient groups defined a priori for stratified random selection into the study: the high-risk drug population and the failing-health population.

*The High-Risk Drug Population.* This subgroup includes patients who filled prescriptions for a "high-risk medication" during the baseline period. The definition of what constituted a high-risk medication was based on the professional opinion of pharmacists at Kaiser and USC. The medications identified as high risk were considered to have substantial potential for harm to the patient if misused, and it was considered likely that a pharmacist in the ambulatory setting could successfully intervene to prevent a drug misadventure. These high-risk medications consisted of nonsteroidal anti-inflammatory drugs and drugs for anxiety, chronic obstructive pulmonary disease, diabetes, epilepsy, and seizure disorders.

*The Failing-Health Population.* The final subpopulation consists of patients who reported their health status at baseline as "worse" or "much worse" than the previous year. This population was believed to be particularly at risk for adverse health events because of avoidable drug misadventures during the demonstration period.

#### Data

Data for prescription drugs, hospital admissions, and outpatient visits were retrieved from KP data systems for the baseline period consisting of calendar year 1992 and the 2-year period of the demonstration. All participants included in the following statistical analyses had to have filled at least 1 new prescription during the 2-year demonstration period and maintained continuous enrollment in the KP medical plan during the study period. Participants included in any analysis involving survey data had to have complete baseline survey data for all the independent variables used in the statistical analysis.

*Specification of the Treatment Variable.* The presence in the random-assignment sites of significant crossover among the 3 alternative models of

pharmacist consultation made it inappropriate simply to conduct the analysis on an intent-to-treat basis in these sites. Instead, the detailed prescription drug data available for analysis made it possible to create time-dependent variables for intervention exposure and after-hours pharmacy use (State model pharmacies). These variables were calculated from daily prescription records in the random-assignment sample to measure patients' actual exposure to the 3 pharmacist consultation interventions. These variables, which were calculated on a daily basis, measured the cumulative number of new prescriptions filled for each patient in a given pharmacist consultation model. As a result, the estimated effect of the exposure variables in the analyses involving data from the random-assignment sites represents the marginal effect on outcomes (mortality or hospitalization) per new prescription filled by a pharmacy model type. Conversely, crossover by patients among the alternative models of pharmacist consultation in the areawide sites was minimal, thus allowing for a traditional intent-to-treat analysis that measured the global impact of the KP and State models of pharmacist consultation on mortality and hospitalizations over the 2-year demonstration period.

*Outcome Measures.* The primary end points of interest in this study were time to death and time to first nonelective hospitalization. All-cause mortality information was derived from 3 sources: Kaiser records, county death certificates, and family reports. Those patients for whom information on date of death was unavailable were assigned death event times by using the dates when they were last seen in either the pharmacy or clinic. The lack of uniformity in mortality data sources precluded the possibility of doing detailed cause-of-death analyses. Given the difficulty of tracing and matching death certificates across 5 counties from Ventura to San Diego, it wasn't possible to obtain and verify accurate and complete death records for the 10% areawide sample. The mortality outcome only was evaluated in the 2 survey response groups (random assignment and the surveyed areawide subsample).

The time to first nonelective hospital admission was derived from Kaiser's computerized records system. Because elective hospitalizations are unlikely to reflect differences in appropriate use of medication, the time to first hospitalization event was analyzed for 2 types of inpatient admissions: urgent or emergency and emergency only. Elective hospitalizations were included as a time-dependent explanatory variable in the analyses. We treated

participants who did not have any hospitalization or death events at the end of the demonstration period as censored.

*Explanatory Variables.* In the random-assignment sites, we suspected that acutely ill patients were more likely to use after-hours pharmacies, and if this were so, more acutely ill patients would have a larger proportion of their new prescriptions filled at a State model pharmacy. To control for these confounding severity-of-illness effects, a time-dependent explanatory variable was created to reflect the ratio of cumulative after-hours pharmacy use for filling new prescriptions to the total number of new prescriptions filled. This problem of confounding of treatments due to the use of the after-hours pharmacy did not exist in the areawide sites because all pharmacies in the area provided the same model of pharmacist consultations.

