Medication Therapy Management Programs: Promises and Pitfalls

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ABSTRACT

BACKGROUND: Medication therapy management (MTM) is one form of a medication benefit program offered by public and private health providers and insurers. Although the term was first coined in 2003, MTM in its earlier forms has been used since the 1990s as a mechanism to improve health metrics for medically complex patients. Its role expanded with the passage of Medicare Part D, as a mandated component to help patients with multiple chronic conditions, high drug costs, and high utilization to improve the effectiveness and safety of their medication treatments.

OBJECTIVE: To review the evidence on MTM effectiveness in order to (a) provide information on its establishment and goals and (b) summarize research findings under 3 outcomes: economic, clinical, and humanistic.

METHODS: PubMed, a search engine service of the National Center for Biotechnology Information was utilized by trained research assistants to search for articles with the following key words: *MTM, randomized controlled trials on MTM, evaluation of MTM, comprehensive medication review, medication action plan, special needs population, special needs plans, Medicaid, disease management, adherence, non-adherence, compliance, chronic conditions, disabling chronic conditions,* and *disability*. Additional searches were conducted for key articles in references listed in the most recent review articles. The initial search identified nearly 300 articles.

RESULTS: When evaluated, most studies found economic benefits, but the quality of research design and end point measures varied considerably across evaluations. Clinical outcomes encompassed a wide range of potential metrics, from service utilization, to individual patient and population outcomes, and quality of care. Quality measures such as provider-prescribing habits and medication adherence were frequently found to improve. As noted with the economic outcomes studies, overall rigor of study design was suboptimal, and often underpowered. Few studies have focused on humanistic outcomes such as improved patient quality of life.

CONCLUSIONS: Evidence suggests that MTM services are a promising way to manage complex patients, but there are gaps in the literature largely because of the limited number of studies with strong designs. Stronger evaluation of MTM programs is warranted.

J Manag Care Pharm. 2014;20(12):1162-82

Medication therapy management (MTM) is a mandated component of the Medicare Part D drug benefit program implemented to help patients with multiple chronic conditions, high drug costs, and high utilization improve the effectiveness and safety of their medication treatments. The program is voluntary for patients, but approved prescription drug plans (PDPs) must offer the service.[1] MTM can be viewed from many perspectives (e.g., medical provider, patient, pharmacist, or payer). Each perspective comes with a different set of motivations and concerns associated with MTM programs. This review will primarily focus on the emerging evidence of MTM effectiveness. First, we provide information on MTM establishment and goals. Then, we summarize research findings under 3 outcomes: economic, clinical, and humanistic. Finally, we describe gaps in our understanding of MTM programs based on this literature review.

Background on MTM Programs

The federal government officially coined the term "medication therapy management" in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, although similar services have been provided to various populations since the 1990s.[2] In 2006, the Centers for Medicare & Medicaid Services (CMS) incorporated an MTM program requirement for individuals with Part D coverage to ensure that drug regimens provide optimal therapeutic outcomes.[3] According to the CMS guidelines in 2009, targeted beneficiaries need to meet 3 criteria to be eligible for MTM services: (1) have multiple chronic conditions, (2) use multiple covered drugs, and (3) be likely to incur $4,000 or more in annual Part D drug costs.[2,4]

Under Medicare Part D, the main objective of the exemplified federal MTM program is to improve the quality and safety of medication use for targeted beneficiaries with high need for prescription modifications.[5] Medicare Part D provides outpatient prescription drug insurance to disabled and older adult beneficiaries. Accordingly, MTM was designed to optimize health outcomes through improved medication use, thereby reducing adverse drug events.[3,6] Additionally, the provision of MTM programs should lower prescribed drug costs, improve patient adherence to medication regimens, and reduce clinical risk, as well as reduce the rate of inappropriate spending for certain prescription drugs for targeted beneficiaries. Various pharmacy, medical, and insurance organizations have established guidelines and definitions to distinguish MTM programs from other types of community pharmacy activities.[3] MTM programs differ from disease state management in their focus on medications and multiple conditions. MTM programs also differ from patient counseling because of the emphasis on collaboration with patients and providers, which is conducted independently of dispensing.

On March 23, 2010, President Obama signed the Patient Protection and Affordable Care Act (PPACA) into law, followed on March 30 by the Health Care and Education Reconciliation

Act of 2010.[7-9] The PPACA authorizes expanded roles for pharmacists in the reformed health care model to ensure the appropriate use of medications. The law provides grants to establish community-based, multidisciplinary teams to support inclusion of pharmacist-delivered MTM services primary care practice. These grant programs will support the delivery of pharmacist-provided MTM services for the treatment of chronic disease based on the "core elements" of the MTM service model.[10] Core elements include the following: (a) medication therapy review, (b) personal medication record, (c) medication-related action plan, and (d) appropriate documentation and follow-up.[8,10] MTM services offered through coordinated care programs may also receive grants through the CMS Center for Medicare and Medicaid Innovation.[8]

Part D is undergoing its first major revision with the gradual elimination of the coverage gap by 2020.[6] It is, therefore, timely to review the emerging evidence on the impact of Part D and MTM programs concerning the quality of medication use to help inform future directions. Evidence shows that Part D has improved medication affordability and accessibility. Nonetheless, it remains unclear whether Part D MTM has optimized health outcomes, increased the quality of medication use, and reduced clinical risk. As noted by previous authors, the emerging literature has documented the measurable economic, clinical, and humanistic outcomes of MTM programs reimbursed by government financed payers and community-based insurance providers.[11] Yet, outcome information is not always available for certain major MTM programs. As of 2011, no published studies have examined the impact of MTM services offered under Part D in comprehensive evaluations.[6] Even for non-Part D MTM services, evaluations are limited.[1,11,12] This is primarily because public-use Part D data do not include MTM program-specific information.[6]

Further, the initial goal of MTM programs was widely defined to provide education, improve adherence, or detect adverse drug events and medication misuse.[11] The broad goals and variety of designs among MTM programs makes assessment of these programs challenging. Finally, evaluations in this area are confronted by the lack of easily measurable or definitive outcomes common across MTM programs.[6] Systematic reviews conducted before 2007 underscored the shortfall in assessments of clinical and humanistic outcomes, compared with economic outcomes mostly obtained from the payers' perspective.[13,14] All of these factors make the review of MTM a complex and challenging task.

Methods

PubMed, a search engine service of the National Center for Biotechnology Information (NCBI), was utilized by trained research assistants to search articles, using the following set of key words: *MTM, randomized controlled trials on MTM, evaluation of MTM, comprehensive medication review, medication action plan, special needs population, special needs plans, Medicaid, disease management, adherence, nonadherence, compliance, chronic conditions, disabling chronic conditions,* and *disability.* Additional searches were conducted for key articles in the most recent systematic reviews. The initial search identified nearly 300 articles with a broad array of literature. We then integrated data from a separate search under these terms and selected only outcome evaluation studies. The final review included major MTM studies and covers the available evidence, with special attention on recent studies using more rigorous designs and research methods. As a result, we gathered available studies for program populations covered by Medicare and Medicaid (dual eligibility) and for program populations covered by nonfederal programs; both may include some poor, racial and ethnic minorities, and disabled populations.

Results

Findings of our literature search are summarized in this section, following 3 outcomes in the literature: economic, clinical, and humanistic. For major studies cited, this review covers central aspects of research design, service setting, and study populations. Some details are presented in the tables that follow. Special attention is paid to economic and clinical outcomes in more recent evidence to address the weakness of research in earlier evaluations.[6,13,14] Accordingly, studies without substantive end-point measures or on non-MTM-related interventions are excluded. The findings on the available evidence for MTM are summarized in 2 tables: randomized controlled trials (RCT) in Table 1 and quasi-experimental studies in Table 2. Acronyms and abbreviations used in the tables are listed in Table 3.

Economic Outcomes

Economic outcomes from past studies have included utilization-related expenditures for the following interrelated categories: (a) individual services (pharmacy, physician office visits, hospital inpatient care, emergency department (ED) visits, and nursing home admissions); (b) preventable care services and total Medicaid care; and (c) overall pharmacy and selected service utilization (e.g., hospital, institutional, and primary care settings). Costs of these services are covered by health care plans and patients. Beyond earlier reviews, mostly from the payer's perspective, we found limited research evaluations regarding the MTM impact on economic outcomes at regional and state levels. The results of major national and state studies using various research designs and objectives are classified under several of the following subsections.

Large-Scale Population Studies on Overall Cost Savings. Christensen et al. (2004) investigated the impact of pharmacy management intervention on reducing polypharmacy among Medicaid recipients in 253 nursing homes.[15] This study was

