Draft Systematic Review

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Medication Therapy Management

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:
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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content

expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Medication Therapy Management

Structured Abstract

Objectives: To describe intervention components and implementation features (Key Question 1 [KQ 1]) for medication therapy management (MTM); assess the effectiveness of MTM on intermediate, patient-centered, or resource utilization outcomes (KQ 2); identify intervention features (KQ 3) and patient characteristics (KQ 4) that moderate the effect of an intervention on outcomes; and assess harms associated with interventions (KQ 5).

Data Sources: MEDLINE, Cochrane Library, International Pharmaceutical Abstracts (IPA), grey literature, additional studies from reference lists and technical experts.

Review Methods: Two trained reviewers selected, extracted data from, and rated the risk of bias of relevant trials and systematic reviews. We used random-effects models to estimate pooled effects for outcomes with three or more similar studies with a low or medium risk of bias. For other outcomes, we synthesized the data qualitatively.

Results: We included 36 eligible studies (19 randomized controlled trials, 3 controlled clinical trials, and 14 cohort studies) reported in 42 articles. Evidence was insufficient on the effect of MTM on most outcomes. For a limited number of outcomes, we found evidence that MTM results in improvement when compared with usual care (low strength). Specifically, these outcomes include medication appropriateness, the rate of hospitalization among heart failure patients with home medicines review, and the use of generic medications for patients receiving MTM from community pharmacy when compared with educational mailings.

Similarly, we found sufficient evidence to conclude that MTM conferred no benefit for a limited number of outcomes. When MTM is implemented in settings with a broad range of patients, it does not reduce the number of hospitalizations (low strength of evidence). MTM does not improve most measures of health-related quality of life (low strength of evidence).

We found evidence on four intervention components and intervention features: one study provided information on each feature and yielded insufficient evidence for most outcomes with two exceptions. MTM programs with pharmacist access to brief clinical summaries from the medical record reduced the mean number of adverse drug events when compared with basic MTM programs without such access (low strength of evidence). Community pharmacists increase the generic dispensing ratio more than call-center–based pharmacists (low strength of evidence). Similarly, the evidence on harms associated with MTM was limited to one study each on confusion and inconvenience and was rated as insufficient.

Conclusions: The evidence base is insufficient to address the effectiveness of MTM on most outcomes. Given the widespread implementation of MTM and urgent need for actionable information, funders may wish to weigh the relative value of information on overall effectiveness, effectiveness of implementation features, and program implementation and accountability when commissioning new research.

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Executive Summary

Background

Used appropriately, medications can alleviate distressing symptoms that compromise physical and psychological well-being, help prevent the onset of many acute and chronic health illnesses, and improve patient health outcomes. Too often, however, medications are not used appropriately.[1-3] In the United States in 2001, an estimated 4.3 million ambulatory visits were for adverse drug events.[4] In addition to problems involving adverse drug events, many patients do not receive optimal pharmaceutical prescriptions. Even when optimal therapy is prescribed, patient inability to adhere closely to medication regimens may lead to poor health outcomes.[5]

Medication-related problems are especially pronounced among older adults.[6] Individuals 65 years or older constitute 13 percent of the U.S. population, but they consume more than 30 percent of all prescription medications.[6,7] A 2006 report found that nearly 60 percent of people in this age group were taking five or more medications and that nearly 20 percent were taking 10 or more medications,[8] placing them at increased risk for experiencing adverse drug events.

Medication therapy management (MTM) services are intended to address issues of polypharmacy, preventable adverse drug events, medication adherence, and medication misuse.[9] MTM is the current term that represents services that have evolved out of the philosophy and processes first implemented in the early 1990s as "pharmaceutical care."[9] In 2008, 11 national pharmacy organizations achieved a consensus framework for MTM services and established 5 core elements for MTM in practice; these included a medication therapy review, a personal medication record, a medication action plan, intervention and/or referral, and documentation and follow-up.[9]

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173)[10] established the requirements that sponsors of Part D Prescription Drug Benefit Plan have to meet with respect to cost, quality, and the requirements for MTM programs. The evolution from pharmaceutical care research interventions to large-scale MTM programs in routine practice represents a journey involving multiple practice settings, patient populations, and intervention components and features. Over time, standards for these services in routine practice have evolved, as have standards for describing and conducting research studies involving these interventions. Thus, we established a broad scope for this comparative effectiveness review and did not limit our perspective to Medicare Part D-defined MTM programs.

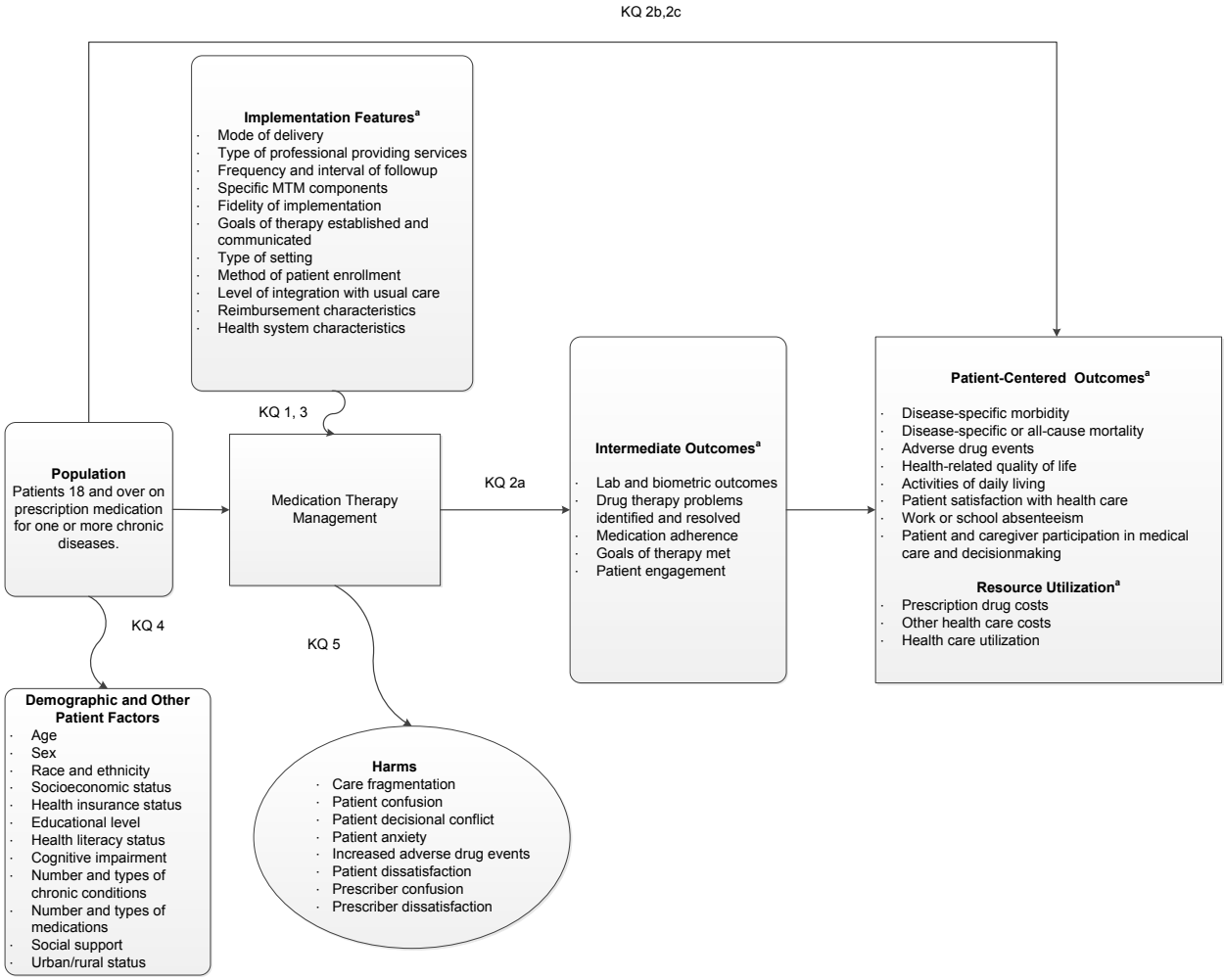
Scope and Key Questions

MTM is a complex intervention with numerous and differing components. This review seeks to catalog MTM intervention components, assess the overall effectiveness of MTM in comparison with usual care, examine the factors under which MTM is effective and optimally delivered, determine what types of patients are likely to benefit from MTM services, and clarify what types of patients may be at risk of harms from the program.

The KQs are listed below and placed in relation to another and the PICOs in the analytic framework (Figure A). Specific details regarding patient population, intervention components, and outcomes are provided in the section that follows the analytic framework.

Analytic Framework

Figure A. Analytic framework for medication therapy management



[a] The population, intervention, outcomes, and setting are described in detail in the text.

Abbreviations: KQ = key question; MTM = medication therapy management

Question 1: What are the components and implementation features of MTM interventions?

Question 2: In adults with one or more chronic diseases who are taking prescription medications, is MTM effective in improving the following:

a. Intermediate outcomes, including biometric and laboratory measures, drug therapy problems identified, drug therapy problems resolved, medication adherence, goals of therapy met, and patient engagement in medication management?

b. Patient-centered outcomes, such as disease-specific morbidity, disease-specific or all-cause mortality, adverse drug events, health-related quality of life, activities of daily living, patient satisfaction with health care, work or school absenteeism, and patient and caregiver participation in medical care and decisionmaking?

c. Resource utilization, such as prescription drug costs, other health care costs, and health care utilization?

Question 3: Does the effectiveness of MTM differ by MTM components and implementation features?

Question 4: Does the effectiveness of MTM differ by patient characteristics, including but not limited to patient demographics and numbers and types of conditions and medications?

Question 5: Are there harms of MTM, and if so, what are they?

Populations, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS)

Table A lays out the PICOTS for this review. For this review, we take a broad perspective on the population and interventions evaluated; we did not require CMS Part D MTM eligibility criteria. Specifically, we did not require multiple chronic conditions or a minimum number or level of expenditures on prescription drugs. We included randomized and controlled clinical trials, systematic reviews, and prospective and retrospective cohort studies.

Table A. Populations, interventions, comparators, outcomes, timing, and settings

PICOTS	Criteria
Populations	○ Patients ages 18 or older with one or more chronic conditions requiring the use of prescription medication to manage symptoms or prevent progression of chronic disease ○ Patient characteristics that may influence intervention effectiveness: – Age, sex, race and ethnicity, socioeconomic status, health insurance status, education level, health literacy status, cognitive impairment, number and types of chronic conditions, social support, and urban/rural status
Interventions	○ Explicitly termed *MTM* services, generally provided as a bundle of related services, that include *at a minimum* the following four elements: – Comprehensive medication review – Patient-directed medication management action plan with or without an equivalent prescriber-directed action plan – Patient-directed education and counseling or other resources to enhance understanding of the use of medication – Coordination of care, including prescriber-directed interventions; documentation of MTM services for use by the patient's other providers; and referral to other providers, clinicians, or resources when appropriate[11]

Table A. Populations, interventions, comparators, outcomes, timing, and settings (continued)

PICOTS	Criteria
Interventions (continued)	○ MTM-like services that are provided as a bundle or multicomponent intervention, even if not explicitly termed "medication therapy management" ○ The following types of interventions generally are not considered MTM interventions and are not included: – Medication reconciliation interventions – Integrated pharmacy services within inpatient settings – One-time corrective actions related to medication management – Disease-management interventions[12] – Case- or care-management interventions[12] ○ The following types of interventions may include MTM services, but MTM may represent only one component of the overall intervention: – Patient-centered models of home health care – Fully integrated, collaborative care models involving multiple disciplines and specialties ○ Studies should contain the same level of overall medical care or health care services among different study arms such that the effect of MTM interventions can be isolated. For example, a study with two arms that has one arm with a care management intervention that includes MTM services and the other arm that has the care management intervention without MTM services could be included. By contrast, a study that includes a care management intervention with MTM in one arm and usual medical care (no care management intervention) in the other arm would not be included. ○ Implementation features that may influence intervention effectiveness include the following: – Mode of delivery: telephone, face-to-face, virtual (Web/online/Internet), and remote video – Type of professional providing initial and followup MTM service: pharmacist, nurse, physician, other clinician – Frequency and interval of followup for MTM services – Specific MTM components used – Fidelity in implementing MTM components: to what extent were services delivered as designed or intended – Establishing and communicating goals of drug therapy to patients and among care providers – Method of identifying patients for enrollment (e.g., population health data, provider referral for services, enrollment during a transition in care, targeting highly activated patients, targeting patients at time of high risk for event [e.g., when prescribing a new drug]) – Level of integration of MTM with usual care, which includes access to real-time clinical information and laboratory values, and regular and consistent communication among prescribers and persons providing MTM services – Reimbursement characteristics (e.g., who is paying for cost of MTM services, who is reimbursed for MTM services, whether services are separately reimbursable) ○ Health system characteristics (e.g., are services being provided within an accountable care organization, patient-centered medical home, or some other unique system setting, such as the Veterans Health Administration, the Indian Health Service, non–U.S. single-payer system)
Comparators	○ Usual care, as defined by the studies ○ Individual components of MTM services (e.g., MTM services with four components vs. a single component) ○ Different bundles of MTM services ○ Same MTM services provided by different health care professionals (e.g., pharmacist, physician, nurse, other) ○ Same bundles of MTM services delivered by different modes (e.g., telephone or in person) ○ Same MTM services provided at different intensities, frequencies, or level of integration with prescribers

Table A. Populations, interventions, comparators, outcomes, timing, and settings (continued)

PICOTS	Criteria
Outcomes	○ Intermediate outcomes – Disease-specific laboratory or biometric outcomes (e.g., hemoglobin A_{1c}; blood pressure; total, low-density lipoprotein, or high-density lipoprotein cholesterol; pulmonary function; renal function; left ventricular ejection fraction; or other laboratory or biometric outcome specific to diseases covered) – Drug therapy problems identified as defined by primary studies but typically include the following: medications being taken but not indicated; medications indicated but not prescribed; patient adherence issues; supratherapeutic doses; subtherapeutic doses; generic, formulary, or therapeutic substitution issue; complex regimen that can be simplified with same therapeutic benefit; and potential for drug-drug interactions or adverse event. – Drug therapy problems that are resolved as defined by primary studies but typically include the following: needed drug initiated; unnecessary drug discontinued; change in drug dose, form, or frequency; or generic, formulary, or therapeutic substitution – Medication adherence – Goals of therapy met – Patient engagement (e.g., initial and continuing patient participation in the MTM program) ○ Patient-centered outcomes – Disease-specific morbidity, including falls and fall-related morbidity, and outcomes specific to the patient's underlying chronic conditions (e.g., Patient Health Questionnaire 9 [PHQ9], disease-specific symptoms, reduced number of disease-specific acute exacerbations or events) – Disease-specific or all-cause mortality, including fall-related mortality – Reduced (actual) adverse drug events (frequency and/or severity) – Health-related quality of life as measured by generally accepted generic health-related quality-of-life measures (e.g., short-form questionnaires, EuroQOL) or disease-specific measures – Activities of daily living as measured by generally accepted standardized measures of basic and/or instrumental activities of daily living (e.g., Katz, Lawton, or Bristol instruments) or with instruments that have demonstrated validity and reliability – Patient satisfaction with care – Work or school absenteeism – Patient and caregiver participation in medical care and decisionmaking ○ Resource utilization – Prescription drug costs and appropriate prescription drug expenditures – Other health care costs – Health care utilization (hospitalizations, emergency department visits, and physician office visits) ○ Harms – Care fragmentation – Patient confusion – Patient decisional conflict – Patient anxiety – Increased (actual) adverse drug events – Patient dissatisfaction with care – Prescriber confusion – Prescriber dissatisfaction
Timing	○ Interventions should have at least two separately identifiable episodes of MTM services (either patient or provider directed or both), with any interval of time in between episodes. ○ For studies that report outcomes at different points in time, we only considered outcomes measured after the second episode of care.

Table A. Populations, interventions, comparators, outcomes, timing, and settings (continued)

PICOTS	Criteria
Setting	○ Ambulatory settings (e.g., outpatient clinics or private physician offices), long-term-care setting, or retail pharmacy settings) ○ However, the MTM intervention itself may be delivered by home visits, telephone, via the Web, or in other non–face-to-face modalities, such as video teleconferencing. ○ MTM services that are delivered mostly in inpatient settings are not included. ○ Interventions conducted in the United States and other countries and are published in English are included.

Methods

Topic Refinement and Review Protocol

The topic of this report and preliminary key questions (KQs) arose through a nomination from the Pharmacy Quality Alliance. Key Informants representing several clinical and scientific disciplines provided input on the initial KQs; we revised them as needed. An initial draft of the revised KQs was posted for public comment from March 6, 2013, through April 2, 2013, on the AHRQ Effective Health Care program Web site. We received comments from 23 professional organizations and individuals and further revised KQs as appropriate.

Literature Search and Identification Strategy

To identify articles relevant to each KQ, we began with a focused MEDLINE® search for MTM interventions using a combination of medical subject headings and title and abstract keywords and limiting the search to English-language and human-only studies. We also searched the Cochrane Library and the International Pharmaceutical Abstracts database using analogous search terms. We selected these databases based on preliminary searches and consultation with content experts. We conducted quality checks to ensure that the searches identified known studies (i.e., studies identified during topic nomination and refinement). Based on these quality checks, we revised and ran additional searches (specifically, drug therapy management, drug therapy problem, and medications management) to avoid missing articles that might prove eligible for this systematic review.

In addition, we searched the gray literature for unpublished studies relevant to this review and included studies that met all the inclusion criteria and contained enough methodological information to assess risk of bias. Specifically, sources of gray literature included ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, Health Services Research Projects in Progress (HSRProj), the National Institutes of Health Research Portfolio Online Reporting Tools, the Database of Promoting Health Effectiveness Reviews, the New York Academy of Medicine Grey Literature Report, and CMS.gov.

