

# A Multidisciplinary Intervention for Reducing Readmissions Among Older Adults in a Patient-Centered Medical Home

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Older adults are an exceptionally vulnerable population during transitions of care. Nearly one-fifth of hospitalized Medicare beneficiaries are rehospitalized within 30 days, with fewer than half having a physician visit between the time of discharge and rehospitalization.<sup>1</sup> These rehospitalizations have been estimated to account for roughly \$44 billion per year in hospital costs<sup>2</sup>—three-fourths of which are viewed as potentially avoidable.<sup>3</sup>

In 2 recent reviews of published research on transitions-of-care activities,<sup>4,5</sup> no universal intervention was found to be effective at reducing 30-day readmission rates in either older or younger adults. However, shared characteristics of many successful interventions include activities taking place before, during, and after discharge provided by multiple members of the allied health professional team.<sup>4,5</sup> Care coordination in older adults is especially challenging due to complex medical and social needs.<sup>6</sup> Many transitions of care interventions have provided reduced readmissions in this high-risk population.<sup>7-14</sup> Koehler found that the most successful of these interventions in older adults are ones that continue in the outpatient setting.<sup>15</sup> Despite cost and quality concerns with poor transitions of care, however, traditional reimbursement models have disincentivized institutions from implementing high-quality care coordination efforts until recent federal healthcare reform.<sup>16</sup>

With value-based hospital payment penalties now in place for excessive 30-day readmission rates, and a call for improved care coordination by the Affordable Care Act, improved models of care are necessary.<sup>17,18</sup> Patient-centered medical homes (PCMHs) are designed to achieve the triple aim of higher quality, improved satisfaction, and lower costs through patient-centered, coordinated primary care. The PCMH structure is well suited to implement care coordination activities for patients in the outpatient setting. While evidence for PCMHs accomplishing the triple aim is mostly favorable, some studies have found increased costs, and the volume of high-quality evidence is limited.<sup>19-21</sup> Comparison among high-quality evaluations is difficult due to the vary-

## ABSTRACT

### Objectives

To evaluate the effectiveness of a multidisciplinary practice model consisting of medical providers, clinical pharmacists, and social workers on reducing 30-day all-cause readmissions.

### Study Design

Retrospective cohort study.

### Methods

This study included adults 60 years or older discharged from a large academic medical center. Patients were grouped as either receiving the primary care-based transitional care program (intervention group) or usual care (control group) after an index hospitalization. Only 1 index hospitalization was included per patient. All-cause 30-day readmission rates between propensity score matched study groups were analyzed by intention-to-treat, per protocol, and as-treated methods. Secondary outcomes included time to readmission, subgroup analysis, process measures, and cost avoidance influence of covariates on chance of readmission measured by logistic regression.

### Results

Over 27 months, 19,169 unique patients had 18,668 index hospitalizations and 572 interventions scheduled after discharge. Among matched subjects, 30-day readmission rates were not significantly different between those scheduled for the intervention and those never scheduled (21% vs 17.3%, respectively;  $P = .133$ ). However, when those completing the intervention ( $n = 217$ ) were examined, readmission rates were significantly reduced (11.7% vs 17.3%, respectively;  $P < .001$ ). Likewise, time to readmission was significantly longer among those receiving the intervention ( $18 \pm 9$  days compared with  $12 \pm 9$  days with usual care;  $P = .015$ ) and potential cost avoidance was observed only when the intervention was completed.

### Conclusions

A community-based multidisciplinary transitional care program may reduce hospital readmissions among older adults.

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ing design of programs, incorporation of PCMH components, and different target populations. Additional evaluations of PCMH interventions have been called for.<sup>19,20</sup> The purpose of this retrospective cohort study was to describe the characteristics and feasibility of implementing a multidisciplinary PCMH-based post discharge intervention, and to determine the effect of the intervention on the rate of all-cause 30-day readmissions.

### Take-Away Points

A patient-centered medical home (PCMH)-based post hospital discharge intervention with a clinical pharmacist, social worker, and primary care provider may reduce readmission rates among older patients when performed soon after discharge.

- Older adults are at high risk for hospital readmission.
- A PCMH-based intervention allows collaboration between the outpatient team and promotes responsive care to the patients' evolving needs.
- A multidisciplinary intervention may identify more threats to recovery among a high-risk older population than any single discipline alone.
- PCMHs and other coordinated care models offer opportunities to implement effective transitions of care interventions.