TABLE 1 Randomized Controlled Trials

Authors, Publication Year, Reference Number	Type	Patients/Subjects	Interventions	Outcomes
Al-Rashed et al., 2002[36]	NRCT	Elderly pts. RA; 2 wards to G1: mean age (SD) = 80.2 (5.7) years, no. of Rxs = 7.1 (1.8), 27/16 m/f; CTRL: mean age (SD) = 81.1 (5.8) years, no. of Rxs = 7.1 (2.3), 20/20 m/f. BL 15-22 days (V1), 3 mos. (V2).	G1 (n = 43): pre-d/c counseling by clinical pharmacist re: med. information compliance; CTRL (n = 40): usual care.	G1 vs. CTRL: greater compliance (% of total items 48.4 vs. 15.9, $P > 0.001$ at V1, 70.0 vs. 15.8, $P > 0.001$ at V2), fewer GP visits (19 vs. 27 at V1, $P > 0.05$; 24 vs. 32, at V2, $P > 0.05$), and fewer hospital readmissions (5 vs. 13 at V1, $P > 0.05$; 3 vs. 15, at V2, $P > 0.05$).
Borges et al., 2011[27]	Controlled trial without mentioning the randomization procedure	Adult pts. of Brazilian public. health system Dx type 2 diabetes mellitus. Casual assign to G1: 69.4 ± 8.4 yrs., 60.6/39.4% m/f; CTRL: 64.6 ± 11.4, 64.5/35.5% m/f.	G1 (n = 40): PCM, monthly F/U with pharmacist; CTRL (n = 31): standard care—clinical appointments and meds., only F/U med. records.	G1 had statistically significant reduction in metformin cost (25.0%) and ED visits (0.8 [1.6] at BL vs. 0.6 [1.2], $P < 0.05$) and increased costs with family physician visits (0.2 [0.3] at BL vs. 0.5 [0.9], $P < 0.05$); CRTL: statistically significant increase in general costs of TRx and visits (21.3%).
Carter et al., 2009[46]	CRCT	Patients with uncontrolled HTN, mean age 58.3 yrs. RA 6 clinics in IA to G1 (n = 3) and CTRL (n = 3). BL 3 mos., 6 mos.	G1 (n = 192): pharmacist/physician collaboration; CTRL (n = 210): no treatment.	G1 mean (SD) guideline adherence scores increased 55.4%, from 40.4 (22.6) at BL to 62.8 (13.5) at 6 mos.; CTRL increased 8.1%, from 49.4 (19.3) at BL to 53.4 (18.1) at 6 mos. ($P = 0.09$ for adjusted between-group comparison). G1 mean BP decreased 20.7/9.7 mmHg vs. CTRL 6.8/4.5 mmHg ($P < 0.05$ for between-group systolic BP comparison); BP was controlled in 63.9% of G1 and 29.9% of CTRL patients (adjusted OR = 3.2; 95% CI = 2.0-5.1; $P < 0.001$).
Doucette et al., 2009[43]	RCT	Pts. with diabetes, 60.0 ± 12.0 yrs., 35/43 m/f. RA to G1 and CTRL.	G1 (n = 36): community pharmacist-provided extended diabetes care service up to 4 quarterly visits; CTRL (n = 42): no treatment.	G1 significantly increased no. days/week pts. engaged in diet and diabetes self-care activities (1.25 and 0.73 more days/week, respectively). No between-group difference in mean 12-mo. changes for HbA1c, LDL-C, and BP.
Jack et al., 2009[37]	RCT	Adult pts. in urban hospital in MA. Block RA G1: 176/47 m/f, mean age (SD) = 49.6 (15.3) yrs.; CTRL: 195/42 m/f, mean age (SD) = 50.1 (15.1) yrs. BL 30 days post-d/c.	G1 (n = 370): in-hospital consult., aftercare plan, and post-d/c call from pharmacist; CTRL (n=368): usual care.	G1 had lower rate of hospital utilization vs. CTRL (0.314 vs. 0.451 visit per person per month; incidence rate ratio, 0.695, 95% CI, 0.515-0.937; $P = 0.009$). Intervention most effective for participants with hospital utilization in the 6 mos. before index admission ($P = 0.014$).
Koehler et al., 2009[38]	RCT (pilot study)	Elderly pts. of 2 hospital med. Gs in TX. RA to G1: 3/17 m/f, mean (SD) age = 77.2 (5.3) or CTRL: 8/13 m/f, mean (SD) age = 79.8 (5.6). BL 30 and 60 days post-d/c.	G1 (n = 20): med. counsel by pharmacist, education and d/c plan by care coordinator, phone F/U; CTRL (n = 21): usual care.	G1 readmission/ED visit rates were reduced at 30 days (10.0% vs. 38.1%, $P = 0.04$), but not at 60 days (30.0% vs. 42.9%, $P = 0.52$) compared with CTRL for pts. who had readmission/post-d/c ED visits; the time interval to event was longer for G1 vs. CTRL (36.2 vs. 15.7 days, $P = 0.05$).
Murray et al., 2009[26]	RCT	Low-income HF patients in university ambulatory care practice, n = 314 pts. aged 50+ yrs. O/C 30-day post-d/c IP admit and ED.	G1 = pharmacist intervention; CTRL = usual care.	ED and IP were 19.4% less in G1; adherence 67.9% (G1) and 78.8% (CTRL); significant difference = 10.9%, 95% CI = 5.0-16.7; no significance 90% post-F/U; effect dissipated.
Nazareth et al., 2001[39]	RCT	Pts. >75 yrs. on 4+ meds. Pts. d/c from 4 London hospitals were RA to G1 (n = 181, mean SD age 84 ± 5.2, 38/62% m/f); CTRL (n = 181, mean SD age 84 ± 5.4, 34/66% m/f).	G1 = pharmacist review, F/U; CTRL = usual care.	No significant between-group difference in proportion of pts. readmitted to hospital at 3 or 6 mos., no. deaths, visits to hospital outpatient clinics, and GP, and no. days in hospital as % of F/U days.
Nietert et al., 2009[40]	RCT	Pts. overdue for med. refills. RA of pts. of 9 SC pharmacies to G1 (n = 1,018, mean age 59.9 ± 6.7 yrs.), G2 (n = 1,016, mean age 60.6 ± 16 yrs.), and CTRL (n = 1,014, mean age 38.2 ± 16.5). BL 30 days, 60 days.	G1 = pharmacist contact via telephone; G2 = pharmacist contact with prescribing physician via facsimile; CTRL = usual care.	No between-group differences in study outcomes re: persistence of Rx refills.

TABLE 1 *Randomized Controlled Trials (continued)*

Authors, Publication Year, Reference Number	Type	Patients/Subjects	Interventions	Outcomes
Planas et al., 2009[44]	RCT	Pts. with diabetes and HTN. RA OK MCO enrollees to G1 (n = 32, 11/21 m/f, mean age 64.2 ± 10.5) and CTRL (n = 20, 8/12 m/f, mean age 65.2 ± 14.1).	G1 = monthly HTN MTM services; CTRL = 3-mo. visits, inform of BP goals for patients with diabetes.	G1 systolic BP decreased 17.32 mmHg; CTRL systolic BP increased 2.73 mmHg ($P = 0.003$); G1 % pts. at goal BP increased (16.0% to 48.0%); CTRL decreased (20.0% to 6.67%); G1 pts. 12.92 x more likely to meet BP goal ($P = 0.021$). No significant group difference for mean adherence rate.
Sarangarm et al., 2013[35]	CRCT	Internal med. patients aged > 18 years. Assigned 6 teams from NM hospital to G1 (n = 140, 53.6/46.4% m/f) and CTRL (n = 139, 58.3/41.7% m/f). BL 30 days post-d/c.	G1 = d/c counseling by pharmacist, usual care, F/U phone call from pharmacist; CTRL = usual care.	20.7% of patients had readmission or ED visit within 30 days of d/c, no difference between groups ($P > 0.05$); G1 higher pt. satisfaction; mean summative scores were 40.4 (CTRL) and 43.1 (G1) out of 45 ($P < 0.0001$); G1 greater med. adherence (58.5% vs. 75.7%, $P = 0.05$).
Schnipper et al. 2006[42]	RCT	Pts. d/c from Boston hospital. RA to G1 (n = 92, 60.7 ± 17.2 yrs., 33/67% m/f) and CTRL (n = 84, 57.7 ± 15.9 yrs., 35/65% m/f). BL 30 days post-d/c.	Pharmacist pre-d/c review for DRPs; 30-day post-d/c trial O/C: preventable ADE.	Unexplained discrepancies pre-admission med. regimens and d/c med. orders (49%); unexplained discrepancies between d/c med. lists and post-d/c regimens (29%); NA in 23%; 30-day post-d/c preventable ADE G1 1%, CTRL 11%, $P = 0.01$.
Stowasser et al., 2002[41]	RCT	Pts. from pre-admission to orthopedic clinic and acute wards. RA to G1 (n = 113, 67.4 ± 13 yrs., 56/44% m/f) and CTRL (n = 127, 65.6 ± 14, 54/46% m/f). BL 30 days post-d/c.	G1 = MLS intervention, GP and CP contact; CTRL = usual care.	G1 vs. CTRL: more changes to therapy (97% vs. 90%), interventions (1.43 [1.5] vs. 0.77 [1.1], and med. changes per pt. (3.75 [2.6] vs. 3.10 [2.3]); G1 had significantly fewer health care professional visits per pt. (7.54 [7.4]) vs. CTRL (9.94 [10]).

Note: Definitions of abbreviations and acronyms used in this table are provided in Table 3.

the first phase of the North Carolina Polypharmacy Initiative. A pre-post design was used to assess a systematic pharmacist drug regimen review and consultation with prescribing physicians, delivered by 110 pharmacists who participated in the 2002 study. Prescription profiles were generated from Medicaid claims data. Pharmacists returned 7,548 (82%) profiles for 9,208 patients and offered a mean of 1.58 recommendations to each prescriber. After excluding 13% of those who were discharged or deceased, 6,344 patients (69%) remained for analysis. These patients used an average of 9.5 prescriptions per month at baseline, costing the North Carolina Medicaid program an average $502.96 monthly. After physician consultation, 1 or more recommendations for change were implemented for 72% of patients, and 68% of patients experienced a switch to a lower-cost drug. Drug cost savings were an average of $30.33 per patient per month.

A subsequent smaller study evaluated 92 Kerr Drug pharmacies in North Carolina from 2006 to 2007.[16] Subjects included 88 North Carolina Medicaid beneficiaries who received at least 12 prescriptions per month and also completed 4 quarterly medication reviews and/or recommendations by a Kerr Drug pharmacist. The rate of providers accepting recommendations ranged from 42% to 60%. The rate at which the accepted recommendations were implemented at Kerr Drug pharmacies ranged from 62% to 86% across the 4 quarterly reviews. Overall economic impact results were demonstrated with an average cost savings of $107 per beneficiary to North Carolina Medicaid per year. Quarterly economic impact suggested that the highest impact occurred during the first quarterly review at $63 per beneficiary. Finally, prescriber acceptance and pharmacy implementation of cost-savings alternatives revealed an annual average cost savings of $9,444 to North Carolina Medicaid. This savings totaled $2,724 after adjusting for pharmacist reimbursement.[16]

A statewide MTM program in North Carolina called Checkmeds NC offered face-to-face service with community pharmacists for Part D beneficiaries.[17] Participating pharmacies served 11,671 members in 23,826 encounters during a 7-month period in 2010. Costs attributed to the program included implementation and drug costs. Benefits attributed to the program were cost savings in medications and medical care avoided. The program manager reporting these findings indicated that there were $13.2 million in savings based on less than a $1 million investment.[17] The programs manager's report has not been subjected to a published independent evaluation nor has precise information on cost savings been made available.

In a 10-year data analysis, Ramalho de Oliveira et al. (2010) provides a comprehensive evaluation of the face-to-face MTM program offered by Fairview Health Services (FHS), a network of 7 hospitals, 48 primary care clinics, 55 specialty clinics,