In the analysis of the first nonelective hospitalization event in the random-assignment sites, an additional time-dependent dichotomous variable was created to reflect whether patients had a history of an elective hospital admission at the time of their first nonelective hospitalization. We postulated that a prior elective admission might be correlated with subsequent urgent or emergency admission, and this effect also might confound the true impacts of pharmacist consultation models.

A number of non-time-dependent baseline covariates were included in all statistical analyses to control for differences in patient demographics, disease severity, and other characteristics across the 3 pharmacy models and to improve parameter estimation precision. These baseline characteristics have been described previously.<sup>7,16</sup> The demographic characteristics by risk group in the random-assignment and areawide studies have been reported elsewhere as well.<sup>7</sup> The variables available for all analyses, including the 10% random sample of areawide patients, include computerized data for age and the number of hospital admissions and outpatient visits and 28 dichotomous variables detailing the mix of drug classes used by the patient during the baseline year (1992). Survey-specific explanatory variables included a measure for medication compliance behavior based on a scale described by Morisky et al<sup>17</sup>; variables for pain, mental function, physical function, emotional role function, physical role function, social function, vitality, and general health based on the 36-item short form health survey; race; education; marital status; employment status; smoking; and drinking. In addition, a 5-level variable reporting the patient's

trend in health status (much better to much worse) was used to create a set of 5 dichotomous variables for the patient's general health trend. Survey respondents who failed to answer this item were coded as having no change in health (the comparison category).

The 28 dichotomous drug classes derived from the patients' prescription drug use data in 1992 include medications for anxiety, cystic fibrosis, respiratory illness, asthma, Crohn's disease, ulcerative colitis, cardiac conditions, depression, diabetes, seizures, end-stage renal disease, glaucoma, gout, HIV infection, hypertension, hyperlipidemia, liver failure, bipolar disorders, cancer, arthritis, Parkinson's disease, severe mental disorders, rheumatologic conditions, renal disease, tuberculosis, thyroid disease, organ transplants, and acid peptic disease.

**Model Specification**

Time-dependent Cox proportional hazards models of survival and hospitalization were estimated as a function of pharmacist consultation treatment assignment and other patient-specific explanatory factors. The analysis was done separately for the areawide and random-assignment patients because of the differences in the specification of the treatment variables. A separate analysis was conducted for the 10% sample in the areawide sites because of the lack of the more detailed patient-specific survey data in this sample.

The time-dependent Cox model is specified as follows:

$$\text{Log } \lambda_i(t) = \text{log } \lambda_0(t) + \tilde{\beta} \tilde{X}_i + \gamma_1 \text{KKP}_i(t) + \gamma_2 \text{SST}_i(t) + \gamma_3 \text{TTT}_i(t) + \gamma_4 \text{Ratio}_i(t) + \gamma_5 \text{Elect}_i(t),$$

where  $t$  = event time,

$\text{Log } \lambda_i(t)$  = the logarithm of the hazard function for an individual  $i$ ,

$\text{log } \lambda_0(t)$  = the logarithm of baseline hazard,

$\tilde{\beta}$  = a vector of coefficients of baseline covariates,

$\tilde{X}_i$  = a vector of baseline covariates,

$\gamma$  ( $\gamma_1 \gamma_2 \gamma_3 \gamma_4 \gamma_5$ ) = coefficients of time-dependent covariates,

$\text{KKP}(t)$  = the cumulative number of new prescriptions filled in the KP model at time  $t$ ,

$\text{SST}(t)$  = the cumulative number of new prescriptions filled in the State model at time  $t$ ,

$\text{TTT}(t)$  = the cumulative number of new prescriptions filled in all 3 models at time  $t$ ,

$\text{Ratio}(t)$  = the ratio of the cumulative number

of new prescriptions filled in after-hours pharmacies to the total number of new prescriptions filled at time *t*, and

Elect (*t*) = whether patients had a prior elective admission (Y/N).