We reviewed our search strategy with an independent information specialist and the Technical Expert Panel and supplemented it according to their recommendations. In addition, to avoid retrieval bias, we manually searched the reference lists of landmark studies and background articles on this topic to identify any relevant citations that our electronic searches might have missed.

Two trained members of the research team independently reviewed each of the titles and abstracts against the inclusion/exclusion criteria listed in Table A. We applied the same criteria to systematic reviews and primary studies. For each article that either or both reviewers chose to

include based on the abstract review, two reviewers reviewed their full texts for eligibility against our inclusion/exclusion criteria. During full-text review, if both reviewers agreed that a study did not meet the eligibility criteria (including designation of high risk of bias), we excluded the study. Reviewers resolved conflicts by discussion and consensus or by consulting a third member of the review team.

For studies that met our inclusion criteria, a trained reviewer abstracted information into structured evidence tables; a second senior member of the team reviewed all data abstractions for completeness and accuracy. Reviewers resolved conflicts by discussion and consensus or by consulting a third member of the review team.

Assessment of Risk of Bias of Individual Studies

To assess the risk of bias of individual studies, we used predefined criteria developed by AHRQ.[13] For randomized controlled trials (RCTs), we relied on the risk-of-bias tool developed by the Cochrane Collaboration.[14] We assessed the risk of bias of observational studies using an item bank developed by RTI International.[15]

In general terms, results of a study with low risk of bias are considered valid. A study with medium risk of bias is susceptible to some bias but probably not sufficient to invalidate its results. A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results. Primary concerns for our review included selection bias, confounding, performance bias, detection bias, and attrition bias. Specifically, we evaluated studies on the adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.

We excluded studies that we deemed at high risk of bias from our main data synthesis and main analyses. We included them for sensitivity analyses; in cases when we had no other available or credible evidence, we included in the report a brief synopsis of studies assessed as high risk of bias.

Data Synthesis

When we found three or more similar studies for a comparison of interest, we conducted meta-analysis of the data from those studies. For all analyses, we used random-effects models to estimate pooled or comparative effects. To determine whether quantitative analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance;[16] that is, we qualitatively assessed the PICOTS of the included studies, looking for similarities and differences. When we conducted quantitative syntheses (i.e., meta-analysis), we assessed statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., the p-value from the chi-squared test or a confidence interval for I^2). Where relevant, we examined potential sources of heterogeneity using sensitivity analysis.

When quantitative analyses were not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. Whenever possible, we computed confidence intervals for individual outcomes.

Numerous articles about both trials and observational studies often did not provide complete information about findings (e.g., 95 percent confidence intervals; statistical significance values, or between-group data). In many cases, therefore, we had to calculate odds ratios, mean differences, or standardized mean differences, the relevant 95 percent confidence intervals, and p-values.

Grading Strength of Evidence for Individual Comparisons and Outcomes

We graded the strength of evidence based on the guidance established for the AHRQ Evidence-based Practice Center program.[17] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: study limitations (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. We evaluated optimal information size criteria to make judgments about precision based on guidance from Guyatt and colleagues[18] and based our grades on low or medium risk-of-bias RCTs or observational studies unless none were available, based on guidance from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group[19] and the AHRQ EPC program.[17]

Table B describes the grades of evidence that can be assigned.[20] Grades reflect the strength of the body of evidence to answer the KQs on the overall effectiveness, comparative effectiveness, and harms of the interventions examined in this review. Two reviewers assessed each domain for each major outcome resolved any differences by consensus discussion or referral to a third, senior member of the team. We graded the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those commonly reported in the literature; we did not grade the strength of evidence for KQ 1 (on components and features of MTM services).

Table B. Definitions of the grades of overall strength of evidence

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Assessing Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[21] We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age and health status of enrolled populations, health insurance coverage and access to health care, and complexity and intensity of the MTM intervention.

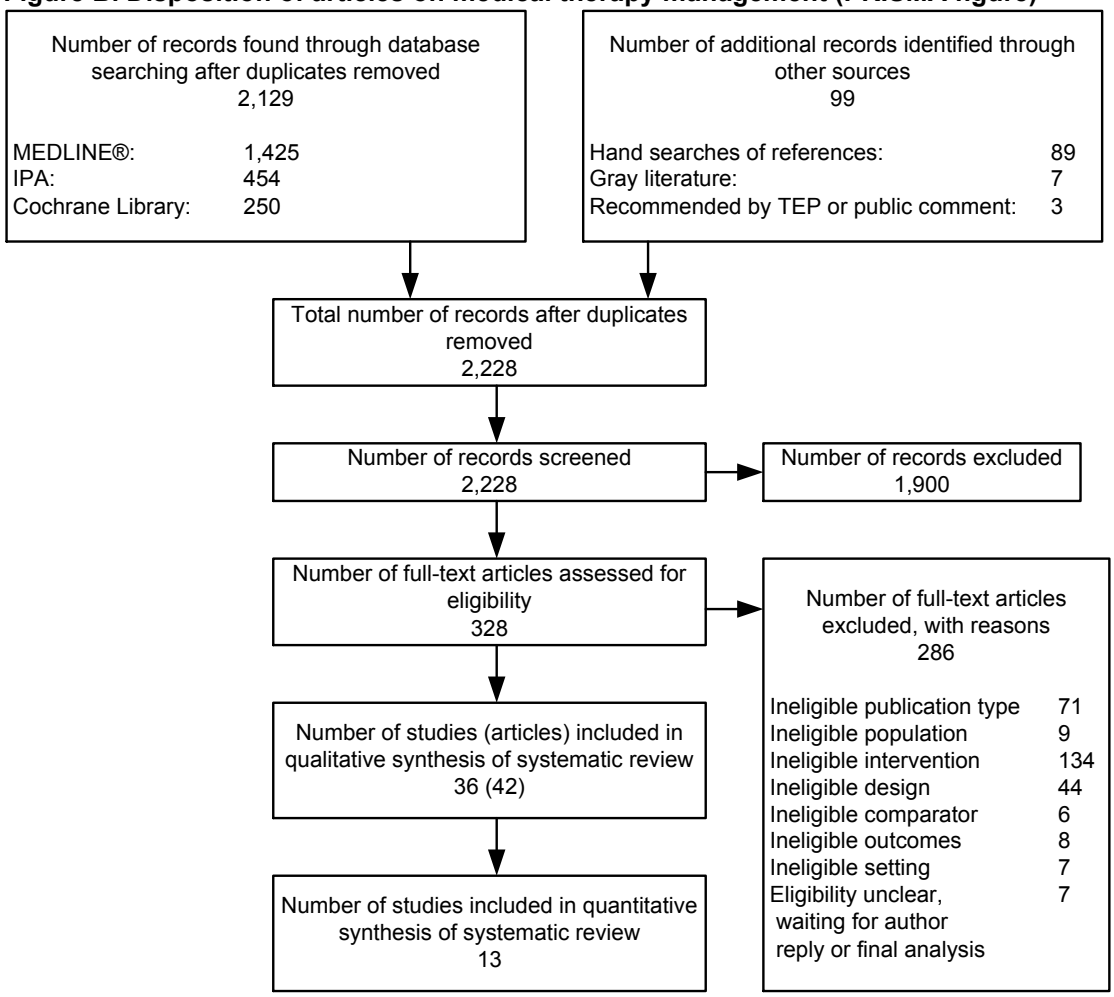
Results

We provide a summary of results by KQ below. Detailed descriptions of included studies, key points, detailed synthesis, summary tables, and expanded SOE tables that include the magnitude of effect can be found in the full report. Our summary of results below presents the SOE grades.

Results of Literature Searches

Figure B presents our literature search results through June 27, 2013; for the draft report, we identified 2,129 unduplicated citations. In addition, we identified 99 publications through grey literature searches, suggestions from technical experts or public comments received during topic refinement, or hand searches of included studies. After applying our eligibility and exclusion criteria to titles and abstracts of all 2,228 identified citations, we obtained full-text copies of 328 published articles. We reapplied our inclusion criteria and excluded 286 of these articles from further review before doing the risk-of-bias assessment. The 42 articles included after full-text review represent 36 studies.

Figure B. Disposition of articles on medical therapy management (PRISMA figure)



Abbreviations: IPA, International Pharmaceutical Abstracts; PICOTS, populations, interventions, comparators, outcomes, timing, settings; TEP, technical expert panel.

This evidence base consisted of 36 studies (19 randomized controlled trials [RCTs] trials and 17 observational studies) reported in 42 articles. Most RCTs compared an MTM intervention with usual care rather than with a different active intervention; most observational studies were cohort studies. Numerous studies had methods problems that led us to rate them as having a medium or high risk of bias; only a few studies were of low risk of bias. When possible (enough studies similar in intervention, populations, and outcomes measured), we conducted meta-analyses of data from RCTs or cohort studies separately; when relevant, we did two sets, one with and one without the high risk-of-bias trials.

Because of the wide variation in types of interventions classified as MTM, we first catalogued intervention components and implementation features of MTM interventions (Key Question [KQ] 1). We then evaluated the effect of MTM on intermediate, patient-centered, and resource utilization outcomes (KQ 2). We also reviewed the evidence to identify how these effects might vary by specific intervention components and features (KQ 3) and patient characteristics (KQ 4). Finally, we reviewed the evidence on harms associated with MTM (KQ 5).

Below, we summarize the main findings and strength of evidence, where applicable. We then discuss the findings in relationship to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions.

Key Findings and Strength of Evidence

KQ 1: Intervention Components and Implementation Features

Nearly two-thirds of included studies were broadly focused on patients with a wide-ranging collection of conditions; the remaining studies were narrowly focused on patients with a specific condition. All studies used a pharmacist as the interventionist. Services were provided face-to-face in just over half of included studies. Included studies provided interventions in a variety of clinical settings, including community pharmacies, centralized pharmacies or pharmacy call centers, and outpatient medical clinics, and some used home visits; half of the narrowly focused interventions were delivered exclusively in an outpatient medical clinic.

Whether termed "pharmaceutical care" or "MTM," studies did not describe intervention components and features in a consistent manner or in sufficient detail. These drawbacks were especially prevalent for intervention intensity and frequency, method of patient enrollment for services, level of integration with usual care, and reimbursement characteristics for rendered MTM services. KQ 1 was descriptive in nature, so we did not grade strength of evidence.

KQ 2: Overall Effectiveness

Of the 36 studies included in this review, we rated 14 as high risk of bias overall; that is, concerns about randomization failure, confounding, or overall attrition increased the risk of bias for all outcomes. In addition, we rated some studies that were otherwise of low or medium risk of bias as high for individual outcomes, chiefly because of measurement bias. These instances are specified in the relevant results section in Chapter 3.

We rated the strength of evidence for each outcome from low- or medium risk-of-bias studies when available. MTM significantly improved medication appropriateness assessed in general (Table C). However, we did not find evidence of benefit for any other intermediate outcomes on which we had data. No studies addressed either goals of therapy or patient engagement.

Table C. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions

Intermediate Outcome	Study Design: No. Studies (N Analyzed)	Results	Strength of Evidence
Anticoagulation	RCT: 1 (10)	Imprecise	Insufficient
Hemoglobin A1C	RCT: 2 (102)	Inconsistent, imprecise	Insufficient
Low density lipoprotein cholesterol	RCT: 1 (38)	Imprecise	Insufficient
Hypertension: achieving blood pressure goals	RCT: 1 (44)	Imprecise	Insufficient
Hypertension: systolic blood pressure	RCT: 1 (23)	Imprecise	Insufficient
Hypertension: diastolic blood pressure	RCT: 1 (23)	Imprecise	Insufficient
Drug therapy problems identified	RCT: 1 (332) Cohort: 2 (668)	Indirect, imprecise, high study limitations	Insufficient
Drug therapy problems resolved	Cohort: 1 (120)	Indirect, imprecise, high study limitations	Insufficient
Medication adherence	RCT: 8 (2,415) Cohort: 2 (1,493)	Inconsistent, imprecise (across heterogeneous measures)	Insufficient
Medication Appropriateness General Index Scores	RCT: 1 (208)	Improvement in MTM group from score of 17.7 to 13.4 and to 12.8 at 3 and 12 months, respectively	Low for benefit
Medication-specific appropriateness	RCT: 2 (261)	Indirect, imprecise, inconsistent	Insufficient
Medication dosing	RCT: 2 (90)	Inconsistent, imprecise	Insufficient
Goals of therapy	0	NA	NA
Patient engagement	0	NA	NA

Abbreviations: CI = confidence interval, MTM = medication therapy management; N = number; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial.

Similarly, we did not have evidence of benefit for most patient-centered outcomes (Table D). MTM did not improve most measures of health-related quality of life (low strength of evidence for no benefit). We graded the "vitality" domain of the Medical Outcomes Study Short-Form (SF36) questionnaire as insufficient for this domain. For the SF-36, neither the other seven domains nor the two component scores (physical health, mental health) showed significant benefit from MTM interventions. The various patient satisfaction items also showed no impact from MTM programs (low strength of evidence for no benefit).

Table D. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions

Patient-Centered Outcome	Study Design: No. Studies (N Analyzed)	Results	Strength of Evidence
Adverse drug events	RCT: 2 (806)	Inconsistent, imprecise	Insufficient
Cognitive, affective, and physical function	RCT: 1 (133)	Imprecise	Insufficient
Mortality	RCT: 2 (335) Cohort: 1 (795)	Inconsistent, imprecise	Insufficient
Gastrointestinal bleeding events	Cohort: 1 (1,373)	High study limitations	Insufficient
General health-related quality of life domains other than vitality	RCT: 4 (1,169)	Variable mean difference with confidence intervals consistently spanning the null effect	Low for no benefit
General health-related quality of life vitality domain	RCT: 4 (1,169)	Imprecise	Insufficient
Condition-specific health-related quality of life (diabetes)	RCT: 1 (73)	Imprecise	Insufficient
Patient satisfaction	RCT: 3. (1,625)	No differences on 17 or 21 items of patient satisfaction	Low for no benefit
Activities of daily living	0	NA	NA
Work or school absenteeism	0	NA	NA
Patient and caregiver participation in medical care and decisionmaking	0	NA	NA

Abbreviations: CI = confidence interval, MTM = medication therapy management; N = number; NA = not applicable; RCT = randomized controlled trial.

Outcomes related to using health resources were similarly not much influenced by MTM interventions (Table E). Two exceptions may merit attention: (1) the use of generic medications for patients receiving MTM from community pharmacy when compared with educational mailings (low for benefit from the community pharmacy approach) and (2) the rate of hospitalization among heart failure patients with home medicines review when compared with usual care. When MTM was implemented in settings with a broad range of patients, it did not reduce the number of hospitalizations (low strength of evidence).

Table E. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions

Use of Resources Outcomes	Study Design: No. Studies (N Analyzed)	Results	Strength of Evidence
Number of high-risk medications	Cohort: 1 (2,211)	High study limitations	Insufficient
Use of generic medications for call-center pharmacy-based MTM vs. educational mailings	2; 97,124 (75,166)	High study limitations, inconsistent	Insufficient
Use of generic medications for community pharmacy-based MTM vs. educational mailings	Cohort: 1 (73,793)	Calculated mean difference in weighted generic dispensing ratio: 1.2 (95% CI: 0.724 to1.676 to; p<0.001)	Low for benefit for community pharmacy
Medication costs: patient copayments	NRCT: 1 (1,626)	High study limitations, indirect	Insufficient
Medication costs: health plan expenditures	RCT: 2 (835); NRCT & Cohort: 2 (1,746)	Indirect, imprecise	Insufficient
Medication costs: total outlays	RCT: 3 (1,975)	Inconsistent, indirect, imprecise	Insufficient
Medication costs: medication costs plus other expenditures	RCT: 2 (>779); NRCT: 1 (675)	Indirect, imprecise	Insufficient
Number of outpatient visits	RCT: 2 (2,038)	Inconsistent, imprecise	Insufficient
Outpatient costs	RCT: 2 (1,842)	Inconsistent, indirect, imprecise	Insufficient
Number of laboratory tests	RCT: 2 (1,842)	Inconsistent, indirect, imprecise	Insufficient
Costs of laboratory tests	RCT: 2 (1,842)	Inconsistent, indirect, imprecise	Insufficient
Number of emergency department visits	RCT: 2 (1,344) Observational: 1 (795)	Inconsistent, imprecise	Insufficient
Costs of emergency department visits	RCT: 1 (779)	Imprecise	Insufficient
Hospitalization: number	RCT: 2 (2,398)	Mean difference of 0.038 (95% CI −0.005 to 0.080)	Low for no benefit
Hospitalization: percentage	RCT: 2 (710)	Inconsistent. Imprecise	Insufficient
Hospitalization: rate (patients with heart failure and home medicine review)	Cohort: 1 (5,717)	Adjusted HR (95% CI): 0.55 (0.39 to 0.77)	Low for benefit
Costs of hospitalization	RCT: 2 (1,842)	Inconsistent, imprecise	Insufficient
Length of hospital stay	RCT: 1 (46)	High study limitations, imprecise	Insufficient

Abbreviations: CI = confidence interval, HR = hazard ratio; MTM = medication therapy management; N = number; NA = not applicable; NRCT = nonrandomized controlled trial; OR = odds ratio; RCT = randomized controlled trial.

Over all three categories of outcomes, each of which had a substantial number of individual measures, MTM improved outcomes in only a couple of instances. Study limitations and lack of precision of the estimates of effects limited the strength of evidence considerably. As discussed later, even the minimal findings of effectiveness are at best only narrowly applicable.