TABLE 2 Quasi-Experimental Studies

Authors, Publication Year, Reference Number	Type	Patients/Subjects	Interventions	Outcomes
Abdelgawad et al., 2006[53]	QE	Transaction records for statin Rxs filled April 2003-March 2005, Medicaid enrollment figures for 2003 and 2004. 3 test states (G1 = AL, TX, VA) and 3 CTRL states (NJ, NC, PA). 9-mo. average pre-post intervention.	G1 = PDLs with restrictions on Rxs for statins, PA needed for drugs not on list; CTRL = no PDLs.	PDLs reduced no. of "high Medicaid" physicians/enrollee 22.4% (6.5% margin of error, 95% CI), reduced no. Medicaid NRx 22.8% (6.3%), and reduced no. Medicaid TRx 26.1% (6.3%). Physicians who are "high Medicaid" prescribers declined by 15.8% (3.7%) more in PDL vs. CTRL states. NRx and TRx written for Medicaid pts. declined 20.2% and 21.1% more than in PDL vs. CTRL states.
Bunting et al., 2008[22]	QE	Pts. Dx with HTN and/or dyslipidemia (50.4 ± 8.55 yrs., 262/303 m/f). Pt. inclusion in clinical (C) and financial (F) cohorts dependent upon data available. BL3, BL2, BL1, yr. 1, 2, 3, 4, 5, 6.	C (n = 565) and F (n = 620): CV risk reduction education; regular, long-term F/U by pharmacists.	CV health improvements: mean systolic BP (137.3-126.3 mmHg); mean diastolic BP (82.6-77.8 mmHg; % of pts. at BP goal (40.2%-67.4%); mean LDL-C (127.2-108.3 mg/dL); % of pts. at LDL-C goal (49.9%-74.6%). Mean cost per CV event decreased from $14,343 to $9,931 during study period. CV-related med. costs decreased from 30.6% to 19% of total health care costs.
Chrischilles et al., 2004[28]	QE prospective cohort design	Pts. taking 4+ meds. IA Medicaid beneficiaries eligible for PCM services. G1 (n = 524, 54.1 ±0.8 yrs., 105/419 m/f); CTRL (n=1 ,687, 48.4 ± 0.5 yrs., 518/1,169 m/f). 6 mos. pre, 12 mos., 6 mos. post.	G1 = reimbursement for PCM services; CTRL = usual care.	G1 had significant ($P < 0.05$) decrease in prevalence of high-risk med. use (43.4%-32.6%) vs. no significant change for CTRL (35.8%-34.4%). G1 mean MAI score improved significantly (9.4-8.3, $P < 0.001$) and % of meds. with problems decreased in 8 of 10 MAI domains. No between-group difference in health care utilization or charges.
Christensen et al., 2004[15]	QE	Residents of 253 NC nursing homes with ≥ 18 Rx refills in the previous 90 days and PDTPs. G1 = 6,344 residents; 75% f; mean age (SD): 76.8 (2.5) years; pts. used a mean of 9.52 Rxs/mo.; no CTRL. Before: 3 mos./after design.	Targeted reviews of drug regimens, physician consultation by pharmacists.	Mean of 1.58 recommendations offered to prescribers, ≥ 1 recommendations implemented after physician consult for 72% of patients with change recommendation; 68% switched to lower-cost drugs. Drug cost savings: $30.33/pt. per mo.
Christensen et al., 2007[62]	QE before/after design with 2 control groups	Pts. Rx highest no. meds. Pts. of NC pharmacies and clinic volunteer, G1 (n = 67, 67.7 ± 11.4 yrs., 37.7/62.3% m/f); CTRL 1 (n = 689, 67.6 ± 12.2 yrs., 57/43% m/f); CTRL 2 (n = 870, 66.0 ± 12.1 yrs., 28.7/71.3% m/f). 6 mos. pre, 6 mos. post.	G1 = pharmacist-conducted MTM reviews, education re: med. use, disease management, adherence, self-care; CTRL 1 = no MTM services; CTRL 2 = no MTM services.	Pharmacists identified mean of 3.6 PDTPs per pt. at first visit ("potential underuse," "more cost-effective drug available" most common). Pharmacists recommended med. change in about 50% of pts. and contacted prescriber for > 85%. About 50% of pts. with PDTPs had change in drug therapy; Rx use decreased in all Gs but was statistically significant only for CTRL 1 & 2. No significant differences were observed in copayment or insurer Rx costs.
Hirsch et al., 2011[20]	QE cohort study	Pts. Dx HIV/AIDS, Medi-Cal beneficiaries. Pts. of pilot pharmacies = G1 (n = 1,353, 46.0 ± 8.9 yrs., 1,032/321 m/f); pts. of nonpilot pharmacies = CTRL (n = 5,665, 46.7 ± 8.7, 4,589/1,076 m/f). BL 1 yr., 2 yrs., 3 yrs.	G1 = HIV/AIDS pharmacy MTM services compensation pilot program; CTRL = usual care.	G1 vs. CTRL pts. more likely to remain on single type of ART regimen (e.g., 2007: 71.7% vs. 49.1%, $P < 0.001$) and less likely to have excess fills (e.g., 2007: 12.9% vs. 35.5%, respectively, $P < 0.001$). Predicted mean (SE) total health care costs/pt. were not significantly different (e.g., 2007: $38,983 [$1,023] vs. $38,856 [$633], $P = 0.915$). Predicted non-ART med. costs were 30%-40% greater for G1 vs. CTRL (e.g., 2007: $10,815 [$538] vs. $8,190 [$252], $P < 0.001$) and predicted expenditures for IP services were significantly lower for G1 vs. CTRL (e.g., 2007: $3,083 [$293] vs. $5,186 [$300], $P < 0.001$).
Hirsch et al., 2009[21]	QE cohort study	Pts. Dx HIV/AIDS, Medi-Cal beneficiaries. Pts. of pilot pharmacies = G1 (n = 1,353, 46.0 ± 8.9 yrs., 1,032/321 m/f); pts. of nonpilot pharmacies = CTRL (n = 5,665, 46.7 ± 8.7, 4,589/1,076 m/f). BL 12 mos.	G1 = HIV/AIDS pharmacy MTM services compensation pilot program; CTRL = usual care.	G1 vs. CTRL: more remained on single type of ART therapy (56.8% vs. 34.2%, $P < 0.001$), greater adherence (56.3% vs. 38.1%, $P < 0.001$), and fewer excess med. fills (19.7% vs. 44.8%, $P < 0.001$). No between-group difference for rate of opportunistic infections between groups (28.2% vs. 26.1%, $P = 0.121$); G1 total mean (SE) annual health care cost/pt. 10% higher vs. CTRL ($40,596 [$889] vs. $36,937 [$479], $P = 0.001$) due to use of non-ART med. and mental health services.

TABLE 2 Quasi-Experimental Studies *(continued)*

Authors, Publication Year, Reference Number	Type	Patients/Subjects	Interventions	Outcomes
Hui et al., 2014[25]	QE retrospective matched cohort	Pts. of CA health care delivery system; Rx ≥2 MPD meds., Dx ≥2 chronic conditions. Participation voluntary; G1 (74.8 (7.9) yrs./42.5/57.5% m/f); matched group=CTRL (74.8 (7.9) yrs., 42.5/57.5% m/f). BL 1 yr.	G1 (n=34,532): MTM services; CTRL (138,128): no MTM services.	G1 vs. CTRL: significantly reduced mortality (HR=0.86, 95% CI=0.84-0.88; $P<0.001$), reduced odds for hospital admin. (OR=0.97, 95% CI=0.94-0.99; $P=0.018$), higher odds for ED visits (OR=1.17, 95% CI=1.14-1.20; $P<0.001$), and no difference in change in daily med. costs.
Isetts et al., 2008[19]	QE	Pts. with ≥1 of 12 Dx. Pts. of 6 ambulatory clinics in MN=G1 (97/188 m/f, 40 pts. ≥65 yrs.); pts. of 9 clinics without MTM=CTRL. BL 1 yr. services, F/U.	G1 (n=285): MTM services; CTRL (n=126 Dx HTN, 126 Dx HDL): no MTM services.	637 drug therapy problems resolved and therapy goals achieved increased from 76%-90%; G1 HEDIS measures improved vs. CTRL for HTN (71% vs. 59%) and cholesterol (52% vs. 30%). Total health expenditures/pt. decreased from $11,965-$8,197 (n=186, $P<0.0001$); reduction in total annual health expenditures surpass MTM service cost by >12 to 1.
Michaels et al., 2010[16]	QE retrospective analysis	NC Medicaid beneficiaries with Rx for 12+ meds./mo. No demographic info available. 3 mos., 6 mos., 9 mos., 12 mos.	G1 (n=88): 4 quarterly reviews by pharmacist, recommendations to PCPs.	42%-62% of recommendations from pharmacists accepted; average annual cost savings of $107/beneficiary to NC Medicaid; total annual average cost savings of $9,444 to NC Medicaid ($2,724 after pharmacist reimbursement).
Moore et al., 2013[24]	QE pre-post intervention w/matched control	Adult pts. with ≥14 claims over 120-day period. Participation voluntary; G1 (n=2,260); CTRL (n=6,463). 1 yr. pre, 1 yr. post.	G1=MTM program, 3+ consults with clinical pharmacist; CTRL=declined program, usual care.	G1 reduced plan-paid health care costs by 10.3% or $977 vs. CTRL increase of 0.7% or $62 ($P=0.048$); G1 vs. CTRL decreased IP visits (18.6% vs. 24.2%, $P<0.001$); G1 average days supply increased 72.7; CTRL decreased by 111.1 days ($P<0.001$). G1 pts. Dx HTN and dyslipidemia had pre-post increases in MPR of 2.29% and 2.10% vs. decreases of 2.31% and 2.61% (both $P<0.001$) for CTRL MTM program had an ROI of 2.0 in 2009.
Pindolia et al., 2009[3]	QE	Pts. of MI health system insurance company enrolled in MA-PD Part D. Participation voluntary; G1 2006 (36/64% m/f, 75.5±9.7); 2007 (36/64% m/f, 73.0±9.1); CTRL 2006 (40/60% m/f, 74.2±9.8); 2007 (37/63% m/f, 73.9±9.8). 6 mos. pre, 60 mos. post.	G1 2006 (n=292) and 2007 (n=228): telephone-based MTM services; CTRL 2006 (n=1,081) and 2007 (n=1,080): declined MTM services, usual care.	G1 2006 vs. CTRL 2006 had improved adherence to drug therapy for HF and insulin use, significant reduction in gastrointestinal bleeds ($P=0.001$), lower $PMPM (17.2% vs. 7% reduction, $P=0.001$); G1 2006 also had lower $PMPM for Rxs through 2007.
Ridley and Axelson, 2006[54]	QE retrospective cohort	Data from Medicaid recipients Rx statins in 2 southern states. G1 AL: pre-PDL (n=1,664, 44% ≥65 yrs., 22/78% m/f), post-PDL (n=1,771, 44% ≥65 yrs., 23/77% m/f); CTRL NC: pre-PDL (n=4,520, 50% ≥65 yrs., 26/74% m/f), post-PDL (n=5,562, 52% ≥65 yrs., 26/74% m/f). Pre: BL 1 yr. F/U, post: BL 1 yr. F/U	G1=state policy change: PDL for statins; CTRL=no PDL for statins.	G1 post-PDL had 82% higher relative odds of statin therapy NA vs. CTRL (OR=1.82, 95% CI=1.57-2.11). Pts. Rx restricted statin vs. unrestricted pts. more likely NA (OR=1.42, 95% CI=1.12-1.80); G1 post-PDL ≥65 yrs. were more likely to be NA than pts. <65 yrs. post-PDL (OR=1.33, 95% CI=1.02-1.73); 51% G1 post-PDL NA with statin therapy vs. 39% G1 pre-PDL and 36% CTRL pre- and post-PDL.
Walker et al., 2009[34]	QE prospective, alternating month	Pts. with ≥1 risk factors d/c from general med. service of southeast MI hospital. RA; G1 (n=358, 57.8 yrs., age 19-95, 46.1/53.9% m/f); CTRL (n=366, 57.4 yrs., age 19-97, 48.1/51.9% m/f). 72 hours, 14 days, 30 days	G1=pharmacist facilitated d/c; CTRL=usual care.	Med. discrepancies at d/c: 33.5% of G1 pts. V 59.6% of CTRL pts. ($P<0.001$); readmission rates did not differ significantly for G1 vs. CTRL at 14, 30 days; ED visit rates did not differ significantly.