The SAS PHREG procedure (SAS Institute, Cary, NC) was used to create the Cox proportional hazards model with a time-dependent covariate structure.<sup>18</sup> To deal with large number of events that occur on the same day (ties) in this study, the Efron method was used for partial likelihood estimation because it is relatively less time-consuming than the Exact method.<sup>19</sup>

RESULTS

Random-Assignment Patients

*Mortality.* The 5499 continuously enrolled patients who filled at least 1 new prescription in any of these alternative models during the 2-year demonstration are included in this analysis. **Table 1** shows the event distribution for various risk groups. A total of 83 died during the 2-year period (1.51%). Patients who both used more than 5 drugs (polypharmacy) and used target medications had the highest mortality rate (5.19%); whereas among the 1270 patients without polypharmacy or target medications during the baseline or study periods, and

**Table 1.** Total (Unadjusted) Sample and Subgroup Deaths and Hospitalizations

Subgroup	No.	Death		Urgent/Emergency Hospitalization		Emergency Only	
		No.	Percentage (95% CI)	No.	Percentage (95% CI)	No.	Percentage (95% CI)
Random-assignment site							
Total sample	5499	83	1.51 (1.19, 1.83)	592	10.77 (9.95, 11.59)	174	3.16 (2.70, 3.62)
Target medication sample	3102	31	1.00 (0.65, 1.35)	336	10.83 (9.74, 11.59)	96	3.0 (2.48, 3.70)
Polypharmacy + target medication sample	751	39	5.19 (3.60, 6.78)	168	22.37 (19.39, 25.35)	62	8.26 (6.29, 10.23)
Failing-health sample	746	28	3.75 (2.39, 5.11)	111	14.75 (12.21, 17.29)	34	4.56 (3.06, 6.06)
High-risk drug sample	3752	65	1.73 (1.31, 2.15)	492	13.11 (12.03, 14.19)	151	4.02 (3.39, 4.65)
Low-risk group sample	1270	12	0.94 (0.41, 1.47)	63	4.96 (3.77, 6.15)	14	1.10 (0.53, 1.67)
Areawide survey site							
Total sample	3925	78	1.99 (1.55, 2.42)	416	10.60 (9.64, 11.56)	NA	NA
Target medication sample	2312	38	1.64 (1.13, 2.16)	225	9.73 (8.52, 10.94)	NA	NA
Polypharmacy + target medication sample	640	33	5.16 (3.44, 6.87)	140	21.89 (18.67, 25.08)	NA	NA
Failing-health sample	556	24	4.32 (2.63, 6.01)	83	14.93 (11.97, 10.41)	NA	NA
High-risk drug sample	2827	57	2.02 (1.50, 2.53)	348	12.31 (11.10, 13.52)	NA	NA
Low-risk group sample	737	9	1.22 (0.43, 2.01)	35	4.75 (3.21, 6.28)	NA	NA
10% Areawide site							
Total sample	37 750	NA	NA	3054	8.09 (7.81, 8.37)	688	1.82 (1.69, 1.95)
Target medication sample	10 078	NA	NA	695	6.90 (6.41, 7.39)	165	1.64 (1.39, 1.89)
Polypharmacy + target medication sample	12 488	NA	NA	1560	12.49 (11.91, 13.07)	374	2.99 (2.69, 3.29)
High-risk drug sample	24 800	NA	NA	2491	10.04 (9.67, 10.41)	571	2.30 (2.11, 2.49)
Low-risk group sample	12 638	NA	NA	628	4.97 (4.59, 5.35)	118	0.93 (0.76, 1.10)

CI indicates confidence interval; NA, not available for this sample.

without failing health in the baseline period, only 12 died (low-risk group mortality rate: 0.94%).