KQ 3: Effectiveness of MTM by Intervention Features

We found evidence from one study each on four intervention features: (1) access of pharmacists to patient records,[22] (2) community pharmacy versus call center,[23] (3) level of intensity of intervention,[24] and (4) type of payer (private vs. Medicaid).[25] With the exception of the study on pharmacists' access to patient records, we rated these studies as high risk of bias. Evidence was insufficient for most outcomes for the first two intervention features, with two exceptions. First, MTM delivered by community pharmacists increased the weighted generic dispensing ratio when compared with call-center pharmacists (low strength of evidence). Second, enhanced MTM with pharmacists' access to patient records reduced the mean number of adverse drug events; this finding suggested benefit when compared with basic MTM (low strength of

evidence). We found insufficient evidence for all outcomes for intensity of intervention and type of payer.

KQ 4: Effectiveness of MTM by Patient Characteristics

We did not identify any studies that analyzed outcomes of MTM by patient characteristics.

KQ 5: Harms of MTM Interventions

Lack of precision and the limitations of a single high risk-of-bias study meant that evidence was insufficient to judge whether MTM resulted in greater confusion[26] or inconvenience[27,28] than usual care. We found no evidence on other prespecified harms, specifically including care fragmentation, patient decisional conflict, patient anxiety, increased (actual) adverse drug events, prescriber confusion, and prescriber dissatisfaction.

Discussion

Key Findings

We identified 36 studies that offered information on a range of intermediate outcomes, patient-centered outcomes, and resource utilization. Evidence was insufficient on the effect of MTM on most outcomes. For a limited number of outcomes, we found enough evidence to show that MTM results in improvement when compared with usual care (low strength). Specifically, these outcomes include medication appropriateness, the rate of hospitalization among heart failure patients with home medicines review when compared with usual care, and the use of generic medications for patients receiving MTM from community pharmacies when compared with educational mailings. Similarly, we found sufficient evidence to conclude that MTM conferred no benefit for a limited number of outcomes. When MTM is implemented in settings with a broad range of patients, it does not reduce the number of hospitalizations (low strength of evidence). We found evidence on four intervention components and intervention features: one study provided information on each feature and yielded insufficient evidence for most outcomes with two exceptions. MTM programs with pharmacist access to brief clinical summaries from the medical records reduce the mean number of adverse drug events when compared with basic MTM programs without such access (low strength of evidence). Community pharmacists increase the generic dispensing ratio more than call-center–based pharmacists (low strength of evidence). Similarly, the evidence on harms associated with MTM was limited to one study each on confusion and inconvenience and was rated as insufficient.

Findings in Relation to What Is Already Known

Our findings contrast with conclusions that Chisholm-Burns and colleagues reached in a recent systematic review.[29] In that review, the authors concluded that "Pharmacist-provided direct patient care has favorable effects across various patient outcomes, health care settings, and disease states."[29, p. 923] Several differences between the Chisholm-Burns review and the current review may account for the discrepant conclusions. First, the Chisholm-Burns review included all studies that cited evidence of pharmacist involvement in direct patient care. The interventions examined included chronic disease management and prospective and retrospective drug utilization review; we excluded these types of efforts because our intended focus was on the MTM intervention itself. Notably, the Chisholm-Burns review did not use the term "medication

therapy management" to categorize the interventions in the articles they reviewed. Second, approximately 30 percent of the papers in the Chisholm-Burns review were conducted entirely in institutional settings. In contrast, we did not identify any studies within institutional settings that met our MTM intervention definition criteria. Third, the Chisholm-Burns review included a total of 298 articles and did not omit from their analyses studies with a high risk of bias; by contrast, we based our strength-of-evidence grades in this review on only those studies with no more than medium risk of bias.

The striking differences between the conclusions reached in these two reviews emphasize two important needs for both conceptual and practical efforts to systematically review MTM programs. The first is to create a systematic system for classifying the different types of direct patient care services that pharmacists can provide. The second is to develop consensus guidelines for describing intervention features in publications reporting findings from evaluation studies. Progress on these two steps would enable systematic reviews to differentiate better between different types of services and avoid the problem of overgeneralizing review results.

The Centers for Medicare & Medicaid Services (CMS) supported a large evaluation of MTM programs that we were unable to include in this draft because of the timing of the release of that report.[30] We will include it in our final report along with our update of the published and grey literature. Although we have not yet incorporated the findings of this large evaluation into our systematic review, we note that the report finds that MTM improved patient adherence to medication regimens and the quality of prescribing. Our review did not find sufficient evidence to evaluate the effect of MTM on improved adherence, but we did find low strength of evidence that MTM improves medication appropriateness, which is conceptually similar to "quality of prescribing." The discrepancy between the CMS findings regarding adherence and findings of studies included thus far in our review may reflect the greater precision that the CMS investigators might have had in their use of pharmaceutical prescription refill records to assess adherence when compared with other studies that primarily used self-report to assess adherence. The report also found some reduction in resource use, but these results were for patients with diabetes or congestive heart failure. Our review found that for patients with heart failure, MTM was likely to reduce hospitalization rates, but we found no effect on mean number of hospitalizations for broadly defined populations.

Applicability of the Findings

This body of evidence has significant clinical and methodological heterogeneity, which limits the ability to make any universal statements about effectiveness. However, the range of study designs, which includes RCTs, nonrandomized trials, and cohort studies, enhances the applicability of findings for real-world settings.[31] Included studies ranged from relatively small interventions in single clinics provided by a single interventionist to evaluations of MTM services delivered on a large scale through integrated health systems or health plans as a Medicare Part D or other drug plan benefit. This diversity of studies enhanced the applicability of findings to a wide variety of settings, including outpatient clinics, community pharmacies, and centralized pharmacy call centers. A few studies conducted outside the United States included MTM as part of a home visits program; findings from this model may not be directly applicable within the United States.

The studies in this review are broadly applicable to a range of chronically ill, adult patient populations. The majority of interventions were directed at populations with multiple and common chronic conditions, such as diabetes, chronic heart failure, and hypertension. Several

specifically targeted adults aged 65 years or older. Few studies reported sociodemographic characteristics beyond age and sex; thus, the applicability of findings to specific populations (e.g., rural, low socioeconomic status, cognitively impaired, uninsured) is unknown. The nature of the MTM intervention, which includes involving patients as active participants in the process, limits the extent to which findings can be generalized beyond patients who agreed to participate in such interventions. Patients who agree to participate may be systematically different from those who decline to be in such a program. For that reason, the impact of such interventions at a population or health-plan level may be limited by the degree of uptake among interested patients.

The intervention used across most studies can be characterized as complex and moderately resource intensive. Components involve identifying applicable patients; initially assessing patients; providing counseling, education, and care coordination; and following patients over time. These services were provided per protocol in some studies and as needed or ad hoc in others. Most studies described intervention components in terms of "pharmaceutical care model" components or Medicare Part D MTM program criteria, but few provided detailed descriptions or measurement of implementation fidelity.

The comparator arm in all studies was usual medical care. This does not typically include distinct MTM services by health care providers other than prescribing providers (not common for the time period covered by most of the studies). Models of collaborative health care delivery are evolving, and the changing roles and training of pharmacists increase the potential applicability of MTM interventions in future models of health care.

The broad sets of outcomes evaluated across this body of evidence spanned a substantial range of both intermediate and health outcomes as well as outcomes related to resource use. Proximal and intermediate outcomes included number of drugs, identification of drug therapy problems, appropriateness of medication prescribing, and laboratory or biometric markers of disease control (e.g., hypertension, hemoglobin A1c, low-density lipoprotein cholesterol). Patient-centered outcomes focused on numerous measures of quality of life as well as adverse drug events. Many studies also reported outcomes involving health care resource use and expenditures (e.g., number and costs of hospitalizations, emergency department visits, outpatient visits).

Most studies did not, however, clearly indicate the expected, desired, or intended direction of effect on most resource use outcomes, making the applicability of using these interventions to reduce drug-related health care costs or expenditures difficult to assess. For example, whether one should expect the number of medications prescribed for heart failure to increase or decrease under the careful scrutiny of an MTM intervention is not clear.

The focus of outcome measurement in many studies was the short-term identification and characterization of drug therapy problems and their resolution; these endpoints are thought to be the outcomes most sensitive to change as a result of receiving MTM services. However, by design, because identification of drug therapy problems is a part of the MTM intervention itself, differences between the nature of the intervention and that of the control programs mean that measuring these outcomes cannot be as rigorous in a usual care comparison group as it is in the intervention group. In fact, many studies were able to measure only changes in this outcome in the intervention group. Hence, many studies failed to demonstrate a direct analytic link between the resolution of drug therapy problems as a result of MTM and impact on intermediate outcomes, patient-centered outcomes, and resource utilization. Thus, the applicability of studies that demonstrate an impact on the resolution of drug therapy problems is limited.

Implications for Clinical Practice and Policymakers

Although we found the evidence insufficient in general to draw definitive conclusions about the comparative effectiveness of MTM for most outcomes that we evaluated, our findings do suggest some implications for practice and policy. MTM is already in widespread practice and is now shaped in the United States largely by Medicare Part D policy: this presents both challenges and opportunities. MTM programs of the future, sponsored and administered by Part D drug benefit plans, may be less integrated into routine health care for Medicare beneficiaries than many of the pharmaceutical care interventions included in our review. We were unable to answer definitively whether level of integration matters for effectiveness, but policymakers may need to consider expectations about the impact that MTM might have on patient-centered outcomes and resource use in the context of other health care delivery transformation activities or quality improvement initiatives that are also occurring. More integration of MTM services with other activities may be effective; however, the more integrated MTM becomes within routine medical care, the more difficult it becomes to isolate it as a discrete intervention for evaluation.

Policymakers could thus consider whether MTM services should be positioned as a *contributor* to overall improvement in processes of care, health status, and costs or positioned as an intervention to which effects can be discretely *attributed*. Improvements in medication appropriateness or drug therapy regimens may not always translate into improvements in health or costs, and even if they do, secular improvements in other areas of quality improvement may make measuring outcomes attributable to MTM very challenging.

Future training of MTM providers would benefit from a better understanding of which MTM components really matter. At the moment, such information is lacking. Policymakers and funders who wish to understand the comparative effectiveness of different MTM components could encourage rigorous program evaluation designs that fit within the context of the real-world implementation of these programs. For example, positive deviance analyses[32] with rigorous measurement of implementation features or stepped wedge trial designs[33] may be useful approaches.

A typical approach for evaluating complex interventions is to identify the "core" components for standardization, while allowing for flexibility for peripheral components or variations in implementation. In complex practice-based innovations, such flexibility may reflect desirable (or unavoidable) adaptations to local circumstances. Policy governing MTM programs may warrant modifications to permit investigators to conduct rigorous and innovative evaluative designs to identify core components or effectiveness-enhancing modifications. As future research and evaluation elucidates these components or enhancements, policy will need to evolve to keep pace with best practices.

Finally, considering both patients' and prescribers' perspectives in future design and delivery of MTM services may be needed. In our current analytic framework, MTM interventions require a significant element of engagement by both patients and prescribers if the interventions are to have a reasonable likelihood of improving outcomes. Although "opt in" strategies may increase the reach of such interventions, keeping patients (and their prescribing providers) engaged in the intervention over a reasonable amount of time may be the key to translating the potential of MTM interventions into actual improvements.

Limitations of the Comparative Effectiveness Review Process

The constraints for populations, interventions, and settings that we imposed on this systematic review may limit its applicability as discussed above. During topic refinement and based on technical expert panel inputs and public comment, we expanded the scope by removing an exclusion criterion that would have required MTM interventions to have been directed at a patient population with two or more chronic conditions. As a result, we did include studies that focused on one chronic condition. Because of the prevalence of certain chronic conditions in the adult population, and particularly among Medicare beneficiaries, we think this decision was sensible and permitted us to examine a broader evidence base than would otherwise have been the case.

Although we tried to distinguish MTM from disease or case management interventions, making this distinction was challenging. We created a threshold for what intervention components were required to be present for this distinction. Specifically, we elected to emphasize whether the intervention entailed a comprehensive review of all medications; for that reason, we did not constrain studies of interest to those that targeted a single medication or drug regimen or that focused on a single condition such as diabetes or hypertension.

When we were unable to determine which medications the interventionist had reviewed, we wrote to the authors for additional information. We chose to pursue authors in an effort to permit us to use studies that had been designed as MTM but did not describe the comprehensive medication review component in detail.

Our approach may have been overly inclusive because it led us to include studies that addressed a single disease, as long as the pharmacist reviewed all medications. For example, 12 of the 36 studies were relatively narrowly focused; four of these addressed patients with chronic heart failure and two addressed patients with either hypertension or hypertension and diabetes. The remaining six studies focused on post-transplant patients (kidney, lung), diabetes, glucocorticoid-induced osteoporosis, and hemodialysis. The fact that we drew the line at only one intervention component criterion resulted in an approach that was inclusive of these more narrowly focused (albeit often termed "MTM") studies and may render our results less applicable to MTM interventions targeted to patients with a wide range of chronic conditions.

Also based on feedback during the process of setting out the scope of this review, we chose to include interventions that were broader than the Medicare Part D MTM-defined interventions. Put another way, we broadened our view of patient populations and intervention criteria, and we allowed studies not conducted in the United States into the evidence base. This decision led us to include interventions described as "pharmaceutical care," which were generally based on the pharmaceutical care model as described and refined by Strand and associates;[9] it also permitted us to examine investigations with elements of pharmaceutical care or MTM that did not specifically label the intervention as either MTM or pharmaceutical care. These studies were often described as "clinical pharmacist interventions."

Furthermore, all the non-U.S. studies involved interventions within single-payer health systems. Hence, the interventions in this review constitute a more heterogeneous group than if we had allowed only those labeled as Medicare Part D MTM programs. This is both a limitation and a strength. Although our approach makes results more challenging to interpret, it enhances our ability not to miss interventions that include MTM components but lack the descriptor term MTM.

Studies did not often explicitly describe certain MTM components. In cases when we could not determine whether investigators had provided certain MTM components (such as patient

education and counseling, medication action plan, or coordination with other health care providers), we again contacted the authors to gain additional information that would allow us to make an informed decision. We were fairly permissive in interpreting the presence of the MTM intervention components other than comprehensive medication review (e.g., medication action plan). The main reason is that we recognized that terms describing some components have evolved over time and may have been absent from the lexicon in earlier years or implicitly conveyed by authors by simply using the terms "MTM" or pharmaceutical care to describe their intervention.

Our approach to categorizing interventions for KQ 1 relied primarily on the short descriptions in published manuscripts and those we were able to obtain via email inquiries. Their similarities or differences substituted for any overarching taxonomy, because none that we considered seemed to fit our purpose. Thus, we have introduced intervention labels that, admittedly, do not fully describe or account for clinical heterogeneity among interventions. This approach limits our ability to make definitive statements about the effectiveness of various intervention components. We believe that the clusters and categorizations we used are useful heuristics, but some may regard them more as hypothesis generating than as reflecting settled principles of classification.

Finally, our search process was complicated by having to ensure coverage of all terms that could be used to describe MTM interventions over time. Adding to this challenge was our effort to examine the gray literature, where we thought we might find studies tilted toward effectiveness and real-world program evaluation. As it turned out, studies of these types of interventions were not indexed similarly; for that reason, we needed to rely heavily on hand searches of citation lists from key background articles to identify possibly relevant studies for inclusion. Thus, we may have missed some studies that might have qualified for inclusion. Given the considerable diversity in the evidence base we did have, however, and the general lack of data supporting effectiveness of MTM, we do not think that any potential missed studies would have changed our conclusions in any material way. No meta-analyses included more than five studies; as a result, we did not examine included studies for publication bias quantitatively.

Limitations of the Evidence

As a body of evidence, the MTM literature evaluated in this review has measured numerous outcomes. As indicated in previous sections, very few outcomes, with the exception of harms, remain completely unexamined. Of the 36 studies in this review, we rated 22 as having medium or low risk of bias. The 36 studies included 19 trials and 3 nonrandomized controlled studies. In other words, the literature on this topic is *not* marked by failure to consider important outcomes, universally high risk of bias, or pervasively weak designs.

Despite these advantages, we were unable to identify sufficient evidence on the majority of hypothesized outcomes of MTM. In several instances, our inability to rate evidence as higher than insufficient came from indirect, inconsistent, and imprecise evidence. The choice of outcome measures in this body of evidence limited our ability to come to conclusions in some instances. For example, some studies did not focus on changes that proponents might expect MTM services to produce. Because effective MTM can either increase or decrease expenditures or use of services based on the needs of the patient, studies that did not prespecify the expected direction of change had no way to interpret their results as an appropriate change. Studies that demonstrated inconsistent results in direction of change (i.e., some showing an increase in resource use and others showing a decrease) may well have been consistent in terms of

appropriate change, but because they generally failed to establish a priori the direction in which they expected to find an effect, we rated such evidence as indirect and inconsistent.

Similarly, studies often used nonstandardized or idiosyncratic measures for outcomes such as adverse events, adherence, and expenditures or costs; this tendency limited our ability to meta-analyze results. When studies focused on specific outcomes, they were often significantly underpowered to detect differences between groups (that is, they did not meet optimal information size criteria). As a result, we rated several studies as imprecise.

MTM intervention studies are largely practice based and incorporate substantial heterogeneity in specific intervention elements and in patient populations targeted. Yet the evidence is sharply constrained in its ability to inform questions of the effectiveness of specific MTM components or intervention features (KQ 3 in our review) because study designs did not often capitalize on variants in MTM programs for a prospective evaluation of outcomes by those variants. Neither did they measure fidelity to intended MTM elements for post-hoc evaluation. Similarly, the relatively untargeted nature of the MTM interventions meant that, in many studies, only small numbers of patients had any one specific condition, and most studies did not measure patient characteristics beyond age and sex, thus limiting our ability to address KQ 4 in our review. For this reason, the evidence we identified for this review was most relevant for KQ 2.