TABLE 2 Quasi-Experimental Studies *(continued)*

Authors, Publication Year, Reference Number	Type	Patients/Subjects	Interventions	Outcomes
Welch et al., 2009[1]	QE NRCT	CO HMO MA-PD beneficiaries. Participation voluntary; opt-in = G1 (43.4/56.6% m/f, 68.8 ± 10.7), opt-out = CTRL (45.5/54.5% m/f, 68.9 ± 11.3). BL (180 days pre), F/U (180 days post).	G1 (n = 459): MTM services–med. review, telephone consult; CTRL (n = 336): usual care.	G1 (vs. G2): less likely to die (adjusted OR = 0.5; 95% CI = 0.3-0.9), hospitalization more likely (adjusted OR = 1.4; 95% CI = 1.1-2.0), and med. costs increased (adjusted OR = 1.4; 95% CI = 1.1-1.9) at F/U; no difference in ED visit rates. At least 1 DRP identified in more than 83% of beneficiaries in both G1 and CTRL (drug-drug interaction most common).
Wittayanukorn et al., 2013[23]	QE 2 pre-post retrospective designs	Beneficiaries Dx CVD conditions and enrolled in public university-sponsored insurance plan, 2008-2010. Matched groups design; G1 (61.9/38.1% m/f, 58.3 ± 9.3); CTRL (61.3/38.7% m/f, 56.9 ± 9.6).	G1 (n = 63): MTM services; CTRL (n = 62): comparison group, no MTM services.	G1 had statistically significantly lower costs/pt. for pharmacy (difference of -31.9 ± 25.1, $P < 0.0001$), med. (difference of -$325.6 ± 271.2, $P < 0.0001$), and total direct expenditures (difference of -$359.3 ± 219.2, $P < 0.0001$); ROI was $1.67 per $1 in MTM cost.

Note: Definitions of abbreviations and acronyms are provided in Table 3.

and 28 retail pharmacies that serves Minneapolis and St. Paul, Minnesota.[18] Electronic therapeutic records of 9,068 patients from September 1998 to September 2008 were analyzed. Of patient claims in this sample, 5.5% were paid by Medicaid and 12.5% were paid by Medicare Part D. Of 38,631 drug therapy problems identified and addressed by MTM pharmacists over the 10-year period, a need for additional drug therapy was most frequently reported (n = 10,870, 28.1%), closely followed by subtherapeutic dosages (n = 10,100, 26.1%). Pharmacist-estimated cost savings to the health system over the 10-year period were $86 per encounter, and the total cost of MTM was $67 per encounter. The estimated return on investment (ROI) was $1.29 per $1 in MTM administrative costs.[18] An earlier assessment of the FHS program (Isetts et al., 2008) covering a 1-year period before and after enrolling patients in MTM services found that total health expenditures decreased from $11,965 to $8,197 per person (n = 186, $P < 0.0001$) in that year.[19] The reduction exceeded the cost of providing MTM services by more than 12 to 1.

A large secondary analysis (Pindolia et al., 2009) examined the effectiveness of the telephone-based MTM program implemented for Medicare Advantage prescription drug plan members enrolled with the Health Alliance Plan (HAP), a subsidiary of Henry Ford Health System in southern Michigan during 2006 and 2007.[3] This MTM program aimed to ensure the provision of (a) the safest, most efficacious, and cost-effective drug therapy; (b) education on all aspects of drug therapy; and (c) adherence improvement. A total of 16,723 patients in 2006 and 17,111 patients in 2007 enrolled in the HAP. Part D enrollees accounted for 20% of the participants each year. Cost-savings analysis from 2006 data revealed a greater reduction in total prescription per member per month costs of 17.2% for MTM program enrollees, compared with a 7% reduction for those who declined ($P = 0.001$). The 2006 MTM program enrollees also indicated a sustained positive effect in lowered per member per month costs for prescription drugs in 2007. The enrolled group had higher drug costs at baseline than the group that declined the intervention. Multivariable analysis to adjust for group differences was not conducted. The internal validity of the study is therefore uncertain.

The MTM Effect on Disease-Specific Cost Savings. Hirsch et al. (2011) used a large cohort study (n = 2,234) to examine the expenditures for patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), who were receiving MTM services in community pharmacies over a 3-year period (2004-2007).[20] Data obtained from a pilot pharmacy program, conducted by the California Department of Health Care Services (DHCS) and Medi-Cal (California's Medicaid program), were compared with that of nonpilot pharmacies. The demographics of both groups were similar, except that pilot pharmacies had a higher proportion of Latino patients (19.7% vs. 14.9% in 2007, respectively, $P = 0.006$). The proportion of study patients receiving the majority of their antiretroviral (ART) and non-ART prescription medications at pilot pharmacies was 19.7% in 2005, 27.6% in 2006, and 28.1% in 2007. Results showed that the between-group difference in predicted mean total health care costs per patient did not differ significantly. The cost of MTM services was approximately $1,000 per patient-year among pilot pharmacy patients. Predicted non-ART medication costs per year in 2007 were 30%-40% higher ($P < 0.001$) in the pilot pharmacies ($10,815) than in the nonpilot group. However, predicted inpatient costs in the same year were lower ($3,083 vs. $5,186, $P < 0.001$). An earlier analysis by Hirsch et al. (2009), which evaluated the first year of the program with 7,018 patients, found similar rates of opportunistic infections and 10% higher cost per

TABLE 3 Abbreviations and Acronyms Used in Tables 1 and 2

Abbreviation	Definition
$PMPM	per member per month
ADE	adverse drug event
AL	Alabama
ART	antiretroviral therapy
BL	baseline
BP	blood pressure
CA	California
CI	confidence interval
CO	Colorado
CP	clinical pharmacist
CRCT	cluster randomized controlled trial
CTRL	control group
CV	cardiovascular
CVD	cardiovascular disease
d/c	discharge
DRP	drug-related problem
Dx	diagnosis
ED	emergency department
F/U	follow-up
G or Gs.	group(s)
GP	general practitioner
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
HEDIS	Healthcare Effectiveness Data and Information Set
HF	heart failure
HIV/AIDS	human immunodeficiency virus infection/acquired immune deficiency syndrome
HMO	health maintenance organization
HR	hazard ratio
HTN	hypertension
IA	Iowa
IP	inpatient (hospital)
LDL-C	low-density lipoprotein cholesterol
MA	Massachusetts
MAI	Medication Appropriateness Index
MA-PD	Medicare Advantage prescription drug plan
MCO	managed care organization
med(s).	medical/medication(s)
m/f	male/female
mg/dL	milligram per deciliter
MI	Michigan
MLS	medication liaison service
mmHg	millmeter per mercury
MN	Minnesota
mo(s).	month(s)
MPD	Medicare Part D
MPR	medication possession ratio
MTM	medication therapy management
NA	nonadherence
NC	North Carolina
NJ	New Jersey
NM	New Mexico
NRCT	nonrandomized controlled trial
NRx	new prescriptions
O/C	outcome(s)
OK	Oklahoma
OR	odds ratio
PA	prior authorization
PCM	pharmaceutical case management
PCP	primary care provider(s)
PDL	Preferred Drug List
PDTP	potential drug therapy problem
pt(s).	patient(s)
QE	quasi-experimental
RA	random assignment
RCT	randomized controlled trial
re:	regarding
RED	reengineered discharge
ROI	return on investment
Rx	prescription
SC	South Carolina
SD	standard deviation
SE	standard error
TRx	total prescriptions
TX	Texas
V	visit
VA	Virginia
yr(s).	year(s)

patient on total mean annual health care in pilot pharmacies patients than in other pharmacies.[21]

Bunting et al. (2008) evaluated a community-based long-term MTM program for persons with hypertension and dyslipidemia who received education and long-term MTM.[22] The longitudinal, pre-post study was conducted in 12 community and hospital pharmacy clinics in Asheville, North Carolina, from 2000 through 2005 without a control group.[22] The analysis measured economic outcomes in one group (n = 620) and clinical outcomes in a second group (n = 565). Combined historical event rate for cardiovascular or cerebrovascular (CV) event rate was 77 per 1,000 patient-years. This declined to 38 per 1,000 patient-years in the clinical group. Mean costs per CV event in the clinical group were $9,931 as compared with a historical value of $14,443, even though CV medication use increased nearly 3-fold.[22] However, the lack of control groups is a major limitation of this study.

Wittayanukorn et al. (2013) conducted a match-paired (age, gender, disease, and comorbidity) cohort study to compare economic outcomes of MTM services (n = 63, mean age 56.8) with that of non-MTM usual care (n = 63, mean age 56.9) for patients with cardiovascular disease (CVD).[23] The MTM group received MTM services at a pharmacist-provided pharmaceutical care

center on a university campus via face-to-face consultation for 30-60 minutes per encounter. At the 6-month follow-up, results of chi-square tests showed that the MTM group saved costs, as indicated in the mean costs (SD) for CVD-related pharmacy, all-cause medical, and total expenditures by $22 (19.1), $79.2 (99.6), and $75.1 (136.2), respectively. However, those indices increased in the non-MTM group by $10.7 (24.2), $24 (6.4), and $289 (269.5), respectively. The MTM group had significantly lower expenditure per patients for all 3 measures ($P < 0.0001$). The ROI was $1.67 per $1 in MTM cost.

Moore et al. (2013) reported a large-sample, retrospective, and match-paired (age, gender, baseline [a] supply; [b] plan-paid pharmacy costs; and [c] medical costs, physician visits, outpatient visits, and number of pharmacy-based conditions) cohort study of an MTM program with identified high-risk members in a larger employer program.[24] Subjects in the MTM group with such risks (n = 2,250, mean age 74.1) were invited to receive 3 or more telephone consultations with a clinical pharmacist. Those in the control group (n = 2,250, mean age 73.7) were selected from those who were targeted but declined the services. Baseline data found no differences in most of the matching criteria. However, the control group had a significantly higher number of pharmacy claims, total member pharmacy copayments, ED visits, diabetes, and depression, whereas the MTM group was higher in rates of mail distribution and dyslipidemia. Gender and race/ethnicity comparison were not listed in baseline statistics. At the 365-day follow-up, t-tests were used to compare between group changes. The average plan-paid health care costs (pharmacy costs and total medical costs) were reduced by 10.3% ($977) for the MTM group, compared with the increased costs by 0.7% ($62) for the control group ($P = 0.048$). The difference is most likely related to the reduced inpatient visits by the MTM group, compared with the increase of the control group, an index that showed no differences at the baseline. The estimated ROI for the MTM group was 2.0, slightly lower than the average disease management ROIs typically shown in the literature. A major limitation, as the authors noted, was self-selection, which may add bias to the results. Another limitation in this study and in the Wittayanukorn et al. study[23] may lie in the need for more appropriately controlled variables in multivariate analyses to address the bias introduced by the nonrandomized group assignment (e.g., baseline ED visits, diabetes, and depression).

Most recently, Hui et al. (2014) reported the largest retrospective matched cohort study (age, gender, geographic location, and prospective diagnostic-cost-group risk score) of an integrated health plan—the Kaiser Permanente California region.[25] The economic impact of the pharmacist-run, telephone-based Medicare MTM services for enrolled patients (n = 34,532, mean age 74.8) was evaluated in comparison with a matched control group (n = 138,128, mean age 74.8). For the MTM group, the initial encounter consisted of the pharmacist or a support staff member obtaining a list of current medications, followed by the pharmacist performing a comprehensive medication review. Then, follow-up encounters generally focused on identifying opportunities to improve medication therapy. The MTM staff documented all these encounters and interventions in patients' electronic medical records. Over the 5-year intervention period (2006 to 2010), multivariate statistical modeling revealed no differences in change in daily medication costs between the MTM group and the matched control group on a cost-per-day metric. The subgroup analysis of the 2010 cohort showed similar results with better outcomes than the overall cohort.

Clinical Studies of the MTM Effect on Comprehensive Cost Savings. Murray et al. (2009) used a medium-size RCT design to compare the cost savings of pharmacist intervention with usual care for 314 low-income patients (aged 50 years or older) with heart failure.[26] All participants had low health literacy and limited resources. An interdisciplinary team of investigators designed the intervention to support medication management. All patients were followed for 12 months. A pharmacist at a university-affiliated ambulatory care practice provided a 9-month multilevel intervention followed by a 3-month poststudy phase. Results showed that annual direct health care costs were reduced by $2,960 (95% confidence interval [CI] = $7,603-$1,338) in the intervention group, including reduced ED visits and hospital admissions.