## METHODS

### Study Setting

This study was conducted within the academic health system, whose physician group practices began participating in a Medicare prototype accountable care organization demonstration project in 2005.<sup>22</sup> The Transitional Care Program (TCP) is one of numerous programs created to improve care and contain costs. The study protocol was reviewed and approved by the health system institutional review board.

### Transitional Care Program

The TCP is operated from a geriatrics clinic as part of a large academic health system. The geriatrics center is a community-based PCMH providing comprehensive, multidisciplinary primary and specialty care for patients 60 years or older. Although completely conducted in the community setting, the TCP is considered complementary to inpatient care coordination activities. All hospitalized patients receive comprehensive discharge planning, medication reconciliation, and high-risk medication education. The TCP is scheduled for patients upon recommendation from consulted inpatient geriatric services or for those receiving primary care at the geriatrics center. Appointments are ideally scheduled within 1 week after discharge, coordinated with assistance from discharge planners, and included in discharge paperwork.

The TCP team consists of medical providers (board-certified geriatric medicine physicians and nurse practitioners), clinical pharmacists, and social workers; the program was developed to assist patients transitioning to the community after unscheduled hospitalizations, long-term-care facility stays, or emergency department (ED) visits. The primary goal is to prevent rehospitalization. TCP aims to do so by addressing the multidimensional needs of this complex population (medical, social, psychological, functional domains) and ensure that treatment plans are personalized and implemented optimally using a team-based approach.

The TCP begins with a pharmacist's phone call. This telephonic encounter is scheduled to occur 2 to 4 days after discharge, and serves 3 purposes: to provide a preliminary medical assessment, reconcile medications, and perform a comprehensive medication review. Medication obtainment, adherence, efficacy, tolerability, safety, monitoring, and cost are all assessed. The pharmacist also assesses patient symptoms, stability, and self-monitoring at home, as appropriate. Issues requiring immediate attention are addressed, and findings, recommendations, and the up-to-date medication list are provided to the team prior to the clinic visit via electronic medical record documentation.

The patient is then seen in clinic, ideally within 1 week of discharge, by a social worker and medical provider. Social workers assess the patient's living situation, transportation, medication obtainment, activities of daily living, mental health and/or substance abuse, and in-home assistance with caregivers. Interventions include assisting with accessing community resources, long-term-care planning, and the establishment of advanced directives. The social worker reviews the use of available urgent appointments and the clinic after-hours on-call service to avoid sudden ED visits; home visits and intensive follow-up for up to 3 months are provided as needed.

The medical provider visit is the final component of the TCP. The medical provider performs a modified geriatrics assessment with focus on the reason for hospital admission, and in collaboration with the social worker, assesses the patient's living situation, rehabilitation plan, caregiver network, and social support; patients' self-care abilities and nutritional status are also assessed. Providers then review the goals of care with the patient, family, and caregivers. Lastly, follow-up appointments and referrals are coordinated. If patients receive primary care at the geriatrics center, primary care provider continuity is prioritized when scheduling appointments.

## Study Population

All patients 60 years and older discharged from the health system's primary hospital to home or assisted living from November 1, 2009, to January 31, 2012, were eligible for inclusion. This study window corresponds to a time frame in which the TCP was unchanged. To reduce bias, index hospitalizations were defined as the first hospitalization meeting inclusion criteria per patient. Patients were placed in cohorts as determined by TCP visit status within 30 days of discharge from index hospitalization, and analyzed using 3 different methods. First, all patients scheduled for the TCP, whether completed or not, were compared with those not scheduled (intention-to-treat). Second, only those completing the intervention were compared with those not scheduled (per protocol). Third, all patients completing the TCP were compared with those who did not receive the TCP either by not being scheduled or never completing a scheduled TCP (as-treated).