Research Gaps

In many bodies of research, questions regarding the *comparative* effectiveness of specific intervention components or implementation features are best answered after clear evidence of the overall effectiveness of the intervention relative to usual care has been established. Our review largely indicates insufficient evidence on the primary question of effectiveness relative to usual care. By definition, this limited what we could say about comparative effectiveness.

Nonetheless, the widespread implementation of MTM coexists with the urgent need for actionable information for policy, program policies, and training. This clinical and policy environment means that new research cannot afford to address causal claims relative to usual care first, followed by comparative effectiveness of the intervention elements in a relatively controlled environment, and finally, program evaluation of real-world implementation, all in sequential order.

In choosing among various research goals, therefore, funders may wish to consider the relative value of new evidence on overall effectiveness, effectiveness of implementation features, and program implementation and accountability. Trial research in narrow clinical settings can address questions of effectiveness but may lack applicability to real-world implementation. Likewise, evaluations of real-world programs with variable fidelity to interventions can answer questions about process and implementation, but they offer limited information on effectiveness.

For new studies focusing on causal claims, a critical gap relates to the failure to specify the expected direction of effect. New research requires a strong theoretical foundation to help specify causal mechanisms and hypothesized effects. Without such an edifice, future research will continue to produce inconsistent and uninterpretable results.

Heightened attention to causal mechanisms will also help researchers convey their understanding of what outcomes these types of interventions are likely to influence. For instance, how should researchers wishing to establish direct causal links between MTM programs and outcomes evaluate distal outcomes such as patient-centered outcomes and resource utilization? This effort requires a better understanding of the relationship between proximal outcomes like "drug therapy problems identified and resolved" and distal outcomes. For instance, MTM may

reduce outpatient visits to address side effects. MTM may also result in the need for further testing and evaluation for some patients, which could, in turn, result in more rather than fewer outpatient visits. Unless the nature of change resulting from MTM is specified in relation to goals of drug therapy, studies cannot assert benefit or harm. Further, drug therapy problems are diverse and may not all have the same causal relationship to health, quality of life, patient satisfaction, or resource use outcomes. Furthermore, a causal model of these distal outcomes may need to take into account the competing or complementary contributions of MTM, new models of health care delivery (e.g., patient-centered medical homes), and other quality improvement interventions.

Investigators embarking on new studies focusing on causal links between MTM and outcomes may wish to consider the limitations of studies based on secondary data from existing MTM programs that use opt-in/opt-out patient enrollment mechanisms. Although these studies may provide invaluable information on process measures such as patient engagement, underlying issues of confounding severely limit the validity of causal claims from such studies.

Regardless of the goal of their future research, investigators should consider issues of sample size to ensure precision of their results. This issue is particularly relevant when evaluating outcomes likely to occur in smaller subgroups of patients. Innovative designs (e.g., stepped wedge trials) can permit both rigor and adequate sample size within the context of real-world implementation. With careful attention to fidelity, such designs may also inform questions of the effectiveness of intervention components and implementation features. Such designs may also help inform our understanding of critical training elements for MTM service providers.

Regarding research gaps for specific outcomes such as patient satisfaction, measures specific to the types of services provided through MTM (e.g., patient education about medications) or to the proximal outcomes that MTM is intended to achieve (e.g., reduced medication side effects, improved disease control) may offer better insights into the effects of MTM. Similarly, a medication-related instrument may better measure patients' concerns that are directly related to medication use (e.g., experience of side-effects, intrusiveness of the medication regimen) than generic tools.

Conclusions

The evidence base is insufficient to address the effectiveness of MTM on most outcomes. Given the widespread implementation of MTM and urgent need for actionable information, funders may wish to weight the relative value of information on overall effectiveness, effectiveness of implementation features, and program implementation and accountability when commissioning new research.

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Introduction

Context

Used appropriately, medications can alleviate distressing symptoms that compromise physical and psychological well-being, help prevent the onset of many acute and chronic health illnesses, and improve patient health outcomes. Too often, however, medications are not used appropriately. The Institute of Medicine and other prominent organizations have recognized that medication-related problems plague our health care system.[1-3] In the United States in 2001, an estimated 4.3 million ambulatory visits were for adverse drug events.[4] A cohort study of Medicare enrollees estimated the overall rate of adverse drug events at 50.1 per 1,000 person-years.[5] The study rated more than one-third of the adverse drug events as serious, life-threatening, or fatal; more than 40 percent of these more severe adverse drug events were classified as preventable. Another study found that more than 12 percent of hospitalized patients experienced an adverse drug event within 3 weeks following hospital discharge.[6]

In addition to problems involving adverse drug events, many patients are not prescribed optimal treatment for conditions such as high blood pressure and hyperlipidemia that increase their risk of developing cardiovascular disease. Moreover, even when optimal therapy is prescribed, patient inability to adhere closely to medication regimens may lead to poor health outcomes.[7]

Medication-related problems are especially pronounced among older adults.[5] Individuals 65 years or older constitute 13 percent of the U.S. population, but they consume more than 30 percent of all prescription medications.[5,8] A 2006 report found that nearly 60 percent of people in this age group were taking five or more medications and that nearly 20 percent were taking 10 or more medications,[9] placing them at increased risk for experiencing adverse drug events. Moreover, these figures reflect a substantial increase in the prevalence of polypharmacy since 1998.[9]

Medication therapy management (MTM) services are intended to address issues of polypharmacy, preventable adverse drug events, medication adherence, and medication misuse.[10] MTM services are designed to be distinct from medication-dispensing services; in particular, they employ a patient-centric and comprehensive approach, rather than an individual product or episodic perspective.[11] MTM is the current term that represents services that have evolved out of the philosophy and processes first implemented in the early 1990s as "pharmaceutical care."[10] In 2008, 11 national pharmacy organizations achieved a consensus framework for MTM services and established 5 core elements for MTM in practice, including: a medication therapy review, a personal medication record, a medication action plan, intervention and/or referral, and documentation and follow-up.[10]

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173)[12] established the requirements that Part D Prescription Drug Benefit Plan sponsors have to meet with respect to cost, quality, and the requirements for MTM programs. The law established oversight by the Centers for Medicare & Medicaid Services (CMS) and provided a general framework for MTM programs but allowed Part D Plan sponsors flexibility in design, including the patient eligibility criteria for services. The CMS requirements for Part D MTM programs have evolved since their implementation in 2006.

The evolution from pharmaceutical care research interventions to large-scale MTM programs in routine practice represents a journey along a continuum of practice settings, patient populations, and intervention components and features. Over time, standards for these services in

routine practice have evolved, as have standards for describing and conducting research studies involving these interventions. Thus, we established a broad scope for this comparative effectiveness review and did not limit our perspective to Medicare Part D-defined MTM programs. Throughout this review, we will use the term MTM to describe the general class of intervention. However, when describing individual studies included in this review, we will defer to the terms used by the study author to describe the intervention they were evaluating (e.g., pharmaceutical care, clinical pharmacy services).

Populations

Adult patients with multiple chronic conditions who take many different prescription or nonprescription medications, herbal products, or diet supplements (and combinations of these) are the target population for MTM services.[11] Because older adults are more likely to take multiple medications, MTM services generally target them.

CMS required that MTM programs target Medicare Part D enrollees, who have multiple chronic diseases, are taking multiple Part D drugs, and are likely to incur annual costs for covered Part D drugs that exceed a predetermined level ("annual cost threshold"). Beginning in 2010, CMS established both a ceiling and floor for the minimum number of diseases and medications that plans may require for eligibility into their MTM program.

To be eligible for CMS reimbursement, MTM programs originally had to offer services for at least four of seven core chronic diseases: hypertension, chronic heart failure, diabetes, dyslipidemia, respiratory disease (e.g., asthma, chronic obstructive pulmonary disease), bone disease (e.g., osteoporosis, osteoarthritis, rheumatoid arthritis), and mental health diseases. As of January 2013, this criterion specifies at least five of nine core chronic conditions—Alzheimer's disease and end-stage renal disease were the added conditions. Programs may require no more than eight Part D drugs, although they may set the maximum at any number between two and eight. CMS set the annual cost threshold at $4,000 in 2006, lowered it to $3,000 in 2010, and increased it by an annual percentage each year beginning in 2012. The cost threshold for 2013 is $3,144.

CMS-reimbursable MTM services are required for both community-dwelling beneficiaries and beneficiaries in long-term care settings. Although initial MTM programs were designed as "opt-in," more recently, MTM programs must enroll eligible Medicare Part D beneficiaries using only an opt-out approach. Furthermore, MTM enrollees can refuse individual MTM services without having to disenroll from the MTM program.

CMS eligibility criteria requirements are designed to meet a minimum threshold. The MTM program can also offer MTM services to beneficiaries who do not meet the CMS Part D criteria. The Veterans Health Administration (VHA) includes MTM as one of several clinical activities provided to VHA health beneficiaries by VHA pharmacy services.[13] The VHA does not specify patient eligibility criteria for MTM services. Non-Part D MTM programs and single research studies of MTM or pharmaceutical care interventions may define their own patient eligibility criteria, which may or may not be similar to current CMS criteria, for example, requiring only one chronic condition to be eligible for services.

Interventions and Comparators

Several pharmacy organizations have proposed operational features to describe MTM services and best practices for delivering MTM.[10,11] These features can be summarized as follows:

- A comprehensive medication review (CMR) to identify and resolve medication-related problems that may include the generation of a personal medication report, which is a written list of the patient's prescription and nonprescription drugs, herbal products, and dietary supplements.
- A medication action or treatment plan developed in collaboration with the patient.
- Education, counseling, and resources to enhance patients' understanding about using the medication and to improve adherence.
- Coordination of care, including documenting MTM services and providing that documentation to the patient's other providers and referring patients to other providers as needed.

CMS requires that each beneficiary enrolled in the MTM program be offered a minimum level of MTM services. These include:

- interventions for both beneficiaries and prescribers;
- an annual CMR with written summaries in CMS's standardized format:
  - The beneficiary's CMR must include an interactive, person-to-person, or telehealth consultation that is performed by a pharmacist or other qualified provider (e.g., a nurse or a physician) and may result in a recommended medication action plan.
  - If a beneficiary is offered the annual CMR and is unable to accept the offer to participate, the pharmacist or other qualified provider may perform the CMR with the beneficiary's prescriber, caregiver, or other authorized individual; and
- quarterly targeted medication reviews with follow-up interventions when necessary.

CMS expects the CMR to meet the following professional service definition: "a systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, and developing a prioritized list of medication-related problems, and creating a plan to resolve them with the patient, caregiver, and/or prescriber."[14, p. 6] In addition, CMS expects the CMR to be "an interactive person-to-person or telehealth medication review and consultation conducted in real time between the patient and/or other authorized individual, such as [a] prescriber or caregiver, and the pharmacist or other qualified provider. It is designed to improve patients' knowledge of their prescriptions, over-the-counter medications, herbal therapies, and dietary supplements; identify and address problems or concerns that patients may have; and empower patients to self-manage their medications and their health conditions."[14, p.6] Written summaries of the CMR are to be provided in CMS's standardized written format that includes a beneficiary cover letter, medication action plan, and personal medication list.[15] The service-level expectations of a CMR align closely with the definition of MTMs contained in the official health-reporting nomenclature of Current Procedural Terminology.®[16,17]

Disease-management, case-management, and self-management interventions have components that overlap with MTM components—for example, provision of education and counseling to increase medication adherence. Our preliminary literature search yielded many interventions that can be classified as one of these three types of interventions. To increase the usefulness of this review to stakeholders, we need to exclude disease-management, case-management, and self-management intervention studies by applying stringent intervention-

definition criteria. This will enhance our ability to draw conclusions about the effectiveness of MTM services.

Outcomes

MTM is thought to influence a wide variety of outcomes. Some MTM services relate to health care–delivery issues, such as medication costs, use of other health care services, and the costs of those services (e.g., emergency department visits or hospitalizations). Other MTM services relate to intermediate health outcomes measured typically by laboratory or other biometric tests for the main chronic conditions of interest to CMS; these may include hemoglobin A_{1c}, blood pressure, cholesterol (e.g., total, low-density lipoprotein, and high-density lipoprotein cholesterol), and cardiac function (e.g., left ventricular ejection fraction). Finally, still other MTM services relate to patient-centered outcomes (e.g., morbidity, mortality, reduced adverse drug events, missed days of work or school, patient satisfaction with care, health-related quality of life).[18] Thus, the impact of MTM on health care utilization, intermediate outcomes, and patient-centered outcomes may derive from improved medication adherence, fewer drug-related adverse events, and better or more efficient coordination of care.

Settings

MTM services can be delivered in a variety of settings. These include ambulatory care settings (e.g., outpatient clinics, physician practices), retail pharmacies in the community, and long-term care settings such as assisted living or skilled nursing facilities. In addition, telephone-based MTM services may be provided to community-dwelling adults by professional staff (often pharmacists) employed by pharmacy benefits management companies or other commercial health care companies that have centralized call centers. The setting in which MTM is delivered may depend on the type of provider delivering the service.

One or two specific components of MTM may be delivered within an inpatient setting; medication reconciliation at discharge is an example. However, MTM is designed as a longitudinal intervention. For that reason, it is not an intervention delivered exclusively within inpatient settings.

Contextual Factors

CMS guidelines require that MTM be delivered by a pharmacist or other qualified health care provider. CMS requires MTM plan sponsors to submit information about the MTM program each year, and plan sponsors must indicate which types of providers deliver MTM services within their plan by selecting one or more of the following provider types:

- local pharmacist
- long-term care consultant pharmacist
- plan sponsor pharmacist
- plan benefit manager pharmacist
- MTM vendor local pharmacist
- MTM vendor in-house pharmacist
- physician
- physician assistant
- registered nurse

- licensed practical nurse
- nurse practitioner

Professional pharmacy organizations have been actively involved in proposing delivery models, standards, and recommendations for MTM services. Pharmacist training varies considerably. Before the 1990s, individuals could become registered pharmacists with a bachelor of science (B.S.) degree that required a minimum of 5 years of study. Current regulations require that individuals have a doctor of pharmacy (Pharm.D.) degree, which requires a minimum of 6 years of study and provides more clinical training than B.S. programs. In addition, many Pharm.D. graduates pursue advanced training through residency, fellowship, and certificate programs. Some of these programs focus on areas such as MTM. The influence that provider type, education, and MTM-specific training have on MTM effectiveness is unknown.

Numerous factors other than clinical specialty may affect the quality of MTM services. Mode, frequency, and interval of delivery may influence MTM success, as may specific MTM components and the fidelity of their implementation. One key factor is how well an MTM provider understands the patient-specific goals of medication therapy. Integrating MTM services with usual care may help ensure that the goals of MTM are achieved. Integration of services and usual care refers to the ability of the MTM provider to communicate well with patients and multiple prescribers and ease of access to patients' medical records.

Health care reimbursement systems may also influence the delivery of MTM services. Not all private insurers cover MTM services. The degree to which MTM component services differ for Medicare beneficiaries when compared with non-Medicare beneficiaries is not known.

Finally, certain patient populations may have considerable difficulty accessing or participating in MTM services. Examples include individuals who are homebound, individuals who have physical or cognitive disabilities, patients without health insurance, and patients living in rural areas.

Scope and Key Questions

Scope of the Review

MTM is a complex intervention with numerous and differing components. This review seeks to catalog MTM intervention components, assess the overall effectiveness of MTM in comparison with usual care, examine the factors under which MTM is effective and optimally delivered, assess what types of patients are likely to benefit from MTM services, and assess what types of patients may be at risk of harms from the program.

Relevance of Research Question to Clinical Decisionmaking or Policymaking

The Key Questions (KQs) we address are highly relevant to both clinical decisionmaking and policies regarding MTM services. Identifying demonstrably effective models and components of MTM services will help patients and their health care providers achieve important intermediate and long-term health-related outcomes. Our findings will help providers of MTM services, particularly pharmacists and pharmacy benefit managers, understand what works well in which settings and with which patients; the findings will have the potential to improve the efficiency of delivery and thus improve the value of MTM services. Lastly, a better understanding of the

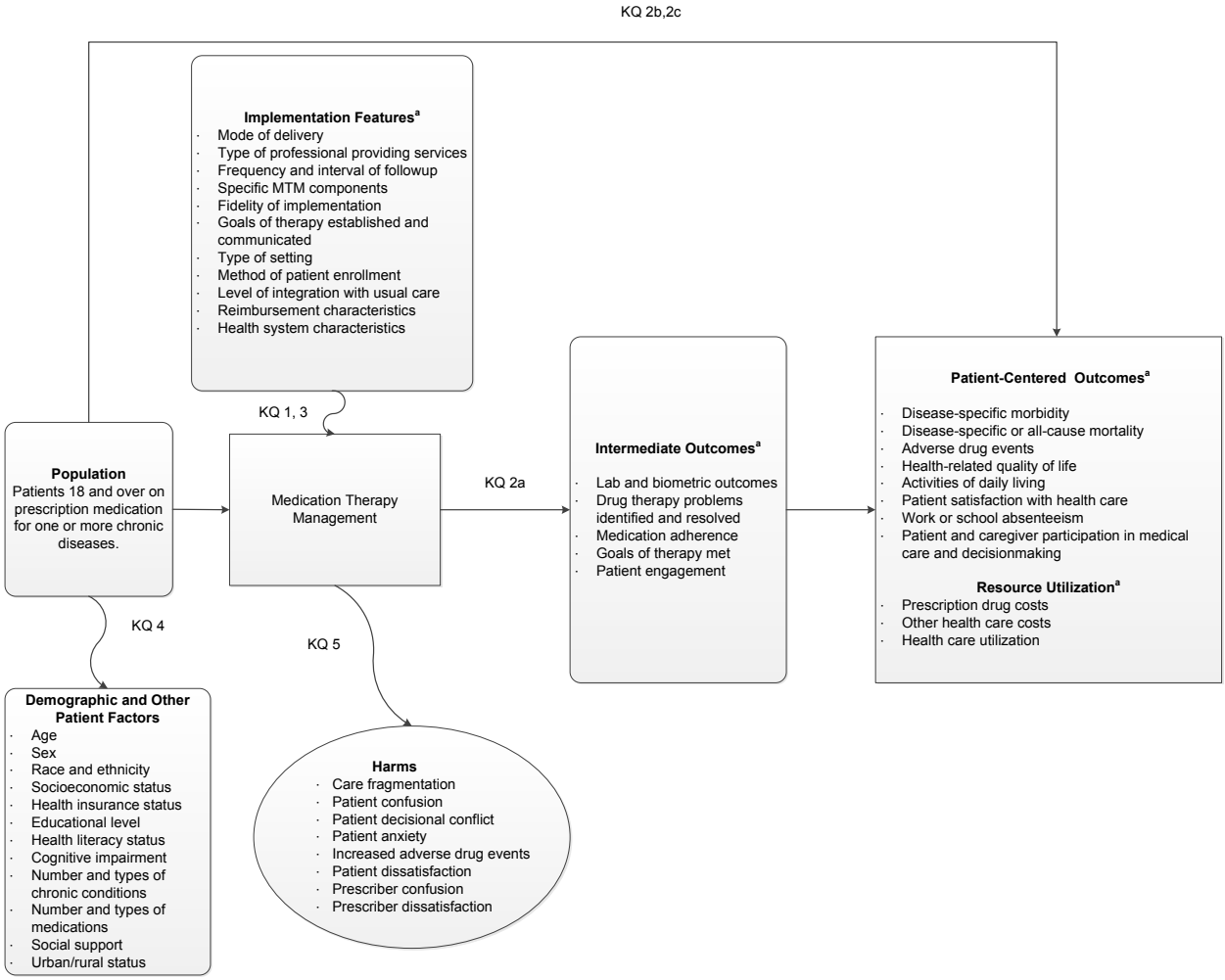
comparative effectiveness of MTM services will assist CMS with future revisions or enhancements to the policies governing coverage for MTM services.