Figure 2 shows the cumulative percentage of new prescriptions filled at alternative pharmacy models during the demonstration period. At the beginning of the demonstration period, there were about 33.3% participants assigned to each of 3 alternative pharmacy models. During the first 200 days of the demonstration period, about half of all new prescriptions were filled at the State model of consultation. Approximately 18% and 30% of new prescriptions, respectively, were filled at the KP and Control models of consultations. This decrease in the percentage of new prescriptions filled at the KP and Control models is mainly due to the fact that patients elected to fill new prescriptions at an after-hours or off-site State model pharmacy, or elected not to go to their assigned pharmacy during normal clinic hours for convenience. The percent distribution of new prescriptions filled at alternative pharmacy models is consistent over the 2-year period. These compliance data strongly suggest that we needed to use a

proxy of “proportion of drugs filled at each treatment pharmacy model” instead of simply using the initial assignment to capture the actual pharmacist consultation treatment that patients received.

Table 2 shows the estimated relative risk (RR) of mortality associated with the KP and State models versus the Control model. Over 2 years, the overall RR of any death for the KP intervention model was 0.921 ( $P < .01$ ), which represented an average 7.9% reduction in total mortality per new prescription filled. A 7.8% mortality risk reduction was also found in the KP model compared with the State model of pharmacist consultation ( $P < .01$ ).

In subgroup analyses, over a 2-year period, a mortality risk reduction was observed with the KP intervention model compared with both the Control and State models in each defined high-risk subgroup (Table 2). These reductions were statistically significant in the target medication and high-risk groups, and not statistically significant in polypharmacy plus target medication or failing-health subgroups.

**Table 2.** Impact of Alternative Pharmacist Models in Total and Subgroup Samples (Random-Assignment Sample)\*

Population Sample Size	Estimated Relative Risk ( <i>P</i> )			
	Regressor	Survival	Hospitalization (Urgent/Emergency)	Hospitalization (Emergency)
Total sample (n = 5499)	KP	0.921 (0.002) <sup>†</sup>	0.972 (0.078)	0.977 (0.402)
	State	1.000 (0.980)	0.987 (0.347)	0.971 (0.254)
Target medication (n = 3102)	KP	0.840 (0.004) <sup>†</sup>	0.945 (0.021) <sup>†</sup>	0.936 (0.152)
	State	1.017 (0.582)	0.990 (0.602)	0.991 (0.813)
Polypharmacy + target medication (n = 751)	KP	0.929 (0.089)	0.966 (0.176)	0.967 (0.398)
	State	0.974 (0.442)	0.981 (0.369)	0.942 (0.130)
Failing health (n = 746)	KP	0.902 (0.075)	0.969 (0.395)	1.000 (0.997)
	State	0.938 (0.171)	1.000 (0.993)	0.999 (0.992)
High risk (n = 3752)	KP	0.922 (0.007) <sup>†</sup>	0.967 (0.045) <sup>†</sup>	0.979 (0.474)
	State	0.996 (0.827)	0.980 (0.134)	0.972 (0.282)
Low risk (n = 1270)	KP	1.963 (0.008) <sup>†</sup>	1.113 (0.209)	0.655 (0.381)
	State	1.314 (0.185)	0.856 (0.082)	0.074 (0.016) <sup>‡</sup>

\*The models were estimated by using the explanatory variables described in the text, but covariate estimates were not reported to improve readability. Detailed statistical tables are available upon e-mail request from the authors at Jhay@usc.edu.

KP indicates Kaiser-Permanente model; State, State model.

<sup>†</sup> $P < .01$ .

<sup>‡</sup> $P < .05$ .



The KP model of pharmacist consultation was found to be associated with a higher risk of mortality relative to the State (RR = 1.494,  $P < .01$ ) and Control (RR = 1.963,  $P < .01$ ) models in the low-risk subgroup, which was not designated for pharmacist consultations in the KP model. Because only 12 of the 1270 low-risk patients died, this result may be a small-sample anomaly. However, this result also may indicate that even low-risk patients benefit significantly from pharmacist consultation.