## Data Collection

Data related to patient demographics (age, sex, and race), index admission (admission and discharge diagnoses, length of stay, and medication count at discharge), and descriptions of medical comorbidities were collected. Comorbidities were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code and categorized according to the High-Risk Diagnoses in the Elderly Scale (HRDES) and the Charlson/Deyo Comorbidity Index (not adjusted for age), which have been associated with risk of hospitalization, morbidity, and mortality.<sup>23-26</sup> Race was collected as 8 distinct categories; however, due to a large proportion reporting as Caucasian and small numbers in the remaining categories, the variables were collapsed into 2 categories: Caucasian and non-Caucasian. Date and status (completed or cancelled) of TCP components (pharmacist, social worker, and medical provider) were also collected. Identification of variables, outcomes, and TCP appointment status was completed using the health system's clinical data repository and systemwide scheduling system.

## Outcome Measures

The primary outcome measure was nonelective all-cause 30-day readmissions. Thirty-day readmissions were defined as a hospital admission occurring within 30 days of the index hospitalization discharge date; readmission rates were calculated as the percentage of discharges with a 30-day readmission. Admissions were excluded as outcomes if the admit diagnosis was for a planned procedure and/or aftercare (based on *ICD-9-CM* codes V50-59.xx).<sup>27</sup>

Secondary outcomes were readmission rate by subgroup, time-to-event analysis, time to receive TCP components, and cost avoidance. All outcomes were evaluated first in intention-to-treat groups. Cost avoidance was calculated by multiplying a predicted difference in readmissions among patients receiving the TCP by the average cost of hospital stays for Medicare beneficiaries in 2009, adjusted to 2012 US dollars.<sup>28,29</sup>

## Statistical Analysis

Data were analyzed using descriptive statistics, univariate, and multivariate analyses. Logistic regression was used to test the effect of the intervention on 30-day readmissions and was adjusted for possible confounders using the enter method. Model goodness of fit was verified with the Hosmer-Lemeshow test and residual value analyses. Propensity score (PS) matching by logistic regression and Mahalanobis distance was used to match intervention to control subjects in a 1:1 ratio<sup>30</sup>; matching criteria included age, sex, race, length of stay, number of medications at discharge, and comorbidity index scores. Time-to-readmission analysis was performed using Kaplan-Meier and log rank tests, censored at 30 days. A total of 880 subjects were needed to provide 90% power to detect an 8% difference in readmission rates between groups with an a priori 2-sided alpha of 0.05.<sup>31</sup> Data analysis was performed using SPSS version 20.1 (IBM Corp, Armonk, New York), SAS version 9.3 (SAS Institute Inc, Cary, North Carolina), and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Over the study period, 19,169 unique patients accounted for 31,436 hospitalizations, of which 18,530 qualified as index hospitalizations. A total of 831 TCP interventions were scheduled. After excluding scheduled TCP visits after ED, long-term care facility, or outside hospital stays ( $n = 131$ ), and patients previously included in the study ( $n = 128$ ), 572 patients remained in the intervention group. These patients were matched to usual-care patients, creating a total sample of 1144 index hospitalizations. The per protocol and as-treated intervention analyses excluded 356 incomplete TCP interventions. By definition, these patients are included in the as-treated analysis control group.

**Table 1** compares the baseline characteristics of the study groups. Prior to matching, patients scheduled for TCP tended to be older, have higher medication burdens, and have shorter lengths of stay compared with the usual care cohort. After matching, the usual care cohort was sim-

■ **Table 1.** Baseline Characteristics

	Transitional Care Program		Control	P
<b>Age in years, mean (SD)</b>				
Intention-to-treat	80 (8)	81 (8)		.378
Per protocol	81 (8)	81 (8)		.802
As-treated	81 (8)	81 (8)		.923
<b>Female, n (%)</b>				
Intention-to-treat	380 (66.4)	363 (63.5)		.321
Per protocol	148 (68.2)	363 (63.5)		.243
As-treated	148 (68.2)	595 (64.2)		.270
<b>Caucasian, n (%)</b>				
Intention-to-treat	483 (84.4)	476 (83.2)		.575
Per protocol	187 (86.2)	476 (83.2)		.330
As-treated	187 (86.2)	772 (83.3)		.356
<b>Number of medications, mean (SD)</b>				
Intention-to-treat	11.8 (14.2)	8.9 (14.6)		.001
Per protocol	11.7 (13.1)	8.9 (14.6)		.013
As-treated	11.7 (13.1)	10.0 (14.8)		.121
<b>Index LOS, mean (SD)</b>				
Intention-to-treat	4.1 (3.8)	4.1 (3.7)		.829
Per protocol	3.4 (2.8)	4.1 (3.7)		.028
As-treated	3.4 (2.8)	4.2 (4)		.006
<b>HRDES score, mean (SD)</b>				
Intention-to-treat	1.5 (1.4)	1.5 (1.4)		.567
Per protocol	1.6 (1.5)	1.5 (1.4)		.235
As-treated	1.6 (1.5)	1.5 (1.4)		.196
<b>CD comorbidity score, mean (SD)</b>				
Intention-to-treat	2.6 (2.3)	2.6 (2.6)		.972
Per protocol	3 (2.4)	2.6 (2.6)		.077
As-treated	3 (2.4)	2.5 (2.5)		.018