Key Questions

The KQs are listed below and placed in relation to another and the PICOs in the analytic framework (Figure 1). Specific details regarding patient population, intervention components, and outcomes are provided in the section that follows the analytic framework.

Analytic Framework

Figure 1. Analytic framework for medication therapy management



[a] The population, intervention, outcomes, and setting are described in detail in the text.

Abbreviations: KQ = key question; MTM = medication therapy management

Question 1: What are the components and implementation features of MTM interventions?

Question 2: In adults with one or more chronic diseases who are taking prescription medications, is MTM effective in improving the following:

a. Intermediate outcomes, including biometric and laboratory measures, drug therapy problems identified, drug therapy problems resolved, medication adherence, goals of therapy met, and patient engagement in medication management?

b. Patient-centered outcomes, such as disease-specific morbidity, disease-specific or all-cause mortality, adverse drug events, health-related quality of life, activities of daily living, patient satisfaction with health care, work or school absenteeism, and patient and caregiver participation in medical care and decisionmaking?

c. Resource utilization, such as prescription drug costs, other health care costs, and health care utilization?

Question 3: Does the effectiveness of MTM differ by MTM components and implementation features?

Question 4: Does the effectiveness of MTM differ by patient characteristics, including but not limited to patient demographics and numbers and types of conditions and medications?

Question 5: Are there harms of MTM, and if so, what are they?

Populations, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS)

Table 1 lays out the PICOTS for this review. For this review, we take a broad perspective on the population and interventions evaluated; we do not limit the review to interventions and populations meeting CMS Part D MTM eligibility criteria. Specifically, we did not require multiple chronic conditions or a minimum number or level of expenditures on prescription drugs.

Table 1. Populations, interventions, comparators, outcomes, timing, and settings

PICOTS	Criteria
Populations	○ Patients aged 18 or older with one or more chronic conditions requiring the use of prescription medication to manage symptoms or prevent progression of chronic disease ○ Patient characteristics that may influence intervention effectiveness: – Age, sex, race and ethnicity, socioeconomic status, health insurance status, education level, health literacy status, cognitive impairment, number and types of chronic conditions, social support, and urban/rural status
Interventions	○ Explicitly termed *MTM* services, generally provided as a bundle of related services, that include *at a minimum* the following four elements: – Comprehensive medication review – Patient-directed medication management action plan with or without an equivalent prescriber-directed action plan – Patient-directed education and counseling or other resources to enhance understanding of the use of medication – Coordination of care, including prescriber-directed interventions; documentation of MTM services for use by the patient's other providers; and referral to other providers, clinicians, or resources when appropriate[14]

Table 1. Populations, interventions, comparators, outcomes, timing, and settings (continued)

PICOTS	Criteria
Interventions (continued)	○ MTM-like services that are provided as a bundle or multicomponent intervention, even if not explicitly termed "medication therapy management" ○ The following types of interventions generally are not considered MTM interventions and are not included: – Medication reconciliation interventions – Integrated pharmacy services within inpatient settings – One-time corrective actions related to medication management – Disease-management interventions[19] – Case- or care-management interventions[19] ○ The following types of interventions may include MTM services, but MTM may represent only one component of the overall intervention: – Patient-centered models of home health care – Fully integrated, collaborative care models involving multiple disciplines and specialties ○ Studies should contain the same level of overall medical care or health care services among different study arms such that the effect of MTM interventions can be isolated. For example, a study with two arms that has one arm with a care management intervention that includes MTM services and the other arm that has the care management intervention without MTM services could be included. By contrast, a study that includes a care management intervention with MTM in one arm and usual medical care (no care management intervention) in the other arm would not be included. ○ Implementation features that may influence intervention effectiveness include the following: – Mode of delivery: telephonic, face-to-face, virtual (Web/online/Internet), and remote video – Type of professional providing initial and followup MTM service: pharmacist, nurse, physician, other clinician – Frequency and interval of followup for MTM services – Specific MTM components used – Fidelity in implementing MTM components: to what extent were services delivered as designed or intended – Establishing and communicating goals of drug therapy to patients and among care providers – Method of identifying patients for enrollment (e.g., population health data, provider referral for services, enrollment during a transition in care, targeting highly activated patients, targeting patients at time of high risk for event [e.g., when prescribing a new drug]) – Level of integration of MTM with usual care, which includes access to real-time clinical information and laboratory values, and regular and consistent communication among prescribers and persons providing MTM services – Reimbursement characteristics (e.g., who is paying for cost of MTM services, who is reimbursed for MTM services, whether services are separately reimbursable) ○ Health system characteristics (e.g., are services being provided within an accountable care organization, patient-centered medical home, or some other unique system setting (e.g., the VHA, the Indian Health Service, non–U.S. single-payer system)
Comparators	○ Usual care, as defined by the studies ○ Individual components of MTM services (e.g., MTM services with four components vs. a single component) ○ Different bundles of MTM services ○ Same MTM services provided by different health care professionals (e.g., pharmacist, physician, nurse, other) ○ Same bundles of MTM services delivered by different modes (e.g., telephone or in person) ○ Same MTM services provided at different intensities, frequencies, or level of integration with prescribers

Table 1. Populations, interventions, comparators, outcomes, timing, and settings (continued)

PICOTS	Criteria
Outcomes	○ Intermediate outcomes – Disease-specific laboratory or biometric outcomes (e.g., hemoglobin A_{1c}; blood pressure; total, low-density lipoprotein, or high-density lipoprotein cholesterol; pulmonary function; renal function; left ventricular ejection fraction; or other laboratory or biometric outcome specific to diseases covered) – Drug therapy problems identified as defined by primary studies but typically include the following: medications being taken but not indicated; medications indicated but not prescribed; patient adherence issues; supratherapeutic doses; subtherapeutic doses; generic, formulary, or therapeutic substitution issue; complex regimen that can be simplified with same therapeutic benefit; and potential for drug-drug interactions or adverse event. – Drug therapy problems that are resolved as defined by primary studies but typically include the following: needed drug initiated; unnecessary drug discontinued; change in drug dose, form, or frequency; or generic, formulary, or therapeutic substitution – Medication adherence – Goals of therapy met – Patient engagement (e.g., initial and continuing patient participation in the MTM program) ○ Patient-centered outcomes – Disease-specific morbidity, including falls and fall-related morbidity, and outcomes specific to the patient's underlying chronic conditions (e.g., Patient Health Questionnaire 9 [PHQ9], disease-specific symptoms, reduced number of disease-specific acute exacerbations or events) – Disease-specific or all-cause mortality, including fall-related mortality – Reduced (actual) adverse drug events (frequency and/or severity) – Health-related quality of life as measured by generally accepted generic health-related quality-of-life measures (e.g., short-form questionnaires, EuroQOL) or disease-specific measures – Activities of daily living as measured by generally accepted standardized measures of basic and/or instrumental activities of daily living (e.g., Katz, Lawton, or Bristol instruments) or with instruments that have demonstrated validity and reliability – Patient satisfaction with care – Work or school absenteeism – Patient and caregiver participation in medical care and decisionmaking ○ Resource utilization – Prescription drug costs and appropriate prescription drug expenditures – Other health care costs – Health care utilization (hospitalizations, emergency department visits, and physician office visits) ○ Harms – Care fragmentation – Patient confusion – Patient decisional conflict – Patient anxiety – Increased (actual) adverse drug events – Patient dissatisfaction with care – Prescriber confusion – Prescriber dissatisfaction
Timing	○ Interventions should have at least two separately identifiable episodes of MTM services (either patient or provider directed or both), with any interval of time in between episodes. ○ For studies that report outcomes at different points in time, we only considered outcomes measured after the second episode of care.

Table 1. Populations, interventions, comparators, outcomes, timing, and settings (continued)

PICOTS	Criteria
Setting	○ Ambulatory settings (e.g., outpatient clinics or private physician offices), long-term care setting, or retail pharmacy settings) ○ However, the MTM intervention itself may be delivered by home visits, telephone, via the Web, or in other non–face-to-face modalities, such as video teleconferencing. ○ MTM services that are delivered mostly in inpatient settings are not included. ○ Interventions conducted in the United States and other countries and are published in English are included.

Organization of the Report

The remainder of this report describes our methods, presents the results of our synthesis of the literature, discusses our conclusions, and provides other information relevant to the interpretation of this work. The Methods section describes our scientific approach for this systematic review in detail. The Results section presents our findings for all five of the KQs and includes summary and strength-of-evidence tables. In the Discussion section, we summarize the findings and discuss the implications for clinical practice and further research. A complete list of references, acronyms, and abbreviations follows the Discussion section.

This report contains the following appendixes: Appendix A contains the exact search strings we used in our literature searches. Appendix B documents the title and abstract and full-text review forms. Studies excluded at the stage of reviewing full-text articles with reasons for exclusion are presented in Appendix C. Studies that are awaiting further information from authors are presented in Appendix D. Evidence tables appear in Appendix E. Appendix F lists studies rated high risk of bias and reasons for excluding them from relevant KQ analyses. Quantitative analyses are presented in Appendix G.

Methods

The methods for this comparative effectiveness review (CER) on medication therapy management (MTM) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm). We specified methods and analyses a priori in a protocol posted on the AHRQ website,[20] following a standard framework for specifying population, interventions, comparators, outcomes, and settings (PICOTS). The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.[21] We describe below instances in which our a priori methods required further specification during the project.

Topic Refinement and Review Protocol

The topic of this report and preliminary key questions (KQs) arose through a nomination from the Pharmacy Quality Alliance. Key Informants representing several clinical and scientific disciplines provided input on the initial KQs; we revised them as needed. An initial draft of the revised KQs was posted for public comment from March 6, 2013, through April 2, 2013, on the AHRQ Effective Health Care program Web site. We received comments from 23 professional organizations and individuals and further revised KQs as appropriate. Specifically, we

1. added a new KQ (KQ 1) to describe the components and implementation features of MTM interventions,
2. included additional intermediate outcomes in KQ 2,
3. reworded KQ 3 to include MTM components,
4. specified MTM components and implementation features for KQ 3 in the PICOTS,
5. specified additional patient characteristics for KQ 4 in the PICOTS, and
6. rephrased KQ 5 to make the response conditional on identifying whether any harms of MTM exist.

Literature Search and Identification Strategy

Search Strategy

To identify articles relevant to each KQ, we began with a focused MEDLINE® search for MTM interventions using a combination of medical subject headings (MeSH®) and title and abstract keywords and limiting the search to English-language and human-only studies (Table 2). We also searched the Cochrane Library and the International Pharmaceutical Abstracts database using analogous search terms (Appendix A). We selected these databases based on preliminary searches and consultation with content experts. We conducted quality checks to ensure that the searches identified known studies (i.e., studies identified during topic nomination and refinement). Based on these quality checks, we revised and ran additional searches (specifically, drug therapy management, drug therapy problem, and medications management) to avoid missing articles that might prove eligible for this CER.

In addition, we searched the gray literature for unpublished studies relevant to this review and included studies that met all the inclusion criteria and contained enough methodological information to assess risk of bias. Specifically, sources of gray literature included ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, Health Services Research Projects in Progress (HSRProj), the National Institutes of Health Research Portfolio Online Reporting Tools, the Database of Promoting Health Effectiveness Reviews, the New York Academy of Medicine Grey Literature Report, and CMS.gov. AHRQ's Scientific Resource Center managed the process of submitting requests for scientific information packets, which contain information about MTM programs and services of interest from relevant providers.

We reviewed our search strategy with an independent information specialist and the Technical Expert Panel and supplemented it according to their recommendations. In addition, to avoid retrieval bias, we manually searched the reference lists of landmark studies and background articles on this topic to identify any relevant citations that our electronic searches might have missed.

Table 2. Literature search terms for medication therapy management studies

Populations	None; no population terms were used to avoid restricting the search yield
Interventions	("Medication Therapy Management"[Mesh] OR "medication therapy management" OR "comprehensive medication review" OR "personal medication record" OR ("medication" AND "action plan") OR "medication therapy review" OR "Medication Reconciliation"[Mesh] OR (med* AND reconciliation) OR "medication-related problems" OR MTMP OR prescriber intervention* OR "drug utilization management" OR "chronic care improvement" OR "drug therapy services" OR ("utilization management strategies" OR "utilization management strategy") OR "medication counseling" OR "pharmaceutical case management" OR "drug therapy management"
Outcomes	"optimized treatment outcomes" OR (patient OR patients) AND "medication understanding") OR ("drug therapy outcome" OR "drug therapy outcomes")
Study designs	None; no study design terms were used to avoid restricting the search yield
Limits	Humans; English language

We will conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. We will also investigate any literature the peer reviewers or the public suggest and, if appropriate, incorporate additional studies into the final review. The appropriateness of those studies will be determined using the methods and criteria described above.

We will include pooled estimates of effect or other relevant results from systematic reviews in the update search that meet our inclusion/exclusion criteria. We will evaluate the quality of included systematic reviews using the AMSTAR tool.[22] If appropriate and feasible, we may update the results of these reviews quantitatively or qualitatively. Should identified systematic reviews use inclusion or exclusion criteria that differ from ours, we will review their reference lists to ensure that we include all relevant studies.

Inclusion/Exclusion Criteria

We specified our inclusion and exclusion criteria based on the population, intervention, outcome, timing, and settings identified through the topic refinement exercise. We excluded studies published in languages other than English. We excluded study designs without control groups to ensure that our pool of included studies can inform the causal link between the intervention and outcomes.

In conducting the review, we found that we needed to define the intervention with greater specificity than originally thought so that we could include MTM interventions but exclude disease management interventions. Specifically, we required that included studies had conducted a *comprehensive,* rather than condition-specific, medication review, as required in our PICOTS criteria. Although we had not planned to contact study authors routinely for additional information, the lack of clarity regarding intervention elements in numerous published studies necessitated our contacting authors. For these studies, we based our decisions on inclusion or exclusion based on email communication. (Appendix D specifies the studies or publications for which we sought such information but received no response from authors as of the time the draft report was submitted for peer review.)

Study Selection

Pairs of trained members of the research team reviewed each title and abstract independently against our inclusion/exclusion criteria. Studies marked for possible inclusion by either reviewer underwent a full-text review. For studies that lack adequate information to determine inclusion or exclusion, we retrieved the full text and then made the determination.

We retrieved and reviewed the full text of all included titles during the title/abstract review phase. Two trained members of the team independently reviewed each full-text article for inclusion or exclusion based on the eligibility criteria specified in Table 3. If both reviewers agreed that a study did not meet the eligibility criteria, they excluded the study. If the reviewers disagreed, they discussed differences to achieve a consensus. If they could not reach consensus, a third senior member of the review team resolved the conflict. We tracked all results in an EndNote® (Thomson Reuters, New York, NY) database, and we will deposit them in the Systematic Review Data Repository at the end of the study. We recorded the reason that each excluded full-text publication did not satisfy the eligibility criteria. Appendix C lists all studies excluded at this stage together with the reason(s) for exclusion.

Data Extraction

For studies that met our inclusion criteria, we abstracted relevant information into evidence tables (Appendix E). We piloted our approach with a sample of studies and revised the form thereafter. We designed data abstraction forms to gather pertinent information from each article, including the characteristics of the study populations, interventions, comparators, outcomes, timing, settings, study designs, methods, and results. A second member of the team reviewed all data abstractions for completeness and accuracy. (Relevant forms can be found in Appendix B.)