Borges et al. (2011) conducted a controlled clinical study for type 2 diabetes mellitus with users of the Brazilian Public Health System at an outpatient endocrinology unit but did not mention whether a randomization procedure was used to divide groups.[27] All patients were referred by their physicians to pharmaceutical care. Members in the MTM group (n = 33, mean age 69.4) were followed up by a clinical pharmacist on a monthly basis for at least 7 times, whereas those in the control group (n = 31, mean age 64.6) received usual care. The pharmacist delivered verbal and written orientations regarding disease control, treatment compliance, nutrition, and drug usage. The pharmacist also worked with other health professionals on medication adjustment and collected data. At the end of this 12-month study, researchers observed significant reductions in metformin prescription costs for the MTM group and also significant increase in treatment costs (drugs and physician visits) for the control group. However, cross-group comparison showed statistically significant differences only in metformin prescription cost ($P < 0.01$) in 12-month and monthly accounts and ED costs, but not in other medication- or visit-related costs. As noted, this foreign study involved components not typically included in U.S. MTM programs, such as interprofessional collaboration.

Clinical Outcomes

Clinical outcomes may include a wide variety of end points, such as service utilization (pharmacy, physician, hospitalization, nursing home, and ED encounters); mortality; chronic disease prevalence; medication appropriateness; quality control; and medication adherence. Unlike economic outcomes, effectiveness of clinical outcomes must be supported at both population and clinical levels, . The most robust evaluations are classified under the following subsections to reflect the study design.

Large-Scale Studies of Overall MTM Influence. Chrischilles et al. (2004) and Goldman et al. (2007) conducted pre-post evaluations of the Iowa Medicaid Pharmaceutical Case Management Program (PCM), involving 2,211 noninstitutionalized patients.[28,29] All patients took at least 4 medications for chronic conditions and reported at least 1 of 12 specific diseases. They were cared for by pharmacists from 117 pharmacies. The percentage of PCM recipients using high-risk medications decreased significantly compared with that of the PCM-eligible patients who did not receive the service. Patients in the 28 high-intensity pharmacies decreased their high-risk medication use compared with low-intensity pharmacy patients ($P<0.001$). There was also improvement in the average Medication Appropriateness Index (MAI).[30] MAI uses a weighed score of 10 explicit criteria (indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplications, duration, and expense). The MAI declined from 9.4 to 8.3 in the high-intensity group ($P<0.001$). Yet, there was no difference between groups in health care utilization or charges, which included the cost of the high-intensity intervention, even after including reimbursements for the PCM.

Smith and Clancy (2006) evaluated 506 older adults in an uncontrolled study of those enrolled in the Senior PharmAssist Program, supported by Durham County, North Carolina.[5] The MTM service intervention was comprehensive, including regular assessment by pharmacists. Patients or their caregivers met program staff, including a pharmacist, at baseline, 6, 12, and 24 months. At the end of the study, ED visits and hospitalizations decreased during the first year, while patients' self-reported health status improved. However, there was no evidence of overall changes concerning the number of prescription medications or adherence. Functional status of the patients, as measured by Activities of Daily Living and Instrumental Activities of Daily Living scales, remained stable during the study.[31] Despite the comprehensive assessment, the absence of a control group limited the value of outcomes presented by these researchers.

More recently, Pindolia et al.'s evaluation of the HAP in southern Michigan during 2006 and 2007 overcame this limitation.[3] Results from 2006 data showed overall improvement in measurable clinical outcomes for MTM program enrollees compared with those who declined enrollment. The benefit included a trend toward improved adherence to drug therapy for heart failure and insulin use, as well as a significant reduction in gastrointestinal bleeds ($P=0.001$).

Quasi-Experimental Studies of the MTM Effect on Service Utilization and Beyond. In a prospective cohort study of a Medicaid home and community-based waiver program in South Carolina, Shultz et al. (2011) examined nursing home admission rates among 273 persons recruited from a community-dwelling nursing home eligible Medicaid population.[32] The intervention group received MTM services. A group of 800 age-, race-, and gender-matched waiver program clients served as controls. The medication management service was not delivered directly by pharmacists, but the team effort involved 12 pharmacies in 15 locations. Intervention was composed of 2 parts: (1) a calendar card, in which a client's medicines were dispensed instead of in prescription bottles, and (2) a coordinating service by a health educator to address emerging medication-related problems. Results indicated that controls were 2.94 times more likely to be admitted to a nursing home than intervention group members.

Welch et al.'s (2009) large quasi-experimental study with a nonequivalent comparison group assessed clinical and medical outcomes of a telephone-management MTM program operated by Kaiser Permanente Colorado (KPCO).[1] The KPCO service is a pharmacist-managed MTM program established under the Medicare Modernization Act, which was mandated in 2003 and implemented in 2006. It targeted Part D beneficiaries with 2 or more chronic conditions, who were receiving 5 or more covered medications and were likely to incur at least $4,000 in medication costs for 2006.[1] KPCO is a not-for-profit health maintenance organization with approximately 470,000 members who were receiving care in the Denver/Boulder metropolitan area, including approximately 60,000 members as Medicare Advantage beneficiaries. The sample included 459 opt-in and 336 opt-out beneficiaries who agreed or declined to receive MTM. A chronic disease score (CDS) was computed for each patient.[33] Despite similarities in age and patient characteristics, beneficiaries who opted-in had a higher CDS than did those who opted-out ($P=0.016$). Although the difference of less than 1 additional chronic disease per patient was statistically significant, the authors reported that the small difference was likely not clinically relevant.[1] Beneficiaries who opted-out were 41% more likely to have experienced an inpatient hospitalization during the baseline period ($P=0.006$), a clinically relevant difference. The intervention group received a thorough medication review by a clinical pharmacist to identify drug-related problems and a telephone consultation with the beneficiary or his/her caregiver. Results of unadjusted logistic regression analysis showed that compared with opt-out beneficiaries, opt-in beneficiaries had a 50% reduction in the likelihood of

death within 180 days after MTM but were 40% more likely to have had a hospitalization. Participants in the intervention group were also more likely to have had an increase in medication costs (odds ratio [OR] = 1.4, 95% CI = 1.1-1.9). There was no difference in ED visit rates. At least 1 drug-related problem occurred in more than 83% of the intervention and control group members. Drug-drug interactions were the most common problems for the intervention group. It is unclear whether the lower mortality of the opt-in group was related to the intervention or other unmeasured factors.

A quasi-experimental study by Walker et al. (2009) compared the outcomes of patients receiving pharmacist intervention (n = 358).[34] The intervention included medication therapy assessment, medication reconciliation, screening for adherence concerns, patient counseling, and education, while the control group (n = 366) had postdischarge telephone follow-up. The primary outcomes were 14-day and 30-day readmission rates and ED visits within 72 hours of discharge. No differences were shown in 30-day readmission rates and ED visits within 72 hours of discharge. This null finding may be related to the short period of the follow-up.

Sarangarm et al. (2013) assessed 279 patients in a case-control study at the University of New Mexico Hospital.[35] The intervention group received discharge counseling from a pharmacist who provided information about proper medication administration, side effects, and disease state education. This intervention team also reviewed patients' medications and prescriptions by completing medication reconciliation; identifying duplicative, unnecessary, or incomplete therapy; checking for drug interactions; verifying patients' formulary drug overuse and availability of medications; and ensuring prescription completeness. The control group received only usual discharge care, which included routine review of medication orders by a ward-based pharmacist and medication counseling by a nurse at the time of discharge and, typically, was focused on medication directions and sometimes on a discussion of indications or potential side effects, especially for new medications. The groups shared similar characteristics, except more patients in the intervention group were uninsured or enrolled in county-provided indigent patient assistance ($P < 0.001$). The rate of hospital reutilization within 30-days of discharge was similar between the 2 groups, but the intervention group reported improved primary medication adherence.

Moore et al.'s retrospective match-paired controlled study compared clinical outcomes of high-risk members in an MTM program with those who declined the program, with multiple characteristics matched between groups.[24] Over the 12-month period of this study, comparisons of pre-post difference found that the MTM group reduced hospitalization by 15%, compared with an increase in the control group by 7.6% ($P < 0.001$). There were no significant differences in the similar changes in ED visits between the 2 groups. However, the findings showed that the MTM group significantly improved its medication adherence, as measured with medication possession ratios (MPRs). The mean MPR increased in the MTM group for hypertension (2.29%) and for dyslipidemia (2.10%), whereas it decreased in the control group for these conditions (2.31% and 2.61%, respectively, $P < 0.001$). Nevertheless, MPRs did not change for diabetes, depression, and asthma in either group. As noted, the control group had significantly higher rates in diabetes and depression at the baseline period. As such, these findings need to be interpreted with caution because of self-selection bias of the group assignment and unrevealed demographic and clinical conditions in univariate tests. As noted, the different disease pattern of control groups suggests that there might be certain undetected behavioral factors as at least partial rival interpretations for the group differences.

Hui et al.'s large-scale retrospective-matched California cohort study found significant clinical outcomes for the intervention group (n = 34,532).[25] The primary outcome of this study was all-cause mortality within 365 days of study enrollment, while secondary outcomes included percentage of hospitalization and ED visits within each group. The MTM group had a significantly reduced mortality (hazard ratio = 0.86, 95% CI = 0.84-0.88; $P < 0.001$), lower odds for hospitalization (OR = 0.97, 95% CI = 0.94-0.99; $P = 0.018$), and higher odds for ED visits (OR = 1.17, 95% CI = 1.14-1.20; $P < 0.001$). Whereas no differences were found in the unadjusted all-cause mortality rate between the 2 groups (5.7% in the intervention group vs. 5.6% in the control group), the same mortality rate was significantly lower in the MTM group for the cohort enrolled in 2010 only (4.3% vs. 5.0%, $P < 0.001$). Despite its higher hospitalization rate in the postintervention period, the MTM group showed an absolute reduction in hospitalization of 4.1%. The control group, however, showed an increase of 2.1% (absolute between-group differences of +0.5%). Compared with the control group in the 2010 cohort, a significantly lower rate of hospitalization was observed in the MTM group (24.1% vs. 24.9%), despite a higher rate of hospitalization in the preperiod (27.3% vs. 22.1%). The findings in clinical outcomes are promising given the age of subjects, the large sample, and the long period of observation. The mixed results (hospitalization vs. ED visits) may help explain the null findings in economic outcomes, compared with the control group (n = 138,128). However, these types of study design would not completely eliminate rival interpretations for findings (e.g., selection bias).

Randomized Clinical Trials on the MTM Effect on Service Utilization and Beyond. Between 2001 and 2009, several small- to medium-sized clinical trials evaluated the impact of pharmacist interventions at medical discharge. Variable effect was seen on subsequent utilization. Most studies primarily focused on geriatric cohorts and disease-specific patient populations. A small nonrandomized controlled trial, for example, reported the value of using inpatient pharmacist intervention

for elderly patients.[36] A research pharmacist visited patients in their homes approximately 2-3 weeks and at 3 months post-discharge. The intervention group showed improvement in compliance ($P < 0.001$) at visit 2 and reduced unplanned visits to general physicians and rehospitalizations.