CD indicates Charlson/Deyo; HRDES, High-Risk Diagnoses in the Elderly Scale; LOS, length of stay.

ilar to the intervention group in age, gender, race, length of stay, and comorbidity. Patients in the intervention group had a significantly higher medications burden at discharge.

### Primary Outcome

During the study period, patients scheduled for the intervention had a readmission rate of 21.1% (120 readmissions/572 index hospitalizations), compared with 16.4% among unmatched control patients (2952/17,958;  $P = .004$ ). After matching, readmissions were not significantly different among study groups in the intention-to-treat analysis (21.1% in the TCP group vs 17.3% in the control group;  $P = .133$ ) (Table 2). Only the per protocol and as-treated analyses revealed significant reductions in 30-day readmissions after completion of the TCP ( $P < .001$  for both analyses). Compared with those never scheduled for TCP, 1 readmis-

sion was avoided for every 18 patients completing the intervention. Among the 356 patients scheduled but never completing TCP, 97 readmissions occurred.

### Secondary Outcome

The mean  $\pm$  SD time to readmission was not significantly different between the intervention and control groups in the intention-to-treat matched analysis ( $14 \pm 9$  vs  $12 \pm 9$  days; log-rank  $\chi^2 = 2.117$ ;  $df = 1$ ;  $P = .146$ ); however, significant delays in readmissions were observed in the per protocol ( $18 \pm 9$  vs  $12 \pm 9$  days; log-rank  $\chi^2 = 5.871$ ;  $df = 1$ ;  $P = .015$ ) and as-treated analyses ( $18 \pm 9$  vs  $13 \pm 9$  days; log-rank  $\chi^2 = 12.978$ ;  $df = 1$ ;  $P < .001$ ) (Figure). Almost 70% of readmissions were within 2 weeks among control groups, compared with 39% of patients receiving the intervention. The TCP contacted patients within 1 week of discharge in 43% of cases and within 2 weeks in 80% of cases.

After adjusting for multiple factors, patients in the intention-to-treat intervention group did not have a different odds of readmission compared with matched controls (odds ratio [OR], 0.923; 95% CI, 0.636-1.341). Only medication burden (OR, 1.03; 95% CI, 1.01-1.042) and number of HRDES diagnoses (OR, 1.268; 95% CI, 1.053-1.527) were associated with increased odds of readmission. However, as shown in the as-treated analysis (Table 3), those who did not receive or complete the TCP within 30 days of discharge had an increased odds of being readmitted within 30 days. Medication burden and number of HRDES diagnoses also remained significant predictors of readmission. Results of the per protocol analysis were similar to the as-treated groups. Adjusted ORs were all comparable to the unadjusted analysis. Based on results of the as-treated analysis, hospitalization cost avoidance was estimated to be \$737,673 among the 345 completed interventions, or \$2138 per intervention (Table 4). Cost avoidance was not observed in the intention-to-treat analysis.