**Hospitalization.** As shown in Table 1, 592 patients had at least 1 urgent/emergency hospital admission and 174 patients had at least 1 emergency hospital admission in the total random-assignment sample of 5499 patients over 2 years. The polypharmacy plus target medication subgroup had the highest rate of hospital admission (urgent/emergency = 22.37%, emergency only = 8.26%). The failing-health and high-risk drug groups had the second and third highest occurrences of hospital admission. Patients in the low-risk group had the lowest rates of hospital admissions.

The results for urgent/emergency and emergency-only admission events are summarized in Table 2. The KP model of pharmacist consultation was found to be associated with significant risk reduction of urgent/emergency admissions in some high-risk subgroups per new prescription filled at a KP pharmacy. Compared with the Control model, the KP model of pharmacist consultation was associated with a 5.5% risk reduction per prescription filled in the target medication subgroup ( $P < .05$ ) and a 3.3% risk reduction per prescription filled in the high-risk group ( $P < .05$ ). However, in contrast to the mortality analysis, a significant hospitalization risk reduction was not found for the KP model of pharmacist consultation for the total sample.

Compared with the Control model, the State model was found to be

associated with substantially lower risk for emergency-only admissions in the low-risk subgroup per prescription filled during the 2-year period (RR = 0.074,  $P < .05$ ). However, the magnitude of the estimated effect and the small sample size suggest that this result is a statistical anomaly.

**Surveyed Areawide Subsample**

**Mortality.** The mortality data for the areawide survey sample are provided in Table 1. Overall, the mortality rates in the areawide survey sample are comparable to rates reported in the random-assignment sample. The impact of the KP model of pharmacist consultation is reported in Table 3.

**Hospitalizations.** The hospitalization data for the areawide survey sample are presented in Table 1. As with the mortality data, the absolute rates of hospital use are consistent with those reported for the random-assignment survey sample, as is the pattern of use across risk groups. The impact of the KP model of pharmacist consultation on hospitalizations is illustrated in Table 3. A separate analysis of emergency admissions only was not feasible

**Table 3.** Impact of Alternative Pharmacist Models in Total and Subgroup Samples (Surveyed Areawide Subsample)\*

Population Sample Size	Regressor	Estimated Relative Risk (P)	
		Survival	Hospitalization (Urgent/Emergency)
Total sample (n = 3925)	KP	1.174 (0.594)	1.113 (0.395)
	State	1.434 (0.236)	1.016 (.904)
Target medication (n = 2312)	KP	1.260 (0.609)	1.200 (0.302)
	State	1.569 (0.313)	1.125 (0.494)
Polypharmacy + target medication (n = 640)	KP	1.412 (0.462)	1.376 (0.169)
	State	1.772 (0.260)	0.997 (0.989)
Failing health (n = 556)	KP	1.716 (0.359)	1.302 (0.430)
	State	2.400 (0.193)	1.526 (0.253)
High risk (n = 2827)	KP	1.129 (0.743)	1.098 (0.501)
	State	1.704 (0.140)	1.015 (0.914)
Low risk (n = 737)	KP	0.230 (0.239)	0.578 (0.319)
	State	0.525 (0.456)	0.635 (0.376)

\*The models were estimated by using the explanatory variables described in the text, but covariate estimates were not reported to improve readability. Detailed statistical tables are available upon e-mail request from the authors at Jhay@usc.edu.

KP indicates Kaiser-Permanente model; State, State model.

because of the small sample size in some risk groups.

These mortality and hospitalization results suggest that the areawide surveyed study sample size (n = 3925) was not sufficient to detect significant differences in mortality and hospitalization outcomes. No clear pattern of estimated effects of pharmacist consultations on mortality and hospital admission was shone.

**10% Areawide Random Sample**

*Hospitalizations.* Because the areawide sample size of 3925 was not large enough to pick up small changes in hospitalizations, the hospitalization models for the areawide design were reestimated using a much larger 10% random sample of KP members residing the 6 areawide sites (Table 4). This sample of 37 750 patients was used to validate the estimated areawide model effects found by using patients with survey data, but with limited patient-specific covariates included in the model estimation. The 10-fold increase in sample size relative to

the surveyed areawide patients afforded a clearer picture of the differences in hospital admission patterns across the geographic sites in which the 3 alternative models of pharmacist consultation were implemented.