Using a more rigorous RCT design, Jack et al. (2009) examined 749 hospitalized adults (mean age 49.9 years) at an urban academic hospital.[37] A nurse conducted medication reconciliation, arranged follow-up appointments, and conducted patient education with an individualized instruction booklet. After discharge, a clinical pharmacist called patients within 2 to 4 days to reinforce the discharge plan and review medications. The intervention group (n = 370) had a lower rate of hospital utilization compared with the usual care control group (0.314 vs. 0.451 visits per person per month; incidence rate ratio=0.695; 95% CI = 0.515-0.937; $P = 0.009$). Koehler et al.'s (2009) similar trial using only 41 high-risk elderly inpatients at Baylor University Medical Center also showed reduced readmission/ED visit rates with a small effect size in the intervention group compared with the control group at 30 days (10.0% vs. 38.1%, $P = 0.04$) but not at 60 days after discharge (30.0% vs. 42.9%, $P = 0.52$).[38] Nazareth et al. (2001) randomized 180 elderly patients to either a hospital pharmacist-developed discharge plan (e.g., details of medication and support required by the patient) or usual care.[39] The primary outcome was readmission to the hospital within 6 months. Secondary outcomes included the number of deaths, attendance at hospital outpatient clinics, and general practice and proportion of days in hospital over the follow-up period, together with patients' general well-being, satisfaction with the service, and knowledge of and adherence to prescribed medication. The investigators found no significant group differences in either rehospitalization at 3 months or 6 months or in any of the secondary outcomes.

In an RCT conducted by Murray et al.—a pharmacist intervention with low-income heart failure patients—ED visits and hospital admissions were 19.4% less in the intervention group during the 9-month intervention period.[26] Medication adherence was 67.9% in the intervention group and 78.8% in the usual care group, a statistically significant difference during the follow-up period (difference = 10.9 percentage points, 95% CI = 5.0-16.7 percentage points). However, no significant difference was found in the 3-month postintervention follow-up period. Medications were taken on schedule 53.1% of the time in the intervention group compared with 47.2% of the time in the usual care group (mean difference 5.9%). This effect also dissipated by the end of the intervention.

Nietert et al. (2009) conducted a large-scale RCT to evaluate the effectiveness of 2 MTM programs at improving persistence of prescription refills for chronic diseases.[40] The study involved 9 pharmacies within a medium-sized grocery store chain in South Carolina, representing urban, suburban, and rural areas. Patients (n = 3,048) with diverse backgrounds, who were overdue for refills for selected medications, were randomized into 1 of 3 treatment arms: (1) pharmacist contact with the patient via telephone, (2) pharmacist contact with the patient's prescribing physician via fax, and (3) usual care. Prescription refill data were collected routinely from the pharmacy district office's centralized database. Pharmacy employees gathered patient disposition codes based on patient-reported reasons for being overdue for a refill or not picking up a prescription. An intent-to-treat approach was employed for all analyses. No significant improvement was seen in the treatment or usual care groups. The null finding could be partly attributed to modest interventions evaluated, not necessarily to the provision of typical MTM programs.

Other studies showed mixed findings regarding the clinical effect of MTM programs. Stowasser et al. (2002) conducted an RCT of medication liaison services (MLS), with 240 patients at 8 acute wards (servicing 12 medical and 5 surgical units) and an orthopedic preadmission clinic at 2 major hospitals.[41] The MLS used clinical pharmacists to provide consultations prior to discharge for the intervention group as a discharge communication. Pharmacists provided patients with a medication list and therapy changes as well as instructions on the length of therapy, sources for the medication, patient allergies and adverse drug reactions, potential medication-related problems, and actions for the general practitioner to consider. Lower likelihood of a readmission in the 30 days following discharge among the intervention group did not quite reach statistical significance ($P = 0.055$). However, the MLS group significantly improved in 2 of 8 functional health status measures. In another study, Schnipper et al. (2006) randomized 178 patients to the intervention or usual treatment group at the general medicine service of a large teaching hospital.[42] The intervention group received pharmacist counseling at discharge and a follow-up telephone call 3 to 5 days later. Results indicated no group differences in total health care utilization or in total adverse drug events (ADEs), but preventable ADEs were significantly lower in the intervention group at 30 days after discharge ($P = 0.01$). Given the mixed findings in the various studies reviewed in this section, the MTM effect on utilization remains ambiguous. More research with large-scale and rigorous designs is warranted.

Clinical Studies of the MTM Effect on Disease-Specific Outcomes. A few studies on MTM effects used various types of quasi-experimental designs. Bunting et al. conducted a pre-post study of a community-based long-term MTM program for patients with CV diseases.[22] During the study period, the authors observed a 53% decrease in risk of a CV event and greater than 50% decrease in risk of a CV-related ED visit or hospital admission. CV health improved over the course of the study as indicated by reduction in (a) mean systolic blood pressure, (b) mean diastolic blood pressure, (c) percentage of

patients achieving blood pressure goals, (d) mean low-density lipoprotein (LDL) cholesterol, (e) percentage of patients achieving LDL cholesterol goals, (f) mean total cholesterol, and (g) mean serum triglycerides. The absence of a control group, however, limits the causal inference regarding this study's findings.

Wittayanukorn et al.'s small-scale pre-post cohort study examined MTM services for patients with CVD.[23] Of the 40 patients in the MTM group, changes in their mean systolic and diastolic blood pressure, lipid panel, and BMI at the 6 follow-ups were not significantly different from levels obtained at the baseline period. However, the authors claimed significant achievement of certain patients' goals (e.g., change in disease stages). For blood pressure, the percentage of participants who reached their goals increased from 55% to 70% ($P < 0.05$), while normal BMI increased from 13% to 21.7% at follow-up, compared with the baseline.

Borges et al.'s controlled clinical trial for type 2 diabetes mellitus did not mention randomization in group assignment.[27] At the end of the 12-month study, the MTM group (n = 33) showed a reduction of 1.0% in the values of glycosylated hemoglobin A1c (HbA1c), from the baseline mean 8.9 ± 1.4 to the end-point mean 7.9 ± 0.8, whereas the control group (n = 31) observed an increase of 1.6% from the baseline mean 8.6 ± 1.3 to the end point mean 9.3 ± 1.6 (group difference: -0.9 ± 1.5 vs. 0.5 ± 1.5, $P < 0.01$).

For patients with HIV/AIDS, Hirsch et al. noted that as of 2010 only 1 study had examined a large group of patients, although the literature suggested that MTM services had improved antiretroviral therapy (ART) adherence and outcomes.[20] However, previous studies had not examined such outcomes for more than 1 year. Hirsch et al.'s cohort study compared a pilot program with a nonpilot program, conducted by the DHCS and Medi-Cal, concerning ART adherence and outcomes in 2,234 adults receiving MTM services in community pharmacies over 3 years. Most pilot participating patients were adherent to their ART medication regimens in comparison with nonpilot pharmacy patients (e.g., 2007: 69.4% vs. 47.3%, respectively, $P < 0.001$). After controlling for demographics in logistic regression analysis, use of a pilot pharmacy was the most important contributor to adherence (OR = 2.74, $P \leq 0.05$). Pilot pharmacy patients were more likely to remain on a single type of ART regimen than nonpilot patients ($P < 0.001$) and less likely to have excess refills ($P < 0.001$). They were also less likely to use contraindicated regimens ($P = 0.027$). There were no differences by group in the percentage of patients experiencing opportunistic infections each year.

RCT Evaluations for the MTM Effect on Disease-Specific Outcomes. Several more rigorous RCTs have assessed the efficacy of MTM. For a group of diabetic patients, Doucette et al. (2002) evaluated the effect of a diabetes care service provided by community pharmacists on primary clinical outcomes.[43] Specially trained pharmacists discussed medications, clinical goals, and self-management activities in up to 4 quarterly visits per patient. The pharmacists also recommended medication changes to physicians when appropriate. Of the 78 participants, 66 completed the final assessment (31 interventions, 35 controls). The intervention group saw a significant increase in the number of days per week that the patients in the group engaged in a set of diet and diabetes self-care activities. However, there were no significant group differences concerning the mean 12-month changes for HbA1c, LDL cholesterol, and blood pressure levels.

Planas et al.'s clinical trial (2009) of managed care enrollees with diabetes and hypertension demonstrated the effectiveness of a community pharmacy-based MTM program in improving blood pressure control and hypertension.[44] Intervention group patients met their blood pressure goals more often (16.0% to 48.0% improvement), whereas the comparison group actually declined in that metric (20.0% to 6.67%). In addition, Wubben and Vivian (2008) reviewed 21 clinical studies, published through August 2007: 9 RCTs, 1 controlled clinical trial, and 11 cohort studies were included.[45] A variety of interventions and study designs were employed, but all were targeted at adults with type 1 or 2 diabetes. The intervention group generally saw improvement in HbA1c values. However, the authors cautioned against overreliance on these findings given the limitations and identified flaws in the research designs of the reviewed studies, including the high potential for selection bias in the study population.

Carter et al. (2009) enrolled 402 patients with CVD and uncontrolled hypertension (mean age 58.3 years) in an RCT.[46] Clinical pharmacists provided recommendations for drug therapy, based on national guidelines, to physicians in the treatment group. The mean guideline adherence scores increased from 40.4 at baseline to 62.8 at 6 months for the intervention group compared with an increase from 49.4 at baseline to 53.4 at 6 months for the control group ($P = 0.09$ for adjusted between-group comparison). From baseline to the 6-month follow-up, the intervention group achieved statistically significant ($P < 0.05$) improvement in mean blood pressure levels, declining by 20.7/9.7 millimeters mercury (mmHg), as well as overall blood pressure control rates, compared with a control group, declining by 6.8/4.5 mmHg.

In their 2009 study, Murray et al. conducted a post hoc analysis on data from 2 RCTs for pharmacist intervention with 800 hypertensive outpatients stratified into complicated (n = 535; e.g., heart failure) and uncomplicated (n = 265) groups.[26] ADEs were identified from 1 year of electronic record data. Medication errors were classified as preventable and potential ADEs. In the pooled analysis, the risk of any event was 34% lower ($P \leq 0.05$) in the intervention group than in the control group, and the risk of an ADE was 35% lower ($P \leq 0.05$). Medication errors were also 37% lower in the intervention group. There was no difference in the risk of preventable ADEs

or potential ADEs. The study lacked power to detect differences between the complicated and uncomplicated groups except for lower risk in the complicated group for any event and ADEs. Risk reduction in the intervention group was similar to the pooled analysis.

Other Clinical Outcomes. Finally, a 10-year secondary analysis of the FHS MTM program set concrete goals for individual patients as the clinical outcomes measures (Ramalho de Oliveira et al.[18]). A clinical outcome status was recorded as "resolved," "stable," "improved," or "partially improved" for patient-perceived goals of therapy achieved for a specific medical condition (e.g., diabetes with HbA1c < 7%, blood pressure < 130/80 mmHg, LDL cholesterol < 100 milligram per deciliter). The following terms indicated unachieved goals of therapy: "unimproved," "worsened," or "failure." The study assessed the patients' clinical status at the first and at the most recent MTM consultation. For 4,849 patients who were not at their goals when they enrolled in the program, results showed that 7,068 conditions (55%) improved; 2,956 (23%) were unchanged; and 2,827 (22%) worsened during the course of MTM services for the 12,851 medical conditions. Alongside previous publications on FHS, this large-sample follow-up is one of a few reports that assessed outcomes in all 3 categories (i.e., economic, clinical, and humanistic).[19,47,48]

In addition, previous evaluations of the FHS MTM program showed significant improvement in scores on the SF-12 (version 2) physical role, social functioning, and physical component scales.[48] The Healthcare Effectiveness Data and Information Set demonstrated measured improvement in the intervention group compared with the comparison group for hypertension (71% vs. 59%) and cholesterol management (52% vs. 30%).[19] Yet, the lack of controls in these studies result in an inability to determine if history-related factors interfere with interpretation of observed outcomes.