## DISCUSSION

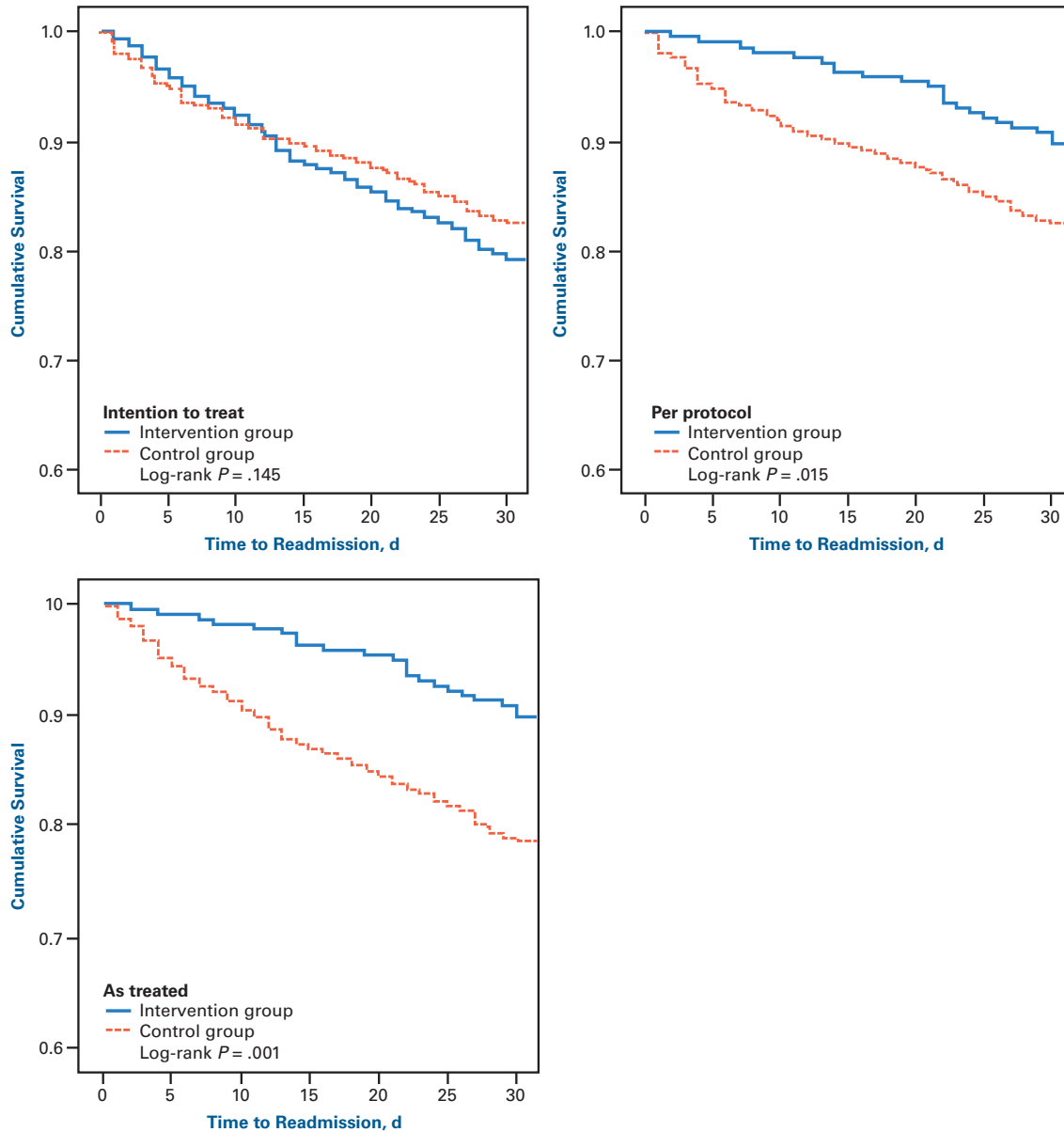
These findings describe the potential impact of multidisciplinary transition-of-care interventions in a PCMH on readmission rates in a highly vulnerable patient population. Despite not finding significant reductions in readmissions in the primary analysis, this study adds to the body of transitions-of-care and PCMH literature, and important conclusions can be drawn from primary and secondary analyses.