The analysis of urgent/emergency hospital admissions with the larger 10% random sample was not consistent with the effects estimated by using only the survey sample. A statistically significant risk reduction for hospitalization was found for the State model of consultation for the total sample and for each patient subgroup, noticeably for the low-risk subgroup. Although the trend was favorable, combined urgent/emergency hospital admission event reductions were not significant for any patient subgroup in the KP model. In contrast to the random-assignment sample, both the KP and State models of consultation were associated with large and significant decreases in the risk of emergency-only hospital admissions in the areawide sites for both the total sample and for each patient subgroup.

DISCUSSION AND CONCLUSIONS

Based on proportional hazards survival analysis, the KP model was associated with an 8% lower mortality risk compared with the State and Control models for both the total population and certain high-risk subgroups. The KP model also was found to be associated with a lower risk of hospitalization than the Control model. The State model of pharmacist consultation, which provided a broader intervention for a more diverse patient population, was shown to reduce hospitalization over 2 years, noticeably in the low-risk group, but patients would have to be followed for a longer study period to demonstrate survival benefits. The latter finding is not surprising, because the

**Table 4.** Impacts of Alternative Pharmacist Models in Total and Subgroup Samples (10% Areawide Sample)\*

Population Sample Size	Regressor	Estimated Relative Risk (P)	
		Hospitalization (Urgent/Emergency)	Hospitalization (Emergency Only)
Total sample (n = 37 750)	KP	0.958 (0.362)	0.295 (0.000) <sup>†</sup>
	State	0.854 (0.000) <sup>†</sup>	0.338 (0.000) <sup>†</sup>
Target medication (n = 10 078)	KP	0.843 (0.084)	0.283 (0.000) <sup>†</sup>
	State	0.775 (0.005) <sup>‡</sup>	0.306 (0.000) <sup>†</sup>
Polypharmacy + target medication (n = 12 498)	KP	0.994 (0.923)	0.281 (0.000) <sup>†</sup>
	State	0.863 (0.022) <sup>§</sup>	0.325 (0.000) <sup>†</sup>
High risk (n = 24 800)	KP	0.968 (0.529)	0.305 (0.000) <sup>†</sup>
	State	0.836 (0.000) <sup>†</sup>	0.331 (0.000) <sup>†</sup>
Low risk (n = 12 638)	KP	0.883 (0.221)	0.314 (0.001) <sup>‡</sup>
	State	0.780 (0.010) <sup>§</sup>	0.316 (0.001) <sup>‡</sup>

\*The models were estimated by using the explanatory variables described in the text, but covariate estimates were not reported to improve readability. Detailed statistical tables are available upon e-mail request from the authors at Jhay@usc.edu.

KP indicates Kaiser-Permanente model; State, State model.

<sup>†</sup>P < .0001.

<sup>‡</sup>P < .01.

<sup>§</sup>P < .05.

State model of consultation used pharmacy resources to provide consultation services in this low-risk subgroup, whereas the KP model did not. In light of these results, we concluded that the KP model of pharmacist consultation was relatively effective for reducing mortality and nonelective hospitalization in the high-risk population during the 2-year demonstration period. The State model provided more benefit to lower-risk patients and reduced acute hospitalizations more significantly, and thus might show significant additional survival benefits over a longer study time horizon.

Kaiser pharmacists in the KP/USC Patient Consultation Study successfully implemented a set of pharmaceutical care interventions (eg, patient education, medication monitoring). These interventions were designed on the a priori assumption that they would benefit patients, but with limited prior outcomes evidence. This analysis confirms that these pharmaceutical care interventions had statistically significant and clinically meaningful beneficial effects on patient mortality and hospitalizations. Extrapolating the 8% death risk reduction found in this study to the US population implies that the serious national problem of medication-related mortality could be substantially reduced with feasible and tested pharmacist interventions. As the US population ages, drug utilization increases, and patient medication regimens get increasingly complex, the benefits of such pharmaceutical care interventions can only continue to increase.