Table 3. Inclusion/exclusion criteria for medication therapy management studies

Category	Inclusion	Exclusion
Population	Patients aged 18 or older with one or more conditions requiring the regular use of prescription medication to manage symptoms or prevent progression of chronic disease	• Children under age 18 • Adults with acute conditions
Interventions	• Those specified in the PICOTS criteria listed in Table 1 (Introduction) • More complex interventions with an MTM component that are compared with identical interventions without an MTM component (including care management and disease management)	• Drug therapy services for a single drug (e.g., warfarin clinics, statin clinics) • Interventions in which the effect of the MTM component cannot be isolated (e.g., case management or disease management with an MTM component) • Self-management programs • Isolated medication reconciliation interventions • Integrated pharmacy services within inpatient settings • One-time corrective interventions related to medication management
Control interventions	• Those specified in the PICOTS criteria listed in Table 1 (Introduction)	
Outcomes	• Those specified in the PICOTS criteria listed in Table 1 (Introduction)	• Studies that do not include at least one of the outcomes listed under the inclusion criteria
Timing of intervention and followup	• Interventions should have at least two separately identifiable episodes of MTM services (either patient directed or provider directed or both) with or without specifying any certain amount of time between those episodes • For studies that report outcomes at different points in time, we considered only outcomes measured after the second episode of care.	• Studies that measure outcomes only after one episode of MTM care
Settings	• Ambulatory (e.g., outpatient clinics, private physician offices, or retail pharmacy settings) and long-term care settings • May be delivered by telephone, via the Web, or in other non–face-to-face modalities, such as video teleconferencing • Interventions conducted in the United States and other countries will be included	• Inpatient settings, if delivery of MTM services occurs almost exclusively in the inpatient setting
Geography	• No limits	• Not applicable
Dates of search	• No limits; searches will be updated while the draft report is out for peer review	• Not applicable
Study designs	• Original research • Eligible study designs include: – Randomized controlled trials – Nonrandomized controlled trials – Prospective controlled cohort studies – Retrospective controlled cohort studies – Case-control studies – Systematic reviews and meta-analyses	• Case series • Case reports • Nonsystematic reviews • Studies without a control group
Study duration	No limits	Not applicable
Publication language	English	All other languages
Publication type	Any publication reporting primary data	Publications not reporting primary data

Abbreviations: MTM = medication therapy management; PICOTS = populations, interventions, comparators, outcomes, timing, and setting

Assessment of Risk of Bias of Individual Studies

To assess the risk of bias of individual studies, we used predefined criteria developed by AHRQ.[23] For randomized controlled trials, we relied on the risk-of-bias tool developed by the Cochrane Collaboration.[24] We assessed the risk of bias of observational studies using an item bank developed by RTI International.[25]

In general terms, results of a study with low risk of bias are considered valid. A study with medium risk of bias is susceptible to some bias but probably not sufficient to invalidate its results. A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results. Primary concerns for our review included selection bias, confounding, performance bias, detection bias, and attrition bias. Specifically, we evaluated studies on the adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity.

We excluded studies that we deemed at high risk of bias from our main data synthesis and main analyses. We included them for sensitivity analyses; in cases when we had no other available or credible evidence, we included in the report a brief synopsis of studies assessed as high risk of bias.

Data Synthesis

When we found three or more similar studies for a comparison of interest, we conducted meta-analysis of the data from those studies. For all analyses, we used random-effects models to estimate pooled or comparative effects. To determine whether quantitative analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance;[26] that is, we qualitatively assessed the PICOTS of the included studies, looking for similarities and differences. When we conducted quantitative syntheses (i.e., meta-analysis), we assessed statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity). The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., the p-value from the chi-squared test or a confidence interval for I^2). Where relevant, we examined potential sources of heterogeneity using sensitivity analysis.

When quantitative analyses were not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. Whenever possible, we computed confidence intervals for individual outcomes.

Because numerous articles about both trials and observational studies often did not provide complete information about findings (e.g., 95 percent confidence intervals; statistical significance values, or between-group data), in many cases we had to calculate odds ratios, mean differences, or standardized mean differences; the relevant 95 percent confidence intervals; and p-values. In all such cases in which we calculated data, we specify this in the Results chapter; information not specifically called out as "calculated" is taken from the original articles.

Grading Strength of Evidence for Individual Comparisons and Outcomes

We graded the strength of evidence based on the guidance established for the AHRQ Evidence-based Practice Center (EPC) program.[27] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: study limitations (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Consistency refers to similarity in direction or magnitude of effect. Study limitations refer to the risk of bias from study design or study conduct. Directness refers to whether evidence links the intervention directly to the health outcome. Precision refers to the certainty around the estimate of effect, after accounting for sample size and number of events. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Dose-response refers to a pattern of a larger effect with greater exposure. Plausible confounding refers to situations where, had these confounders not been present, the observed effect would have been even larger than the one observed. Strength of association refers to instances where the observed effect is large enough that it cannot have occurred solely as a result of bias from potential confounding factors. We evaluated optimal information size criteria to make judgments about precision and based our grades on low or medium risk-of-bias studies unless none were available.

Our approach is consistent with current strength of evidence guidance developed by GRADE and AHRQ EPCs. The GRADE guidance explicitly discourages the inclusion and averaging of risk of bias across studies with different underlying risk of bias criteria. Rather, it suggests considering including only studies with a lower risk of bias.[28] Likewise, the AHRQ EPC guidance notes that reviewers may focus "strength of evidence on the subset of studies that provide the least limited, most direct, and most reliable evidence for an outcome or comparison, after analysis of all the evidence."[27, p. 20]

Table 4 describes the grades of evidence that can be assigned.[29] Grades reflect the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the interventions examined in this review. Two reviewers assessed each domain for each key outcome resolved any differences by consensus discussion or referral to a third, senior member of the team. We graded the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those commonly reported in the literature; we did not grade the strength of evidence for KQ 1 (on components and features of MTM services).

Table 4. Definitions of the grades of overall strength of evidence

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Assessing Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[30] We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age and health status of enrolled populations, health insurance coverage and access to health care, and complexity and intensity of the MTM intervention.

Peer Review and Public Commentary

[To be completed after peer review]

Results

Introduction

This section of this comparative effectiveness review (CER) on medication therapy management (MTM) first presents the results of the literature searches. We then document the results for each Key Question (KQ). KQ 1 describes MTM intervention characteristics. KQ 2 presents evidence on the effectiveness of MTM interventions, focusing on intermediate outcomes, then patient-centered (health) outcomes, and then use of health care resources or costs. The presentation of KQ 3 summarizes the evidence by intervention components and implementation features; KQ 4 summarizes evidence by patient characteristics. KQ 5 examines the evidence on harms of MTM programs. Appendix E has two parts pertaining to these KQs: the first part has the lengthy descriptions of the design of all included studies (for KQ 1); the second presents the evidence tables, organized by outcome, for the remaining KQs.

Generally, for KQs 2 through 5, the text gives key points and the related strength of evidence grades, followed by a detailed synthesis of the relevant studies. We also present pairs of tables for each outcome. One gives basic summary information about the results of included studies, indicating whether the quantitative data had been what the investigators reported or were calculated by us. The other table in these sets documents the strength of evidence grades for major outcomes (showing the ratings for required domains and, in a small number of cases, any ratings for optional domains). Appendix F contains the tables documenting how we arrived at risk of bias assessments for individual studies.

Most data can be found in tables and are not repeated in text. As noted in Methods, we focus on studies of low or medium risk of bias; when we need to summarize information for studies of high risk of bias, we note the principal problems leading to that rating.

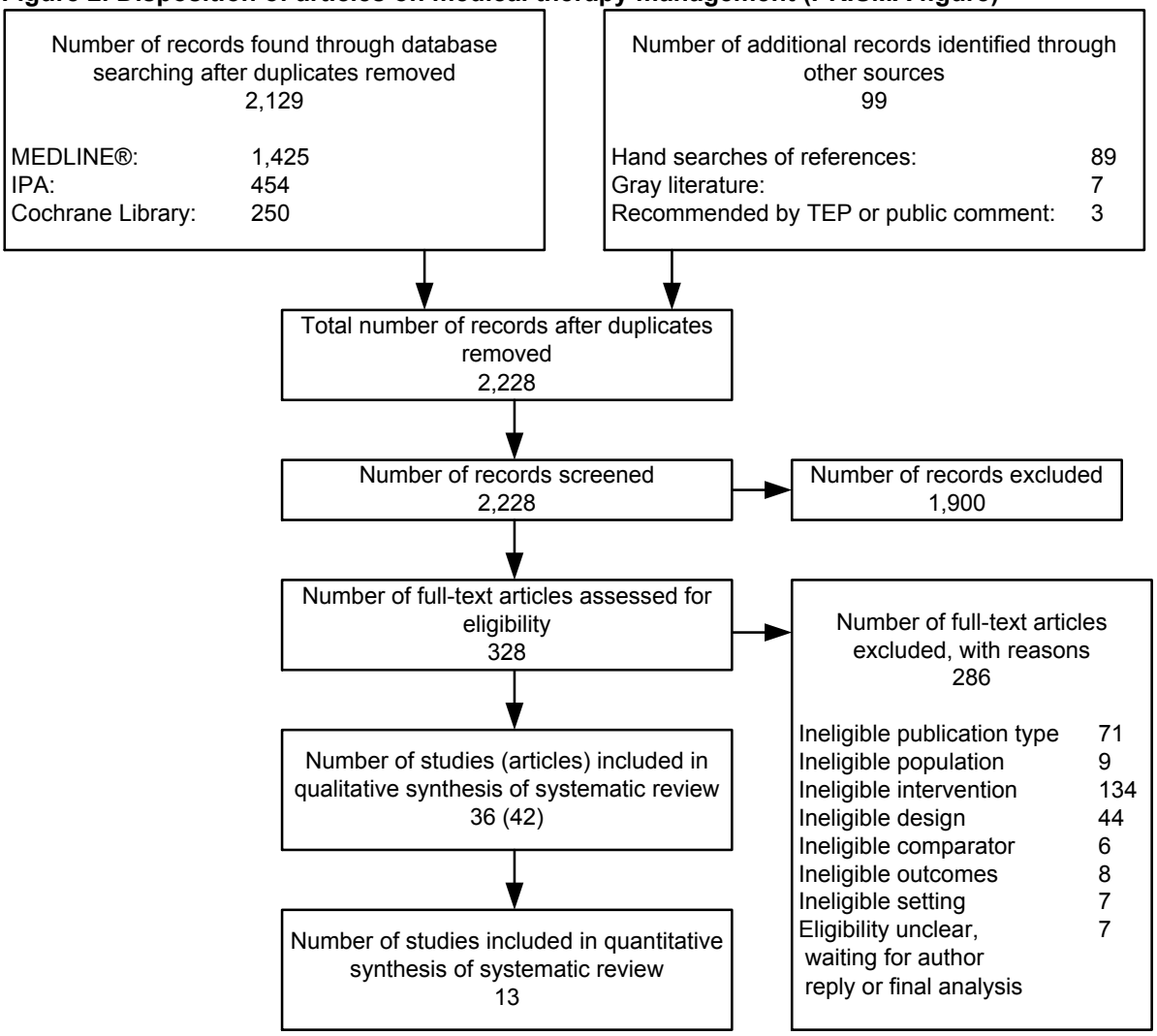
Finally, our inclusion criteria for study designs were expansive and included randomized controlled trials (RCTs) and a variety of observational studies (nonrandomized controlled trials, cohort studies and the like). We use "studies" to refer to all types of investigations; we specify RCTs (or non-RCTs) as appropriate.

Results of Literature Searches

Figure 2 presents our literature search results. Literature searches through June 27, 2013, for the draft report, identified 2,129 unduplicated citations. Appendix A provides a list of all search terms used and the results of each literature search. In addition, we identified 99 publications through grey literature searches, suggestions from technical experts or public comments received during topic refinement, or hand searches of included studies. After applying our eligibility and exclusion criteria to titles and abstracts of all 2,228 identified citations, we obtained full-text copies of 328 published articles. We reapplied our inclusion criteria and excluded 286 of these articles from further review before doing the risk-of-bias assessment. Appendix C provides a list of excluded studies and reasons for exclusion at the full-text stage. Appendix D lists the studies with too little information for us to be able to make a decision on inclusion or exclusion; these are the studies from which we sought further information directly from authors but did not receive a response before sending this draft out for peer review.

The 42 articles included after full-text review represent 36 studies. Evidence tables for these 36 studies are provided in Appendix E.

Figure 2. Disposition of articles on medical therapy management (PRISMA figure)



Abbreviations: IPA, International Pharmaceutical Abstracts; PICOTS, populations, interventions, comparators, outcomes, timing, settings; TEP, technical expert panel.

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Scientific Resource Center placed the request for scientific information packets (SIPs) in the *Federal Register* on September 16, 2013; it posted them for 30 days. The final version of this CER will include any relevant data from responses to this request.

Table 5 summarizes study characteristics of included studies. Overall, 28 (77.8 percent) of included studies were conducted in the US, and 16 (44.4 percent) were conducted prior to the 2003 Medicare Modernization Act, which established the framework for Medicare Part D MTM programs. Just over half of included studies used an RCT design (either parallel or cluster group), three (8.3 percent) used a non-randomized controlled trial design, and the remaining studies (38.9 percent) used a cohort study design. Only three studies used an active treatment comparison group. Intermediate outcomes were the most commonly reported outcomes. Of the 36 studies, two were considered low risk of bias (5.6 percent), 21 were considered medium risk of bias (55.6 percent) and 14 (38.9 percent) were considered high risk of bias.

Table 5. Characteristics of included studies

Study Characteristic	N (%)
Country	
US	28 (77.8)
Non-US	8 (22.2)
Multiple	1 (2.8)
Conducted prior to 2003 Medicare Modernization Act	16 (44.4)
Study Design	
RCT-parallel group	14 (38.9)
RCT-cluster group	5 (13.9)
Non-randomized Controlled Trial	3 (8.3)
Cohort Study	14 (38.9)
Used an active treatment comparison arm	3 (8.3)
Outcomes Measured	
Intermediate outcomes (e.g., disease specific lab values, medication adherence, drug therapy problems)	29 (80.6)
Patient-centered outcomes (e.g., health outcomes, quality of life, patient satisfaction)	17 (47.2)
Utilization and Economic Outcomes	25 (69.4)
Risk of bias	
Low	2 (5.6)
Medium	20 (55.6)
High	14 (38.9)

Abbreviations: US = United States

Key Question 1: Components and Implementation Features of MTM Interventions

KQ 1 was designed to synthesize descriptive findings regarding MTM intervention components and implementation features, which have been identified as important factors related to effectiveness of these interventions. Because this report is a CER, our study inclusion criteria included a requirement for a control or comparison arm. For that reason, our synthesis of descriptive findings related to MTM components and implementation features is limited to investigations that comparatively evaluated MTM; that is, it does not include all studies of MTM interventions, many of which we had excluded because of the lack of a comparison arm. Thus, our findings represent a somewhat circumscribed lens for the descriptive part of this review.

Synthesizing intervention components and implementation features across this body of evidence was challenging. Mainly, studies did not consistently describe the intervention characteristics or implementation features in sufficient detail to allow us to determine the extent to which certain components were used, at which intervals, and at what intensity. Even studies published after the 2003 Medicare Modernization Act, which formalized aspects of pharmaceutical care, lacked sufficient reporting detail in many cases.

Overall Descriptors of Study Interventions

Table 6 specifies the components and implementation features from our analytic framework (Figure 1 in Introduction). It also gives our assessment of the suitability or feasibility of synthesis, based on information available in the included studies across the entire evidence base.

Table 6. Characteristics of medication therapy management interventions

Characteristic of the MTM Intervention (Specified in Analytic Framework in Introduction)	Summarize in Tables and Synthesize With Counts	Summarize in Table but Not Synthesize With Counts	Neither Summarize in Tables Nor Synthesize With Counts
Mode of delivery	X		
Type of professional providing services	X		
Frequency and interval of followup	X		
Specific MTM components			X
Fidelity of implementation			X
Goals of therapy established and communicated			X
Type of setting	X		
Method of patient enrollment		X	
Level of integration with usual care		X	
Reimbursement characteristics	X		
Health system characteristics	X		

Abbreviations: MTM =medication therapy management.

In the best case, we can summarize data in tables and synthesize the information with actual counts across the body of evidence. This is true for mode of delivery, type of professional giving the services, details about followup, settings, modes of reimbursement, and characteristics of health systems. Somewhat less can be done with methods for enrolling patients and level of integrating MTM with usual care, so information is just included in study-level summary tables (but not synthesized with actual counts across the body of evidence). Finally, information on specific MTM components, fidelity of implementation, and MTM goals was so inconsistent or sparse that we could not either synthesize or include information in summary tables.
Table 7 summarizes the intervention characteristics and features that were reported consistently enough to be synthesized with counts and frequencies – namely, those in Table 6 with an X in the first column. It also notes whether the investigators used the phrase "pharmaceutical care" or the phrase "medication therapy management" to refer to the program tested. For details about intervention followup, the information in Table 7 is "as designed" (i.e., however the investigators described their initial intentions).

During our abstraction process, we identified two distinct categories of interventions. One category, of 24 studies, used a broad pharmaceutical care approach or MTM intervention in serving their patient populations; that is, they did not focus specifically on any one disease or clinical condition. We refer to these studies in the review and Table 7 as "broadly focused." The other category, with 12 studies, involved interventions evaluated in the context of a single chronic condition (e.g., chronic heart failure, diabetes) or provided in a highly specialized clinic setting (e.g., transplant clinics). In these studies, the investigators implemented a pharmaceutical care approach or MTM intervention that was comprehensive and attended to the patient's complete drug therapy regimen, but the focus of component interventions (e.g., education, counseling, care coordination) and outcomes measured may have been specific to diseases or conditions. We refer to these studies as "narrowly focused."