Many transitional care interventions have shown benefits of close post discharge care coordination on readmission rates and healthcare utilization.<sup>7-14,32-37</sup> However, most

**Table 2.** 30-Day Readmission Rate in Transitional Care Program and Control Groups

	Transitional Care Program	Control	<i>P</i>
<b>30-day Readmission, n (%)</b>			
Intention-to-treat	120/572 (21.0)	99/572 (17.3)	.133
Per protocol	23/217 (10.6)	99/572 (17.3)	<.001
As-treated	23/217 (10.6)	196/927 (21.1)	<.001

**Figure.** Kaplan-Meier Estimates of Time Until Readmission for Transitional Care Program and Matched Controls



interventions have been hospital- or call center-based, and they do not include provider components similar to those of our community-based intervention. Anderson and colleagues<sup>33</sup> found in a retrospective study that close discharge

phone follow-up by a clinical pharmacist in a PCMH setting was associated with similar reductions in 30-day readmission rates as our per protocol analysis when compared with controls (10.6% vs 19.8%; *P* <.01), despite studying a younger population (mean age, 57 years). The intervention also decreased no-show rates at post discharge clinic



**Table 3.** Logistic Regression Analysis for Effect Covariates on Odds of 30-Day Readmission (as-treated analysis)

Variable	Odds Ratio	95% CI	P <sup>a</sup>
No Transitional Care Program	2.469	1.400-4.347	<.001
Age	1.013	0.990-1.036	.266
Sex (reference, male)	1.046	0.753-1.435	.787
Race (reference, other)	0.982	0.644-1.496	.931
Index LOS	1.027	0.990-1.065	.157
Number of medications	1.030	1.017-1.043	<.001
C/D comorbidity score	0.948	0.866-1.038	.248
HRDES score	1.223	1.089-1.397	.001

C/D indicates Charlson/Deyo; HRDES, High-Risk Diagnoses in the Elderly Scale; LOS, length of stay.

<sup>a</sup>P determined from multiple logistic regression model (enter method) with adjustments for age, sex, race, index hospitalization length of stay, number of medications at discharge, comorbidity at discharge, and index admission diagnosis.

Hosmer-Lemeshow Test: chi-squared = 2.352; df = 8; P = .968.

appointments (33.8% vs 55.5%;  $P < .01$ ). Further, Kirkham et al<sup>10</sup> found close phone follow-up by pharmacists in a community-pharmacy setting, combined with inpatient medication delivery, also reduced readmissions (5% vs 9.5% without intervention;  $P < .05$ ). When patients 65 years or older were compared (31% of the study population), those receiving usual care had significantly increased odds of re-admission (adjusted OR, 6.05; 95% CI, 1.92-19.00). Lastly, Misky and colleagues<sup>35</sup> found that early follow-up with a physician is associated with a trend in reduced 30-day all-cause readmissions (15.6% vs 27.3%;  $P = .05$ ), especially re-admissions for the same condition (3.1% vs 21.2%;  $P < .05$ ). Despite positive results reported for individual care coordination activities, multiple systematic reviews and meta-analyses have found inconclusive evidence of the benefits of nonmultidisciplinary interventions or ones not taking place before, during, and after discharge reducing hospital admissions.<sup>4,5,15,38-40</sup> Additionally, considerations must be made when comparing results from the current study to previously published literature.

Results of our intention-to-treat analysis could be influenced by the inclusion of patients who may have been excluded from other published studies, including those unable or unwilling to complete the intervention, those with altered mental status or inability to speak English, or those admitted for surgical procedures.<sup>7-10,33,34</sup> Including these patients may have reduced participation in our intervention or biased our results by including sicker patients in the intervention group. Additionally, some studies have not excluded elective hospitalizations as 30-day readmissions.<sup>7,11,12,33,34</sup> In our study, 254 elective hospitalizations were excluded as readmissions before matching, all among those never scheduled for the intervention.

As shown by the per protocol and as-treated analyses, our multidisciplinary intervention was effective at reducing readmissions only among those able to receive the

service. There are many possible reasons for the 48% no-show rate for scheduled appointments. Among possible reasons: unawareness of or unavailability for the appointment, feeling too sick to come to a medical appointment so soon after hospitalization, transportation difficulties, refusal to see a medical provider other than their primary care provider, discharge to subacute rehabilitation facility, and rehospitalization. Process measures were analyzed to improve the efficiency of our intervention.

Reaching patients sooner was identified as an opportunity for improvement. We achieved our goal of calling within 2 to 4 days and seeing the patient in clinic within 7 days of discharge for only 21% of our patients. Among the 97 readmissions before any component of the TCP was completed, the average time to readmission was  $8 \pm 7$  days. These observations led to process changes (which came after the study concluded) to accommodate those with discharges later in the week, with transportation difficulty, conflicting appointments, and conflicting preferences. First, all primary care providers began reserving time for TCP appointments daily, rather than scheduling patients only on select days with select providers. Second, pharmacists began making calls on a second day, allowing up to 12 more patients to be contacted per week. Third, a nurse navigator began assisting with scheduling and calling patients. These process improvements allow us to reach patients sooner and to increase continuity with primary care providers when possible.