Humanistic Outcomes

Humanistic outcomes include patient-centered measures such as quality of life, patient satisfaction, and better mental health. Compared with many earlier reports on economic outcomes from the payer's perspective, few published studies have evaluated humanistic outcomes that primarily reflect patients' interests.

Sarangarm et al.'s small-scale study of 60 Part D beneficiaries documented high patient satisfaction after enrolling in a pharmacist-provided telephone MTM program.[35] This 2013 study revealed that pharmacist-provided discharge counseling improved patient satisfaction in a survey: 40.4 (control) versus 43.1 (intervention) out of a possible 45 ($P < 0.0001$).[35]

The 10-year analysis of the FHS MTM program evaluated patient satisfaction surveys that have been administered to all MTM program enrollees since 2001.[18] The survey measured patient satisfaction with MTM services using a 7-item questionnaire that employed a 5-point Likert-type scale. Participants were asked to evaluate the following statements:

1. The pharmacist provided me with education that will help me achieve my goals of therapy.
2. The pharmacist helped me to understand the intended use (purpose) of my medication(s).
3. The pharmacist helped me to understand the intended results (goals of therapy) of my medication(s).
4. The pharmacist helped me understand how to take my medication(s) safely and correctly.
5. I feel that my overall health and well-being improved because of my MTM visit.
6. Health care benefits should include MTM services.
7. I would recommend this MTM service to my family and friends.

Results showed that 95.3% of participants agreed or strongly agreed that their overall health and well-being had improved because of MTM. Further, an earlier analysis of the FHS MTM program found a trend toward higher ratings of patients' personal doctor/nurse and doctors' communications in the Collective Drug Therapy Management intervention group relative to the comparison group.[49]

In Smith et al.'s prospective study of the Senior PharmAssist Program, patient knowledge of the rationale underlying prescribed medications increased during the first 6 months and remained stable thereafter.[5]

Major Gaps and Potential Problems Identified in the Evaluation of MTM

Medication Access Issues

A small number of articles have reflected physicians' perspectives regarding concerns about medication access in certain federal programs (e.g., Part D). In a report from a national sample of American psychiatrists, researchers highlighted a potential clinical risk that Part D patients with severe mental illness may face, who were dual eligible for both Medicaid and Medicare benefits.[50] A sample of 1,183 eligible psychiatrists from a pool of 5,833 psychiatrists randomly selected from the American Medical Association's (AMA) Physician Masterfile participated in a mail survey during the first 4 months of Medicare Part D implementation (January 2006 to April 2006). Respondents spent 45 minutes in administrative tasks for every 1 hour of direct patient care for dual-eligible patients by psychiatrists and their staff. Drug plan features, including prior authorization and preferred drug formularies, and medication access problems related to Part D MTM were associated with significant increases in administrative burden, which may result in less time for direct patient care.

According to West et al. (2009), the same research group surveyed psychiatric patients in 10 state Medicaid programs about medication access problems and associated adverse events.[51]

First, they asked psychiatrists randomly selected from the AMA Physician Masterfile (n = 4,866; 62% responded; 32% treated Medicaid patients) to randomly select 2 Medicaid patients for review (n = 1,625 patients). According to the patients, the most common access problems were (a) no access to clinically indicated medication because they were not covered by the program, (b) being prescribed a less preferred medication only because it was covered by Medicaid, and (c) discontinuing medications as a result of coverage or management issues. Medication access problems in the past year were reported for approximately 48% of the Medicaid patients, although there were considerable differences between states in this measure (absolute difference of about 38% between the lowest and highest reported values by state, $P < 0.001$). Adverse event rates after adjustment for sociodemographic and clinical differences were 3.6 times higher among patients with medication access problems ($P < 0.001$). Measured adverse events included ED visits, hospitalizations, homelessness, suicidal ideation/behavior, or incarceration. All prescription drug management features were associated with increased medication access problems and adverse events ($P < 0.001$). States with the greatest access problems had higher adverse event rates ($P < 0.001$).

St. Peter (2007) raised a similar concern about patients with end-stage renal disease (ESRD).[52] Depending on age, employment status, disability status, and public program eligibility, ESRD service may be completely covered or covered in part by an employer-based health insurance, Medicare Part B, Medicare Part D, and/or Medicaid. Additionally, while Part D extends coverage of prescription drugs in general to the ESRD and general Medicare populations, it specifically excludes coverage for erythropoiesis-stimulating agents and other drugs used during dialysis. These drugs are covered under Medicare Part B.[52] The coverage divide between Part B and D is confusing to physicians and pharmacists. Many ESRD patients who are dual eligible (covered by Medicare and Medicaid) get their medications through PDPs certified by CMS to offer Part D plans. Yet, because of the high cost of drug regimens for treating ESRD, including the highly prevalent comorbidities in this population, many PDPs have elected not to offer drugs that were previously covered under state Medicaid drug coverage plans.

In Goldman et al., socioeconomic differences concerning cost-sharing issues were explored.[29] Reviewed programs require use of older or less expensive medications before covering newer therapies. A major concern raised about these cost-containment policies was that patients may switch to less-effective medications or become nonadherent. As a result, they may experience adverse health effects. Two studies found that Medicaid beneficiaries taking a restricted statin medication filled fewer prescriptions and were more likely to be nonadherent than unrestricted patients.[53,54] A concern is also raised regarding the fact that low-income beneficiaries will be disproportionately affected in their responses to cost sharing.[29] For example, after the imposition of a $0.50 copayment, Medicaid enrollees in South Carolina used significantly fewer drugs. Another study found that elderly Medicaid recipients residing in states with copayment provisions consumed fewer drugs and tended to fill fewer prescriptions during the year than those in states without copayments.[55] Cunningham's survey (2002) revealed that, compared with less than 1 in 10 among privately insured individuals, 1 in 4 Medicaid patients aged 18 to 64 years could not afford to fill at least 1 prescription over the previous year.[55]

Enrollment Gaps and Disparities Related to MTM Programs

Medicare beneficiaries with previous drug coverage through Medicaid were required to choose a Part D plan or to be automatically enrolled in a plan based on random assignment. Lau et al.'s (2011) recent review of studies on Part D in older adults indicated that treatment interruptions during the transition to Part D occurred far less frequently than originally expected for dual-eligible patients and beneficiaries with chronic conditions.[6] However, vulnerable patients (e.g., sicker and dual-eligible beneficiaries) experienced lags in improvement, despite the positive effect of Part D on cost-related medication nonadherence. More vulnerable populations may need more time to adapt to new enrollment and administrative procedures before reaping the benefits of the new program. This means that more vulnerable patients may need additional assistance in gaining benefits from Part D, which could be a component of MTM services. Regardless of engagement efforts, patients with severe conditions (e.g., worsening conditions, poor health, and poor ambulation) will continue to face challenges in access to care.[11]

The CMS eligibility criteria for MTM may inadvertently work against minorities who could benefit from the program. African and Latino Americans tend to have higher rates of certain severe chronic conditions but also use fewer prescription drugs than European Americans.[56] To evalute the racial and ethnic disparities in meeting criteria of MTM services for Medicare beneficiaries, Wang et al. (2010, 2012) conducted a retrospective analysis of the nationally representative sample of Medicare beneficiaries in the Medical Expenditure Panel Survey (MEPS).[56,57] The results showed that the African and Latino populations were less likely to be eligible for MTM than were whites according to 2006 criteria and 2010 criteria. This disparity is primarily because the MTM eligibility criteria are predominantly based on utilization and economic evaluations.

Munshi et al.'s (2013) recent systematic review provided more comprehensive data for the MTM eligibility criteria disparity—involving Medicare, Medicaid, and general populations—in many reports gathered from peer-reviewed journals between 1985 and 2011.[58] In the Medicare population, African and Latino American Medicare beneficiaries had significantly lower medication use and expenditure, as well as disease-specific and drug-specific prescription drug utilization, compared with European

American counterparts. This is the case across various studies reviewed. Therefore, underserved minorities might have fewer opportutities to benefit from MTM services than whites.

Low Participation Rates and Challenges Faced by Stakeholders

A study conducted by Pellegrino et al. (2009) identified various challenges to the long-term success of MTM services from the perspective of patients, physicians, pharmacists, payers, and other stakeholders.[11] Health plans need to be able to identify patients with high resource utilization in order to justify the investment in MTM services. This is not as straightforward as it may seem. After identification, triage to and engagement of patients in appropriate services remain critical challenges. Low rates of patient participation have been common, especially with more intensive programs requiring greater time commitments.[59,60] Physician acceptance of MTM services is also a component to success.[19,60,61] However, previous research found that physicians often accept pharmacist recommendations at a relatively low (approximately 50%) rate.[62,63] MTM service providers and health plans should also consider physician views in order to enhance the willingness of physicians to encourage eligible patient participation in MTM services.[11] Further, despite their increasing acceptance of MTM services, pharmacists continue to face numerous barriers to the delivery of care, such as inadequate time, insufficient staffing, high dispensing workload, and difficulties with billing.[59,60,64] Because of little consistency in covered MTM services or in the preferred delivery method (face-to-face, telephone, or mail), there are considerable variations among programs offered by insurers through Medicare Part D.[65,66] Few studies have presented a comprehensive evaluation of all perspectives.

Lack of Defined Quality Standards from Multiple Perspectives

To fill the vacancy of systematic methodological evaluation on measures across MTM studies, Holtorf et al. (2009) reviewed 76 studies published between 1996 and 2007 on the impact of MTM on economic, clinical, or humanistic outcomes.[13] Most articles were from MTM programs provided in a managed care environment. The goal was to analyze study objectives, end points, and MTM service types. Studies were further categorized by health coverage type (e.g., managed care plans, indemnity insurance, Veterans Health Administration, or Medicaid). The impact of 9 different drug management tools and 11 possible end points was assessed in administrative data and survey data that represented perspectives from patients, health plans, or providers' points of view. Results showed that none of the included publications assessed the overall quality of drug management tools. Only 9.2% of program evaluations included health outcomes. Sixty-eight percent of the studies reported on plan-focused economic end points. Perspectives from the clinical, patient, and provider perspectives were studied less often (45%, 42%, and 12% of the studies, respectively). Just more than half of the 76 studies between 1996 and 2007 evaluated a patient-focused or clinical end point in addition to a plan-focused end point. Only one-third of studies on drug management tools that limit or control access through benefit restrictions assessed patient-focused or clinical outcomes.[13] A small number of studies have addressed patient satisfaction with MTM programs. Little research has examined the perspective of care providers in Part D MTM programs.[50,51]

McAdam-Marx et al. (2008) reviewed 77 studies employing 11 types of outcome end points.[14] Among these studies, 52 (68%) incorporated an economic end point, but 35 of these did not address clinical or humanistic outcomes. Overall, only 33 (43%) evaluated clinical or humanistic end points. Authors found no defined quality standard or benchmarks, including health outcomes, in order to improve the overall clinical and economic effectiveness of MTM programs. The Pharmacy Quality Alliance (PQA) was established in 2006 to address the call for outcome measurement in the performance of Medicare Part D MTM programs.[11,67] In 2012, PQA published 17 medication quality measures across 4 Part D domains: (1) drug plan customer service; (2) member complaints, problems getting services, and choosing to leave the plan; (3) member experience with the drug plan; and (4) drug pricing and patient safety.[68]

Gaps in MTM Research Designs

There is a paucity of multimethod research designs for MTM evaluation. No study has conducted an in-depth qualitative analysis from the perspective of primary care providers and patients. One descriptive study was identified that combined a literature review of 26 peer-reviewed articles and 33 gray literature documents with a semistructured telephone interview of 60 key informants from 46 different organizations. Case studies with 28 representatives from 4 MTM programs were also included.[69] The latter method involved 12 interviews with Medicaid program staff. Funded by CMS, this multimethod evaluation gathered the views of MTM providers in 2007. The study included both Medicare and non-Medicare programs. MTM programs used a variety of practice models. Almost all MTM programs used pharmacists to provide services. Medicare MTM programs used different eligibility criteria than MTM programs sponsored by Medicaid or other payers.