The robustness of the study results across both randomized and geographic control study designs overcomes the separate weaknesses in each design. Random assignment had good validity against unknown confounders because patients were balanced across the 3 treatment groups at baseline. The need to provide random-assignment patients with equivalent nearby pharmacy facilities created a potential for contamination bias. The areawide study design had little possibility for contamination bias because pharmacies tended to be located at the center of large geographic regions, and patients only rarely obtained pharmacy services outside their randomly geographically assigned pharmacy model of care. Moreover, unlike randomized designs, the areawide analysis was resistant to Hawthorne effects (ie, the manipulation of results by study participants), nonrandom study inclusion bias, dropouts, and other threats to external validity. There was, however, the possibility that region-specific demographic or other unknown confounders would bias the areawide results. Combining the consistent results from

both study designs overcomes the weaknesses of each, and provides a solid picture of the intervention benefits.

With the Control model, pharmacists provided patient consultation as deemed necessary according to the pharmacist's professional judgment or upon request of the patient. The pharmacies in this model were not provided with additional resources of the KP and State models, and could not implement counseling beyond that traditionally provided. Nevertheless Kaiser pharmacists practicing in the Control model were able to offer a level of pharmacist consultation that is still not routinely available to the majority of non-Kaiser ambulatory patients nationwide. They had (and continue to have) access to real-time pharmacy data systems showing complete drug histories for all patients, which allows them to assess potential drug interactions and other medical problems comprehensively and prospectively. Kaiser pharmacists, like Kaiser physicians and other healthcare providers, are KP employees, and thus have relatively high levels of coordination, communication, and integration. Thus, the benefits of the KP and State pharmacist consultation models might be greater in less-coordinated pharmacy delivery systems.

Hospital admissions are very sensitive to site-specific events and factors such as changes in physician staffing at the regional KP hospitals. Of particular concern here was the Northridge earthquake in January 1994, which had a significant effect on the 2 areas assigned to the areawide Control model of pharmacist consultation: Woodland Hills and Panorama City. Caution must be used in interpreting these data given that these factors were difficult to control for in the areawide sample analyses. Fortunately, the research design included random-assignment sites in which all 3 treatment groups, although smaller, should have been affected equally by earthquake-related events.

The findings were consistent under a variety of different model specifications. Full versus restricted model specification, backward methods, and stepwise methods all strongly and consistently supported the conclusion that the KP model is a favorable intervention model for reducing mortality in high-risk subgroups, and that both the KP and State models reduced nonelective hospitalizations. Thus, inclusion or exclusion of alternative subsets of explanatory variables had little effect on reported results. Differing assumptions as to whether data censoring was informative or noninformative also didn't affect the overall results.

However, these results must be interpreted cautiously because the KP model of pharmacist consultation also was found to be associated with a higher risk of mortality and hospitalization in the low-risk subgroup. Because of the low numbers of events in the low-risk subgroup, this finding could be a statistical anomaly. However, it also could reflect a real risk if pharmacist consultation resources are focused exclusively on high-risk patients. The State model did show reduced risk of hospitalization for low-risk patients in both the random-assignment and area-wide sites relative to the Control model, suggesting that low-risk patients can benefit significantly from enhanced pharmacist consultation interventions. Pharmacist consultation can be effective when balanced and appropriately delivered to both high-risk and low-risk groups of patients.

**Acknowledgments**

The authors acknowledge the leadership of Albert L. Carver, Vice President of Pharmacy Strategy and Operations for the California Division of the Kaiser Permanente Medical Care Program (KPMCP), for proposing the demonstration project; the resources provided by KPMCP for the project, including a research grant to the University of Southern California (USC) School of Pharmacy; the direct provision of printing, mailing, data entry, and data retrieval by Kaiser Permanente personnel; and collaboration by Matthew T. Nye, PharmD, Gerald Borok, PhD, and Daniel Ershoff, DrPH, with the USC research team on study design, management, and data analysis.