Operational costs of the program are 0.2-0.4 full-time equivalents per member of the team. Appointments are scheduled while staff are already present performing primary care responsibilities, minimizing additional operating costs. Time spent per patient varies. Including chart review, coordinating with other care providers, intervention, and documentation, the pharmacist calls take on average 45 minutes per patient, and up to 24 patients were contacted per week. Social worker time ranges from 1 to 8 hours per

**Table 4.** Calculation of Estimated Hospital Cost Avoidance Resulting From the Transitional Care Program

Number of patients receiving Transitional Care Program and were readmitted	41
Multiplied by the odds of readmission if not receiving Transitional Care Program	× 2.469
Estimated number of readmissions if not receiving Transitional Care Program	102
Minus actual number of readmissions in Transitional Care Program group	– 41
Estimated increase in readmissions if not receiving Transitional Care Program	61
Multiplied by average cost per Medicare admission in 2012 <sup>a</sup>	× \$12,093
Estimated savings in study population as a result of Transitional Care Program	\$737,673

<sup>a</sup>The cost of Medicare admission was based on data from the Healthcare Cost and Utilization Project, and adjusted to reflect national trends in healthcare spending and inflation.

patient per week. Medical evaluations are scheduled for 30- to 40-minute appointments, and can take an additional 30 minutes or longer to complete.

Cost avoidance of the program is dependent on the patient completing the intervention, only includes hospital costs, and does not factor in potential penalties avoided for excessive 30-day readmission rates, the opportunity cost of a hospital bed occupied, or revenue from billed services, all of which likely underestimate true cost savings. It also does not factor in costs of the program. This program was implemented in an established multidisciplinary PCMH, minimizing additional operating costs and aligning with the PCMH goals. The application of such an intervention may be difficult in institutions without such resources, structures, or incentives in place.

### Limitations

The retrospective, nonrandomized design does not allow causality to be established, and may introduce selection bias. Matched analysis was performed but cannot account for all differences between groups. Given our study design, readmission rates may potentially be underreported. First, nearly one-fifth of 30-day readmissions among Medicare beneficiaries do not occur at the same hospital, possibly limiting the findings of this single-center study.<sup>41</sup> Next, excluding individuals with multiple index hospitalizations may reduce capture of readmissions and limit comparison to other reported retrospective studies. The overall readmission rate in our matched study population was comparable to previously reported readmissions rates in this population<sup>22</sup> and also similar when multiple index hospitalizations were included per patient (19.5%). Third, pertinent factors associated with risk of readmission among older adults—including socioeconomic status, prior hospital utilization, self-management skills, home support, and level of education—were not addressed.<sup>26,42-46</sup> Last of all, patient satisfaction was not studied, but is important to consider when assessing the effectiveness of PCMH-based interventions.

## CONCLUSIONS

A PCMH-based, post hospital discharge intervention utilizing a clinical pharmacist, social worker, and medical provider may reduce readmission rates among older patients when performed soon after discharge; however, the effectiveness is dependent on completing the intervention. Further research is needed to study outcomes of similar programs. These results are most applicable to a PCMH focused on the care of older patients. Resources to implement a multidisciplinary intervention may not be available in all clinic settings, and the current study is unable to determine if certain elements were more important than others in improving outcomes; future study is necessary. Nonetheless, this serves as an example of how health system resources can be deployed in an efficient manner to provide coordinated and accountable care for patients.

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Dr Stranges and Mr Marshall had full access to study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Authorship Information:** Concept and design (PMS, PCW, DKG, TR); acquisition of data (PMS, PCW, VDM, TR); analysis and interpretation of data (PMS, PCW, VDM, TR); drafting of the manuscript (PMS, KEH); critical revision of the manuscript for important intellectual content (PMS, PCW, KEH, DKG, VDM, TR); statistical analysis (PMS, VDM); administrative, technical, or logistic support (DKG, VDM, TR); and supervision (KEH, TR).

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