Most non-Medicare MTM programs provided face-to-face interventions, while Medicare MTM programs relied more on telephone or mail. Yet, no research was identified that compared the impact of different modes of contact, especially the use of mailed information.[11] Most MTM programs conducted annual comprehensive medication reviews, but the frequency of services varied considerably across programs, for example, quarterly or monthly visits or based on patient need (e.g., Minnesota

Medicaid, MTM vendors).[18,22] Still other programs allowed enrollees to contact a pharmacist at any time (e.g., call centers). Overall, the authors found little available research on Medicare MTM programs. Economic outcomes were most commonly measured in the MTM literature with variable research design quality and inconsistent results related to costs. Few rigorous studies have demonstrated the effectiveness of MTM. A few studies have showed an impact on health status and quality of life. Mixed findings from the most recent research with sound designs were summarized earlier in this review. These included a few studies that demonstrated an impact on serious sequelae (e.g., decreased rehospitalization or ED visits), and a few studies demonstrated significant improvements in intermediate outcomes (e.g., low-density lipoprotein cholesterol).

Discussion

MTM has been utilized in various forms as a mechanism to improve health metrics for medically complex patients since the 1990s. Its role expanded with the passage of Medicare Part D. Additionally, the use of MTM services is projected to increase as a result of the Affordable Care Act through introduction of accountable care organizations. According to Munshi et al., MTM services are highly valuable for disease management given that, in an aging society, the United States is facing more than 80% of the elderly having 1 or more chronic conditions.[58]

Limitations

In this article, we reviewed the current literature to distill the evidence of the impact of MTM services on vulnerable populations. The emerging literature has documented the measurable economic, clinical, and humanistic outcomes of MTM programs reimbursed by government-financed payers and community-based insurance providers.[11] However, several challenges in the literature exist, as were also noted by previous authors. Outcome information is often unavailable for major MTM programs. This is primarily because public-use Part D data do not include the MTM program-specific information.[6] Therefore, researchers have no access to data on the structure of MTM programs or to the populations that received MTM intervention. Such barriers render it difficult to assess stand-alone PDPs found under Part D because of the inability to examine drug use in the context of other medical claims. The ability to link Part D data to other medical claims would seem a necessary first step toward fully evaluating MTM programs under Part D.[6] As a consequence, the studies summarized represent Medicare MTM and evaluations of nonpublic MTM programs. Despite these gaps, our search resulted in certain evidence concerning promises and shortfalls of MTM.

Economic Outcomes

Most cost-savings studies found economic benefits, but quality of research design and end-point measures varied considerably across evaluations, for example, the positive cost-saving outcomes from North Carolina[15-17] and Minnesota.[18,19] However, the majority of analyses were limited by the absence of control groups. The Pindolia et al. study that took place in southern Michigan employed a nonequivalent control group and showed a greater reduction in per patient per month pharmacy costs for the intervention group, but analysis was limited to bivariate comparisons.[3] One highly cited RCT for low-income participants did demonstrate cost reduction in the MTM intervention.[26]

Beyond reviews from mostly a payer's perspective, we found limited research evaluations regarding the MTM impact on economic outcomes at regional and state levels. Showing promise, several studies from North Carolina and Minnesota provided some important information.[15-19] Overall positive benefits were generally found, with cost reductions above program expenses. Estimated ROIs (when calculated) varied from $1.29 per $1 invested to $12 returned per $1 invested. Disease-specific studies trended toward cost savings, although a longer-term California HIV/AIDS study demonstrated little difference between intervention and comparison groups.[20,21] Murray et al.'s heart failure study found nearly $3,000 in total direct savings in the intervention group, including the cost of program implementation for MTM Medicaid participants.[26] In particular, Hui et al.'s large retrospective matched cohort study of the integrated KP California region health plan over a 5-year intervention period found no change in daily medication costs between the MTM group and the matched control group on a cost-per-day metric.[25] Nonetheless, most studies lacked rigorous design and had limited control groups. Selection bias was also a concern. Our review did not find many other long-term controlled studies of a Medicaid population. Taken together, comprehensive benefits of MTM economic outcomes remain inconclusive based on the mixed findings from current rigorous studies.

Clinical Outcomes

Clinical outcomes encompass a wide range of potential metrics, from service utilization to individual patient and population outcomes and quality of care. Quality measures such as provider-prescribing habits and medication adherence were frequently found to have improved. In particular, Hui et al.'s 5-year California study appears to shed some new light on the promising outcomes regarding the clinical impact of the MTM group on service utilization.[25] Yet, several small-to-medium-sized clinical trials have evaluated the impact of pharmacist interventions occurring at hospital discharge with inconsistent findings regarding other clinical outcomes. Findings from major RCTs were mixed, with process metric improvements not aligning with achievement of better clinical end points. Considering larger studies across the clinical outcomes category, results were also mixed, with clinical processes (measured by associated markers such as HbA1c and mean blood pressure) typically improved, but health care utilization and other long-term clinical indicators were often absent. Lau et al. summarized

the evidence available from clinical studies related to specific diseases in 2011 as generally trending positive but recognized the dearth of long-term clinical impact data.[6] As noted with the economic outcomes studies, overall rigor of study design was suboptimal and often underpowered. Clearly, future investigation must address these methodological concerns about outcome assessment in these 2 most tested categories.

Humanistic Outcomes

Few studies have focused on such humanistic outcomes as improved patient quality of life. Smith et al. found greater patient understanding for the rationale of prescribed medications and use of subsidized transportation services.[5] Self-assessed satisfaction with MTM was modestly higher in 1 longer-term study relative to a comparison group.[18] Similar results were found with 1 small Part D patient satisfaction survey.[35] To date, this category of MTM evaluation remains the weakest so certainly warrants more research attention given the current emphasis on patient-centered health outcome evaluation.

Gaps in the Literature

MTM studies with research representing a prescriber's viewpoint are rare. Two older studies in psychiatric practices found high administrative burden coupled with difficulties accessing desired therapeutics, which resulted in reduced clinical activities and suboptimal treatment for patients with Part D prescription drug benefits.[50,51] Similar medication access issues were noted in an ESRD study, as well as for other Medicaid programs when formularies were restricted.[52] Cost sharing was identified as a barrier to medication adherence. Few minorities are included in MTM. Wang et al. noted that minority populations utilize fewer prescriptions despite having higher rates of chronic illnesses.[56] As a consequence, there is limited data on all outcomes related to MTM for minorities and less ability to generalize findings. Studies in the literature have employed a number of differing approaches to MTM: face-to-face, telephone, and mail. Data comparing results across these modalities are scarce. Use of inconsistent measures compounds the lack of consistent MTM methods from study to study. Reviews of MTM studies indicate that two-thirds of the studies have concentrated on economic outcomes, often to the exclusion of clinical or humanistic outcomes.

Finally, qualitative and mixed methods study designs are rare. In fact, no qualitative study was identified. More particularly, we found that no study has been conducted to evaluate a state Medicaid MTM program using multimethods to compare opt-in and opt-out patient outcomes and opinions among different stakeholders—patient, provider, and payer. Yet, there are clearly quality and safety issues among persons with multiple chronic conditions, persons with low education or low health literacy levels, and those with little social support. Many of these persons are elderly and disabled Medicare beneficiaries and/or Medicaid recipients. Clearly, comprehensive assessment of quality considering plan, patient, and clinical outcomes is lacking. New research is needed to solicit patient and physician opinions concerning MTM factors that are helpful.

Policy Implications

This review suggests that MTM programs have yet to provide strong evidence of their benefit, largely due to the insufficient quality of the evaluations in the published literature to date. Disease management (DM) programs faced a similar problem around 2005 when after 10 plus years of rapid growth in DM programs, evaluations had failed to demonstrate either effectiveness or efficiency. Subsequent steps taken by the DM industry may be instructive for the MTM programs moving forward.

MTM and DM programs have similar goals, mechanisms of delivery, and target populations.[70] However, the 2 programs differ in some significant ways. MTM programs focus on all chronic conditions in a given patient, while DM programs have most typically focused on a single condition. However, it is fair to say that MTM programs are a type of DM or care coordination that focuses on the therapeutic drug regimen. Early reviews of the DM evaluation literature heavily criticized the design and analytic approach of published DM evaluations.[71,72] Subsequent reviews incorporating better study designs have begun to show some positive results for properly targeted DM programs.[70,73] Improved results for DM programs are likely linked to the improved quality of the published evaluations after the industry trade organization published evaluation guidelines in 2006,[74] and changes were made by the National Committee for Quality Assurance to their DM certification standards.[75]

Successfully demonstrating effectiveness and efficiency in DM or MTM programs requires overcoming several challenges in the implementation of programs and evaluations. First, programs need to identify and enroll patients who are well matched to the intensity of the planned intervention. Mattke et al.'s 2007 article lays out the conceptual basis for properly matching patients, ranging from healthy to severely ill to low-, moderate-, and high-intensity interventions.[76] High-intensity services delivered to low-need patients will likely be biased toward no effect because they have little to gain in health-related outcomes. How to generate patient interest in offered MTM services among the patient population merits special attention of its own.[74] Second, suboptimal research designs that do not include an appropriate comparison group, adequate follow-up time, or sophisticated statistical adjustment for observable and unobservable differences between groups are suboptimal and will never provide the required strength of evidence.[70,74] Finally, standard sets of outcome measures across relevant domains and perspectives representing economic, clinical, and humanistic outcomes from the perspectives of patient, provider, and payer provide data for all stakeholders to use as benchmarks.[70,74,77]

Conclusions

MTM is an idea with merit—helping persons manage their drug therapy better and assisting physicians in identifying opportunities to eliminate drug interactions, reduce pill burden, improve effectiveness, and use generics where appropriate. The need is obvious. What is missing is strong evidence of its effectiveness in the community.

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DISCLOSURES

This study was completed in preparation for deliverables required through a contract with the Agency for Health Care Administration. The opinions expressed in this article do not necessarily reflect the views of this organization.

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