Table 7. Characteristics of medication therapy management studies by type of patient population (broad focus or narrow focus on conditions or diagnoses)

MTM Intervention	Characteristic of the Intervention	Overall (N =36) N (%)	Broad Focus (N=24) N (%)	Narrow Focus (N=12) N (%)
Phrase used to describe intervention	Pharmaceutical care	14 (39)	8 (33)	6 (50)
	Medication therapy management	12 (33)	11 (46)	1 (8)
	Other	10 (28)	5 (21)	5 (42)
Mode of delivery	Face-to-face only	19 (53)	10 (42)	9 (75)
	Telephone only	6 (17)	6 (25)	0
	Mixture of face-to-face and telephone	9 (25)	7 (29)	2 (17)
	Not reported	2 (6)	1 (4)	1 (8)
Professional	Pharmacist as interventionist	36 (100)	24 (100)	12 (100)
Frequency of followup as designed	One time with followup as needed	6 (17)	5 (21)	1 (8)
	Two times	6 (17)	6 (25)	0
	Three times	4 (11)	2 (8)	2 (17)
	Every 4 to 8 weeks for between 4 and 24 months	6 (17)	0	6 (50)
	Varied based on trigger (e.g., refill, physician visit, continuous enrollment for certain duration)	3 (8)	3 (13)	0
	Not reported	11 (31)	8 (33)	3 (25)
Clinical settings	Community pharmacy	6 (17)	3 (13)	3 (25)
	Centralized pharmacy	4 (11)	4 (17)	0
	Outpatient medical clinic	14 (39)	8 (33)	6 (50)
	Home visits	4 (11)	2 (8)	2 (17)
	Integrated health system	4 (11)	4 (17)	0
	Multiple settings	4 (11)	3 (13)	1 (8)
Reimbursement characteristics	Services provided through Medicare Part D benefit	7 (19)	7 (29)	0
	Services provided through some other health plan benefit	4 (11)	2 (8)	2 (17)
	Services provided through study-related funding	3 (8)	3 (13)	0
	Reimbursement details not reported	22 (61)	12 (50)	10 (83)
Health system characteristics	Single payer system (outside US)	7 (19)	4 (17)	3 (25)
	Academic medical center	8 (22)	4 (17)	4 (33)
	Integrated health system	9 (25)	8 (33)	1 (8)
	Health plan	8 (22)	7 (29)	1 (8)
	Pharmacies independent of medical care system or health plans	2 (6)	0	2 (17)
	Other	2 (6)	1 (4)	1 (8)

Abbreviations: N = number; US = United States.

In many cases, to distinguish narrowly focused MTM studies from case- or disease-management interventions, we had to contact study authors to clarify that their intervention included a comprehensive drug therapy assessment and drug therapy intervention beyond the single target condition of interest. The distinction between these broad-focus and narrow-focus categories may be important for interpretation of the effectiveness of these types of interventions. Studies included in this review used "medication therapy management" to describe the intervention (Table 7) in only 12 of the 36 studies. With respect to mode of delivery (Table 7), six broadly focused studies used only telephone contact;[31-37] by contrast, no narrowly focused studies used only telephone contact. Nine studies (seven broad; two narrow) used a mixture of face-to-face and telephone contact.[38-49] The studies using a mixture of modes often used face-to-face delivery for the initial consultation and did follow-up contacts by telephone. Except for the two studies that did not report mode of delivery,[50-52] the remaining studies used only face-to-face delivery in pharmacies, clinics, or homes.

All included studies used a pharmacist as the interventionist (Table 7). In some studies, however, the interventionist was described as a community pharmacy resident or ambulatory care pharmacy resident.

Table 7 also summarizes the intervention frequency and interval of follow-up *as designed*, not as may have actually occurred, and these features also differed across studies. Of the 36 included studies, however, 11 did not report the designed frequency of contact and interval of followup. Only six studies reported on the *actual* frequency and interval of follow-up.[38,40-43,47,53-55] Studies evaluating real-world experience with these types of interventions often included a minimum contact threshold for inclusion of patients in the data analysis, but the intervention duration and interval of followup was open-ended and determined by clinical need, as is typical in real-world practice.

Included studies provided interventions in a variety of clinical settings including community pharmacies, centralized pharmacies or pharmacy call centers, outpatient medical clinics, and some used home visits (Table 7). Half of the narrowly focused interventions were delivered exclusively in an outpatient medical clinic.[48,49,53,56-60]

Concerning reimbursement, of the 36 studies in the evidence base, 22 did not report on reimbursement at all. Of the remaining 14 studies, 11 reported that pharmaceutical care or MTM was a covered benefit to patients; pharmacist services were reimbursed through an existing mechanism (e.g., Medicare Part D or other health care benefit).[31-37,40-43,46,61-63] Three studies clearly indicated that pharmacist services were reimbursed through pilot, grant, or study-related funding.[38,47,64] Among the 12 broad studies with such information, 10 used either Medicare Part D or internal study funding. The two narrow studies with reimbursement information used some type of health plan funding.

Finally, the context of the MTM services also varied in terms of features of the health system or organization in which they were provided. Academic medical centers, integrated health care delivery systems, health plans, and single payer health care systems outside the United States were all represented in this evidence base.

Study-level Descriptors of Interventions

In Appendix E (Part 1), we have provided study-level summaries to describe the included interventions. Those tables (Table E.1 and E.2) document: interventions and the amount of integration with usual practice; method of identifying patients for receipt of MTM services; setting, mode of delivery, frequency and interval of followup; and health care system and reimbursement context. Table E.1 describes the 24 broad-focus studies; Table E.2 describes the remaining 12 narrow-focus studies (and additionally specifies the particular focus). We summarize the main elements in text below.

Of the dozen narrow-focus studies, four addressed chronic heart failure and two addressed hypertension or hypertension and diabetes. The remaining six studies focused on post-transplant patients (kidney; lung), diabetes alone, glucocorticoid-induced osteoporosis, and hemodialysis.

Interventions described as pharmaceutical care were generally based on the pharmaceutical care model as described and refined by Strand and associates[40-43,50-54,56-60,63,65-70] Interventions termed medication therapy management (i.e., MTM) were generally based on criteria defined for the Medicare Part D program, which includes elements of the pharmaceutical care model.[31-38,46,47,55,64,71] The remaining interventions included elements of pharmaceutical care or MTM but did not specifically label the intervention as either one or the other.[39,44,45,48,49,61,62,72-74] These studies were often described as "clinical pharmacist interventions."

The level with which pharmaceutical care or MTM services were integrated with usual care has two main element: (1) the degree of access that the interventionist had to clinical information in the patient's medical record, such as laboratory results, diagnoses, and progress notes; (2) the method and process of communication between the interventionist and prescribers. Providing these programs within an outpatient medical clinic, presumably where the patient is also receiving medical care, is one such marker of integration, particularly when the study indicated that the pharmacist was part of a multidisciplinary care team. Some studies, however, described the pharmacy or pharmacist simply as co-located in a clinic. In these instances, we do not know whether the level of integration with medical care would be any higher than if the pharmacist had been located in a community pharmacy. Thus, we could not rely solely on clinical setting as a marker of integration with usual care.

Because many studies did not provide sufficient details regarding specific components of the intervention, whether termed pharmaceutical care, MTM, or clinical pharmacist intervention, we were unable to synthesize the use of specific intervention components beyond the components we required for study inclusion.

Only three studies used an active treatment comparator group.[46,47,55] All other studies (regardless of focus) compared pharmaceutical care or MTM with usual care. This factor also impeded our assessing the effectiveness of individual intervention components. Furthermore, almost no study reported on the fidelity with which intervention components were delivered (relative to the original design or intention), including whether goals of drug therapy were established and communicated.

The methods by which patients were identified and offered pharmaceutical care or MTM services has been proposed as a moderator of effectiveness; the aim is to target patients most likely to benefit. These factors may include, for example, patients using drugs with narrow therapeutic windows, complex drug regimens, or patient characteristics such as age, cognitive status, or social situation. With respect to data sources that studies used to identify and then enroll patients for services, pharmacy prescription records (at a community pharmacy, clinic, or health plan) were the most common source. Except for the studies evaluating Medicare Part D MTM programs, few studies used the same criteria for identifying patients for enrollment. Most required either some degree of regimen complexity, such as the number of drugs taken or use of one or more drugs considered high risk for adverse events. Most studies using pharmacy data or claims mailed or telephoned eligible patients to provide information about enrollment in an MTM program. For Medicare Part D MTM programs, "opt out" is another variation of enrollment for these services. Patients meeting eligibility criteria are enrolled for services unless they specifically "opt-out." Some studies relied solely on provider referral, patient self-referral, or routine medical record screening at time of a provider visit to identify patients for services. Only one study enrolled patients in services during a transition in care from an inpatient to a home setting.[54]

Tables E1 and E2 also provide study-level detail on intervention setting, mode of delivery, frequency and interval of followup and health care system and reimbursement characteristics, which were summarized overall in Table 7 and in the preceding section.

Key Question 2: Effect of Medication Therapy Management Interventions on Intermediate, Patient-Centered, and Resource Utilization Outcomes

We present below key findings and a detailed synthesis of intermediate, patient-centered, and resource utilization outcomes separately. (These outcomes were specified in Table 1 of the Introduction.) When possible (a minimum of three reasonably similar studies for a given intervention or outcome), we pooled study results and document those findings below. When studies were too heterogeneous to pool, we present effect sizes for individual studies whenever possible in summary tables for each outcome that was reported in two or more studies. We also provide strength of evidence tables to support our findings.

Because in many cases the investigators did not report a full set of findings that compared changes over time between intervention and comparisons groups or other details that would permit full analysis, we calculated various statistics ourselves. In these cases, we present in the tables below only these calculated findings and related statistical levels, and we note this explicitly in the tables or text (as "calculated"). The underlying data from the study article(s) can be found in the evidence tables in Appendix E.

Key Points: Intermediate Outcomes

- Evidence was insufficient to evaluate the effect of MTM on anticoagulation after 12 months due to an imprecise, single RCT body of evidence with medium limitations.
- Evidence was insufficient to evaluate the effect of MTM on hemoglobin A1C after 6 to 12 months due to and inconsistent and imprecise body of evidence from two RCTs with medium limitations.
- Evidence was insufficient to evaluate the effect of MTM for decreasing low-density lipoprotein (LDL) cholesterol after 6 to 24 months due to an imprecise, single RCT body of evidence with medium limitations.
- Evidence was insufficient to evaluate the effect of MTM for reducing blood pressure (BP) after 4 to 12 months due to an imprecise, single RCT body of evidence with medium limitations.
- Several studies did not report outcomes such as drug therapy problems identified and resolved for both intervention and control groups. As a result, limited evidence addresses the effectiveness of MTM compared with usual care in improving these important intermediate outcomes. Study limitations, inconsistency, and lack of precision led us to conclude that the evidence is insufficient to judge the effectiveness of MTM in improving these outcomes when compared with usual care.
- Evidence was insufficient to evaluate the effect of MTM on medication adherence (as defined in several ways) as a result of inconsistent and imprecise evidence. The number of trials, consistency, and study limitations varied by specific adherence measure.
- MTM increases the appropriate use of medications as measured by overall scores on appropriateness indices (low strength of evidence).
- Evidence was insufficient for effect of MTM on medication dosing as a result of inconsistent, indirect, and imprecise evidence from two trials with medium study limitations.

Detailed Synthesis: Intermediate Outcomes

Anticoagulation

One RCT (medium risk of bias) reported on the effects of a pharmaceutical care intervention on anticoagulation among patients in family medicine clinics in a rural community after 12 months of followup.[68] This intervention was conducted with 81 patients at high risk for medication-related problems; however, this outcome was reported only for the four patients in the intervention arm and the six patients in the control arm who were taking anticoagulants. The percentage of subjects who achieved a therapeutic international normalized ratio (INR) differed significantly between the intervention and control arms (100 percent versus 16.7 percent (p=0.048); calculated odds ratio [OR], 32.94; 95% confidence interval [CI], 1.06 to 1,021.35). Because of imprecision (wide confidence intervals) and unknown consistency, we graded the evidence as insufficient to evaluate the effectiveness of MTM on improving therapeutic anticoagulation (Table 8).

Table 8. Anticoagulation: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (10)	Medium	Consistency unknown-single study	Direct	Imprecise	Therapeutic INR achieved: 100% vs. 16.7%, p=0.048	Insufficient

Abbreviations: INR, international normalized ratio; RCT, randomized controlled trial; vs. = versus

Hemoglobin A1C

Two RCTs and two cohort studies reported on outcomes related to hemoglobin A1c (HbA1c) among patients with diabetes (Table 9). One RCT (medium risk of bias) reported no significant difference in mean HbA1c between intervention (pharmaceutical care) and control patients in an Australian outpatient hospital diabetes clinic at 6 months.[58] The other RCT (medium risk of bias) reported on changes in the percentage of patients with diabetes who achieved a HbA1c of ≤7.5 percent at 12 months among patients at high risk for medication-related problems seen in family medicine practices in a rural community.[68] The percentage of patients at goal did not differ significantly between intervention and control arms at baseline (23.1 versus 56. 3, calculated p=0.08) but was significantly different at followup (100 versus 26.7, calculated OR, 56.455; 95% CI, 2.811 to 1,133.912. p=0.008,). The two cohort studies (high risk of bias because of self-selection of participants into the intervention arm) were conducted primarily by telephone within large, integrated US health care systems. Of these studies, one study did not report any significant difference in the percentage of patients achieving a HbA1c of less than7 percent at 6 months;[35] the other reported no significant change in mean HbA1c at 6 months.[32]

Table 9. Hemoglobin A1c: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed[a]	Outcome Reported by Study and Time Period	Results
Clifford et al. 2002[58] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1:48 G2:25	Mean HbA1c at 6 months.	Calculated mean difference: -0.20 95% CI: -0.927 to 0.527 p=0.590
Taylor et al., 2003[68] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 13[a] G2: 16[a]	Percentage with HbA1c at goal (defined as less than or equal to 7.5%) at baseline and at 12 months.	Calculated OR: 56.455 95% CI: 2.811 to 1,133.912, p=0.008
Pindolia et al., 2009[35] Cohort study/High	G1: Opted in to a telephone-based MTM Program G2: Usual medical care (opted out of MTM program)	G1: NR[a] G2: NR[a]	Change in percentage of patients with HbA1c less than 7 at 6 months	G1: + 3 G2: + 7 Between-group p: inferred to be NS, exact p NR Within-group p: NR
Jeong et al., 2007[32] Cohort study/High	G1: Participants in Part D Medicare MTM program G2: Control subjects eligible for Part D MTM program but declined enrollment G3: Control subjects without Part D Medicare as their primary drug benefit	G1: 1,211[a] G2: 1,000[a] G3: 743[a]	Mean change in HbA1c at 6 months	Calculated mean difference: G1 vs. G3: 0.004, 95% CI: -0.087 to 0.095 p=0.931 Calculated mean difference of G1 vs. G2: 0.041 95% CI: -0.043 to 0.125 p=0.337

[a] The study included more subjects than the number analyzed and reported in this column, but the investigators assessed this outcome only among patients with diabetes within each study arm.

Abbreviations: CI = confidence interval; DM= diabetes mellitus; G = group; HbA1C= hemoglobin A1C or glycosolated hemoglobin, MTM = medication therapy management; NR = not reported; NS = not sufficient; OR = odds ratio; RCT= randomized controlled trial.

Based on direct, but inconsistent and imprecise, evidence from the two RCTs, both with medium limitations (Table 10) we concluded that the strength of evidence is insufficient to evaluate the effectiveness of MTM interventions to improve mean HbA1c levels or increase the percent of patients achieving a goal HbA1c level.

Table 10. Hemoglobin A1c: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 154 (102)	Medium	Inconsistent	Direct	Imprecise	One trial: no change in mean HbA1c at 6 months. One trial: significantly greater percentage of patients with HbA1c >7.5 at 12 months.	Insufficient

Abbreviations: HbA1c= hemoglobin A1c; RCT= randomized controlled trial

LDL Cholesterol

One RCT and four cohort studies reported on outcomes related to LDL cholesterol (Table 11). The RCT (medium risk of bias), reported the percentage of patients with dyslipidemia who achieved an LDL cholesterol goal based on Adult Treatment Panel III (ATPIII) criteria for lipid management among patients at high risk for medication-related problems in a rural community.[68] The intervention and control groups did not differ significantly in percentage at goal at baseline (10.5 percent versus 15.8 percent, p=0.631) but differed significantly at 12 months (77.8 percent versus 5.9 percent, p=0.001; calculated OR, 56.00; 95% CI, 5.583 to 561.753).

Table 11. LDL cholesterol: Summary of results

Study Design/Risk of Bias	Study Arms	N of Subjects Analyzed	Outcome Reported by Study and Time Period	Results
Taylor et al., 2003[68] RCT/Medium	G1: Pharmaceutical care G2: Standard care	Followup (N inferred from percentage in results) G1: 18[a] G2: 17[a]	Percentage of patients at LDL-C goal based on ATPIII criteria at 12 months.	Calculated OR: 56.00, 95% CI: 5.583 to 561.753 p= 0.001
Isetts et al., 2008[64] Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percentage of patients meeting HEDIS measures related to cholesterol control after cardiovascular event at 12 months.	Calculated OR: 2.544, 95% CI: 1.52 to 4.256 p= 0.001
Pindolia et al., 2009[35] Cohort study/High	G1: Opted in to a telephone-based MTM program G2: Usual medical care (opted out of MTM program)	G1: NR[a] G2: NR[a] (outcome assessed only among patients with coronary artery disease)	Change in percentage of patients with LDL-C >100 mg/dl at 6months.	G1: - 5 G2: + 7 p: NR and could not be calculated.
Fox et al. 2009[31] Cohort study/High	G1: MTM program provided through a health plan G2: Usual medical care (eligible but opt-out from MTM program)	G1: 255 G2: 56 G1: 215 G2: 46	Percentage of patients with diabetes with LDL-C >100 mg/dl at 12 to 24 months. Mean (SD) LDL-C at 12 to 24 months.	Calculated OR: 2.228, 95% CI: 1.238 to 4.008; calculated p=0.008 Calculated mean difference: -7.4 95% CI: -17.297 to 2.497 p: 0.33 as reported by study authors, p=0.143 as calculated

Table 11. LDL cholesterol: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N of Subjects Analyzed	Outcome Reported by Study and Time Period	Results
Jeong et al., 2007[32] Cohort study/High	G1: Participants in Part D Medicare MTM program G2: Control subjects eligible for Part D MTM program but declined enrollment G3: Control subjects without Part D Medicare as their primary drug benefit	G1: NR G2: NR G3: NR	Mean LDL-C at 6 months	Baseline: G1: 94.2 G2: 95.6 G3: 91.9 Followup: G1: 87.4 G2: 92.5 G3: 90.2 p value unable to be reported[b]
			Percentage of patients at goal (defined as less than 100 mg/dl) at 6months	Baseline: G1:62 G2:62 G3:67 Followup: G1:73 G2:67 G2:69 p value unable to be reported[b]

[a] The investigators assessed this outcome only among patients with hyperlipidemia, diabetes, or coronary artery disease within each study arm but did not report the specific number analyzed.