.....  
**REFERENCES**

1. **Lazarou J, Pomeranz BH, Corey PN.** Incidence of adverse drug reactions in hospitalized patients. *JAMA.* 1998;279:1200-1205.  
 2. **Ernst FR, Grizzle AJ.** Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc.* 2001;41:192-199.  
 3. **Berg JS, Dischler J, Wagner DJ, Raia JJ, Palmer-Shevlin N.** Medication compliance: a health care problem. *Ann Pharmacotherapy.* 1993;27(suppl):S5-S19.

4. **McCaffrey DJ, Smith MC, Banahan BF, Juergens JP, Szeinbach SL.** The financial implications of initial noncompliance: an investigation of unclaimed prescriptions in community pharmacies. *J Res Pharm Econ.* 1995;6:39-64.  
 5. **Johnson KA, Parker JP, McCombs JS, Cody M.** The Kaiser Permanente/USC Patient Consultation Study: patient satisfaction with pharmaceutical services. *Am J Health Syst Pharm.* 1998;55:2621-2629.  
 6. **Cody M, McCombs JS, Parker JP.** The Kaiser Permanente/USC Patient Consultation Study: change in quality of life. *Am J Health Syst Pharm.* 1998;55:2615-2620.  
 7. **McCombs JS, Liu G, Shi J, Feng W, Cody M, et al.** The Kaiser Permanente/USC Patient Consultation Study: change in use and cost of health care services. *Am J Health Syst Pharm.* 1998;55:2485-2499.  
 8. **Smith DH, Fassett WE, Christensen DB.** Washington State CARE Project: downstream cost changes associated with the provision of cognitive services by pharmacists. *J Am Pharm Assoc.* 1999;39:650-657.  
 9. **Bluml BM, McKenney JM, Cziraky MJ.** Pharmaceutical care services and results in project IMPACT: hyperlipidemia. *J Am Pharm Assoc.* 2000;40:157-165.  
 10. **Park JJ, Kelly P, Carter BL, Burgess PP.** Comprehensive pharmaceutical care in the chain setting. *J Am Pharm Assoc.* 1996; NS36:443-451.  
 11. **American Pharmaceutical Association.** Pharmaceutical Care/Clinical Evidence of the Value of Pharmacists. Available at: [www.aphanet.org/pharmaceutical\\_care](http://www.aphanet.org/pharmaceutical_care). Accessed December 17, 2002.  
 12. **Hawkins, DW, Fiedler FP, Douglas HL, Eschbach RC.** Evaluation of a clinical pharmacist in caring for hypertensive and diabetic patients. *Am J Hosp Pharm.* 1979;36:1321-1325.  
 13. **Omnibus Budget Reconciliation Act of 1990.** Washington, DC: US Government Printing Office; 1990.  
 14. **Nichol MB, Michael L.** A critical analysis of the content and enforcement of mandatory consultation and patient profile laws. *Ann Pharmacotherapy.* 1992;26:1149-1155.  
 15. **Johnson K., Nye M, Hill-Besingue K, Cody M.** Measuring the impact of patient counseling in the outpatient pharmacy setting: development and implementation of the counseling models for the Kaiser Permanente/USC Patient Consultation Study. *Clin Ther.* 1995;17:988-1002.  
 16. **McCombs J, Cody M, Besingue K, et al.** Measuring the impact of patient counseling in the outpatient setting: the Research Design of the Kaiser Permanente/USC Patient Consultation Study. *Clin Ther.* 1995;17:1188-1206.  
 17. **Morisky DE, Green LW, Levine DM.** Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986;24:67-74.  
 18. **Allison PD.** *Survival Analysis Using the SAS System: A Practical Guide.* Cary, NC: SAS Institute; 1995.  
 19. **Efron B.** The Efficiency of Cox's likelihood function for censored data. *J Am Stat Assoc.* 1997;72:557-565.