[b] p values reported as <0.001 for G1 versus G2 and G1 versus G3, but unclear whether these refer to between-group differences at followup in LDL-C, between group differences in LDL-C change, or to between-group differences in change in percent at LDL-C goal. Calculated mean differences and OR were unable to be calculated due to absence of SD and number analyzed.

Abbreviations: ATPIII = Adult Treatment Panel III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol); HEDIS = Healthcare Effectiveness Data and Information Set; LDL-C = low density lipoprotein cholesterol; MTM = medication therapy management; NR = not reported; OR = odds ratio; RCT = randomized controlled trial.

To assess whether other studies might replicate the unexpectedly high odds of improvement from this trial, we also evaluated the findings from the four cohort studies. All studies (high risk of bias because of selection bias and baseline characteristics of groups not reported or not adjusted for) evaluated MTM programs within large, integrated US health care systems.[31,32,35,64] With the exception of one study,[35] they reported a direction of effect similar to that reported in the RCT but at a much smaller magnitude. The one study reporting an opposite direction of effect did not provide the data necessary to calculate whether the difference between groups was significant. A random-effect meta-analysis (Appendix G-1) of the three remaining cohort studies[31,32,64] included the Jeong et al. study[32] with the assumption that reported Ns for other outcomes applied to this outcome as well. Our analysis yielded an OR of 1.848 (95% CI, 1.146 to 2.980, p=0.012; I^2=76.55). One explanation for the high level of heterogeneity is the variation in sample sizes across the cohort studies. Removing the large cohort study[32] reduced the I^2 estimate to 0; the pooled estimate of effect continued to indicate benefit from MTM (OR, 2.401; 95% CI, 1.630 to 3.536; p<0.001).

Overall, we concluded that the strength of evidence is insufficient for the effectiveness of MTM interventions on lowering mean LDL-cholesterol levels or increasing the percentage of patients achieving a LDL-cholesterol goal, based on direct but imprecise evidence from single study body of evidence with medium limitations (Table 12).

Table 12. LDL Cholesterol: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (38)	Medium	Consistency Unknown - single study-	Direct	Imprecise	Significantly greater percentage of patients at LDL-C goal in MTM group at 12 months (77.8% vs. 5.9%, p<0.001, Calculated OR: 56.00, 95% CI: 5.583 to 561.753).	Insufficient

Abbreviations: LDL-C = low density lipoprotein cholesterol; MTM = medication therapy management; OR = odds ratio; RCT = randomized controlled trial

Blood Pressure

In all, we identified six, mostly small, studies that measured blood pressure outcomes using various followup periods (Table 13). This evidence base consisted of four RCTs and two cohort studies; the outcomes involved achieving blood pressure goals or becoming normotensive, and changes in systolic or diastolic blood pressure levels (SBP; DBP) or both. Of these studies, two RCTs were rated medium risk of bias (listed first in Table 13).The remaining four studies were all high risk of bias but do offer some additional or contextual information useful for interpreting the results from the two medium risk of bias RCTs.

Normotensive or BP Goal Attainment

One RCT (medium risk of bias), conducted among of a small number of patients at high risk of medication-related problems receiving pharmaceutical care through family medicine clinics in a rural community, reported a significant difference in the number of patients at blood pressure goal (SBP ≤ 140 mm Hg and DBP ≤ 90 mm Hg) at 12 months (91.7 percent versus 27.6 percent, calculated OR 28.875, 95% CI 5.486 to 151.993, p< 0.001).[68] Two other trials (both high risk of bias) also demonstrated benefit from MTM for a similar outcome but with a lower magnitude of effect.[71,72]

We conducted a random-effects meta-analysis that combined data from these three trials (Appendix G-2). It produced an odds ratio (OR) of 8.683 with wide confidence intervals and a high I^2 (which indicates that much of the observed heterogeneity is real; 95% CI, 1.665 to 45.276, p=0.01; Q, 6.151; I^2, 67.48 (p= 0.046). The two cohort studies (also both high risk of bias) reported findings that were consistent in direction of effect with the trials.[56,57,64]

Table 13. Blood pressure: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed[a]	Outcome Reported by Study and Time Period	Results
Chisholm et al. 2002[48] RCT/Medium	G1: Clinical pharmacy services within a kidney transplant clinic. G2: Usual medical care in the kidney transplant clinic.	G1: 13 G2: 10	Mean SBP (mm Hg) at quarterly points in time for 12 months.	Calculated mean difference: -22.1, 95% CI: -43.896 to -0.304, p=0.047
			Mean DBP (mm Hg) at quarterly points in time for 12 months.	Calculated mean difference: -18.5 95% CI: -29.039 to -7.961, p=0.001
Taylor et al., 2003[68] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 24[a] G2: 20[a]	Percentage of patients with SBP and DBP at goal at 12 months.	Calculated OR: 28.875, 95% CI: 5.486 to 151.993, p<0.001
Park et al. 1996 [72] RCT/High	G1: Community-pharmacy pharmaceutical care program G2: Usual care	G1:23 G2:26	Percentage of patients who were normotensive (SBP <140 and DBP <90)	Calculated OR: 2.455, 95% CI: 0.764 to 7.888, p=0.132
			Mean SBP (mm Hg) at 4 months.	Calculated mean difference: -13.0 95% CI: -23.739 to -2.261, p=0.018
			Mean (SD) DBP (mm Hg) at 4 months	Calculated mean difference: -4.90 95% CI: -10.3 to 0.50, p=0.075
Planas et al. 2009 [71] RCT/High	G1: Community pharmacy hypertension MTM program for patients with diabetes G2: Control group (BP recorded, informed of BP goals at 3 times during study)	G1: 25 G2: 15	OR (95% CI) for intervention group participant achieving BP goal relative to control group.	OR: 12.9 (1.5 to 113.8) p=0.021
			Mean change in SBP (mm Hg) at 9 months	Between-group difference: -20.0 (95% CI -32.7 to -7.4) p: 0.003
Carter et al., 997[56] Barnette et al. 1996[57] Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: Usual medical care	G1:25 G2:26	Percentage with blood pressure control	Calculated OR: 1.558, 95% CI: 0.496 to 4.898, p=0.448
			Mean SBP (mm Hg) at 6 months	Calculated mean difference: -9.00 95% CI: -19.451 to 1.451, p=0.0914
			Mean DBP (mm Hg) at 6 months.	Calculated mean difference: -1.00; 95% CI: -5.977 to 3.977, p=0.694
Isetts et al., 2008[64] Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percentage of patients meeting HEDIS measures related to hypertension management at 12 months.	Calculated OR: 1.728 95% CI: 1.026 to 2.911, p=0.04

Abbreviations: ATPIII=Adult Treatment Panel III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol); BP, blood pressure; CI = confidence interval; DBP=diastolic blood pressure; G = group; HEDIS= Healthcare Effectiveness Data and Information Set; mm Hg = millimeters of mercury (a unit of pressure); MTM, medication therapy management; NR= not reported; OR, odds ratio; RCT= randomized controlled trial; SBP= systolic blood pressure

[a] The study had more participants but this outcomes was measured in only the number of patients specified.

Overall, we concluded that the strength of evidence is insufficient for the effectiveness of MTM interventions to increase the percentage of patients achieving a blood pressure goal or becoming normotensive based on a single study body of evidence with medium limitations and an imprecise estimate (Table 14).

Table 14. Achieving blood pressure goal: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (44)	Medium	Consistency unknown-single study	Direct	Imprecise	OR: 28.875 (95% CI, 5.486 to 151.993) favoring MTM over usual care	Insufficient

Abbreviations: CI = confidence interval; MTM, medication therapy management; OR, odds ratio; RCT= randomized controlled trial,

Systolic and Diastolic Blood Pressure Levels

Four studies reported on SBP outcomes. One RCT (medium risk of bias),which was conducted among patients receiving medical care in a post-kidney transplant clinic, reported significantly a lower mean difference in SBP of -22.1 mm Hg at 12 months for the intervention group compared with the usual care group (95% CI, -43.896 to -0.304; p=0.047).[48] We conducted a random-effects meta-analysis of this and the two high-risk-of-bias RCTs measuring SBP outcomes.[71,72] The estimated mean difference was -16.774 between intervention and control groups (95% CI, -24.346 to -9.202; p<0.001; Q, 0.970; I^2, 0 (p=0.616)) (Appendix G-3). The single high risk-of-bias cohort study also reported improved SBP levels in the intervention arm, but wide confidence intervals spanned the null effect.

We found similar results for DBP levels from the three studies that reported this outcome. The medium risk-of-bias trial reported a mean difference of -18.50 mm Hg (95% CI, -29.039 to -7.961, p=0.001).[48] The other trial[72] and the cohort study[56,57] (both high risk of bias) both reported benefits from MTM interventions, but both had wide confidence intervals that spanned the null effect.

We concluded that the strength of evidence is insufficient for the effectiveness of MTM interventions to reduce SBP and DBP based on a single study body of evidence with medium limitations and an imprecise estimate (Table 15).

Table 15. Mean change in systolic and diastolic blood pressure: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 26 (23)	Medium	Consistency unknown-single study	Direct	Imprecise	Calculated mean difference SBP: −22.1 mm Hg, 95% CI: −43.896 to −0.304, p=0.047 Calculated mean difference DBP: −18.5 mm Hg 95% CI: -29.039 to −7.961, p=0.001	Insufficient

Abbreviations: CI = confidence interval; DBP=diastolic blood pressure; mm Hg = millimeters of mercury (a unit of pressure); RCT= randomized controlled trial, SBP=systolic blood pressure

Drug Therapy Problems Identified

In all, 11 studies addressed the question of the effectiveness of MTM for identifying drug therapy problems. Of these, eight provided information on drug therapy problems only from the intervention arm.[36,38,44,50,58-60,63,72] Thus, these studies cannot inform the question of the comparative effectiveness of MTM.

The three remaining comparative studies (one trial, two cohort studies) reported findings about the effectiveness of MTM when compared with usual care (Table 16). We rated all three high risk of bias for various reasons: uncontrolled selection bias from the comparison of patients who refused services to patients who accepted services;[37] bias associated with the specific measure and failure to control for patient-level clustering in a comparison of all drug related problems;[73] and failure to control for differences at baseline.[53]

These three studies also did not specify their expected direction of effect. We inferred that the studies expected to find fewer drug therapy problems after the completion of the intervention because the interventions were (apparently) specifically designed to identify and then resolve drug therapy problems. However, studies measuring outcomes during an MTM intervention might, instead, expect to find more drug therapy problems in the intervention arm because the intervention led to greater discovery of various problems. Consequently, we treated the evidence as inconsistent. Given high study limitations, inconsistency (single trial), indirectness, and lack of precision, evidence was insufficient to draw any conclusions about the effect on MTM interventions on drug therapy problems identified (Table 17).

Table 16. Drug therapy problems identified: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Krska et al., 2001[73] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Number of drug therapy problems identified for each study arm at 3 months	G1: 1,206 G2: 1,380
Harrison et al., 2012[53] Cohort/High	G1: Pharmaceutical care G2: Standard care	G1: 43 G2: 43	Drug therapy problems identified per visit, followup 2 weeks after intervention (SD)	G1 baseline: 0.51 ± 0.64 G1 followup: 1.05 ± 1.34 G2: 0.74 ± 0.81 Reported p=0.19 for pharmaceutical care vs. standard care, not controlling for differences between G1 at baseline and G2;CIs for change not calculated because study does not report baseline G2 values
Welch et al., 2009[37] Cohort/High	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 123	Percentage with at least 1 potential drug therapy problem during MTM process (timing unclear)	G1: 89.8% G2: 83.7% Risk difference=6.1%, calculated p=0.062

Abbreviations: CI: confidence interval; G = group; MTM= medication therapy management; RCT= randomized controlled trial; SD = standard deviation; SMD = standardized mean difference.

Table 17. Drug therapy problems identified: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 381 (332)	High	Consistency unknown-single study	Indirect	Imprecise	Cannot be determined because of unit of analysis issues	Insufficient
Cohort	2; 990 (668)	High	Inconsistent	Indirect	Imprecise	Direction and magnitude of effect varied by design and measure	Insufficient

Abbreviation: RCT = randomized controlled trial

Drug Therapy Problems Resolved

In all, we identified nine studies that attempted to report on whether MTM programs resolved drug therapy problems that were identified. Of these, six studies provided information only from the intervention arm.[35,38,40,43,59,60,64,72] Thus, as with drug therapy problems identified, they cannot inform the question of the comparative effectiveness of MTM interventions. Three other studies (two RCTs, one cohort study) provided information on the effectiveness of MTM for resolving drug therapy problems when compared with usual care (Table 18). The cohort study (medium risk of bias) found a significant effect of MTM on the difference in drug therapy problems identified between baseline and a 6-month followup; the investigators interpreted the change in number of drug therapy problems identified over time as drug therapy problems resolved between baseline and followup.[33,34] The two RCTs both had a high risk of bias for several reasons: failure to control for patient-level clustering[73] or country-level clustering[51,52] in a

comparison of all drug related problems; attrition;[51,52] or failure to control for differences at baseline.[51,52]

Table 18. Drug therapy problems resolved: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Krska et al., 2001[73] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Drug therapy problems wholly or partially resolved at 3 months	G1: 998 G2: 569
Bernsten et al., 2001[51,52] RCT/High	G1: Structured pharmaceutical care program in community pharmacy G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164	Number of changes in therapy at baseline	Baseline Calculated mean difference: 0.2, 95% CI: 0.101 to 0.299, p<0.001
		6 months G1: 1024 G2: 953	Number of changes in therapy at 6 months	6 months Calculated mean difference: 0.4, 95% CI: 0.257 to 0.543, p<0.001
		12 months G1: 863 G2: 764	Number of changes in therapy at 12 months	12 months Calculated mean difference: 0.1, 95% CI: -0.051 to 0.251, p=0.195
		18 months G1: 704 G2: 636	Number of changes in therapy at 18 months	18 months Calculated mean difference: 0, 95% CI: -0.156 to 0.156, p=1.0
Moczygemba et al., 2011[33] Moczygemba et al., 2008[34] Cohort/Medium	G1: Opt-in telephone MTM program G2: No-MTM control group	G1: 60 G2: 60	Medication and health-related problems identified at baseline and 6 months	Calculated mean difference:-1.00 (95% CI: -1.967 to -0.033), p=0.04

Abbreviations: CI = confidence interval; MTM = medication therapy management; NS = not significant; RCT = randomized controlled trial; SMD = standardized mean difference

Together (or taking the medium risk of bias cohort study alone), these studies offer insufficient evidence, based on study limitations, inconsistency, and imprecision, to judge the effectiveness of MTM on resolving drug therapy problems (Table 19).

Table 19. Drug therapy problems resolved: Strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 132 (120)	High	Consistency unknown-single study	Indirect	Imprecise	Calculated mean difference:-1.00 (95% CI: -1.967 to -0.033), p=0.04	Insufficient

Abbreviations: CI=confidence intervals;

Medication Adherence

Eleven studies reported on the effects of MTM interventions on adherence outcomes.[33,35,37,39,45,51,67-69,71,72] One prospective cohort study reported nonadherence determined during MTM (during a mock MTM chart review for the control group);[37] any adherence differences noted between the two groups were unlikely to be attributable to MTM effects. Moreover, the description of nonadherence used in that study (percentage of patients "nonadherent" per chart review) cannot be interpreted because of a lack of a clear definition. For these reasons, we excluded this study from further analysis.

The 10 remaining studies in the analysis are described in Table 20. Of these 10 studies, eight were RCTs[37,39,45,51,67-69,71,72]; one was a prospective cohort study;[35] and one was a retrospective cohort study[33]. Most studies assessed one of three different adherence outcomes: (1) the proportion of patients who, based on a threshold of between 75 percent and 80 percent of prescribed doses taken, were deemed to be adherent[35,68]; (2) the percentage of prescribed doses taken[33,71,72]; and (3) the scores from an adherence scale score (such as the Morisky Scale).[39,51,69] Two studies assessed miscellaneous aspects of medication-taking behavior[45,67] these included "remembering to take medication," a medication-taking behavior subscore, and or determining the number of medications (not pills) for which the participant's reported manner of taking (number of pills and frequency per day) exactly matched the prescribed directions. When studies did not report statistical significance, we calculated the standard difference in means, standard errors, and 95% confidence intervals based on raw data.

Table 20. Medication Adherence: Summary of results grouped by type of adherence outcome

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 1: Proportion of patients adherent based on a threshold of percentage of pills taken	Taylor et al., 2003[68] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1:33 G2:36	Percentage of patients adherent defined as self-reported taking 80% or more of medications 12 months after baseline	Calculated OR: 9.277 95% CI: 0.480 to 179.263; p= 0.140
	Pindolia et al., 2009[35] Cohort study/High	G1: Telephone-based MTM program G2: Patients eligible for MTM program who declined enrollment	G1: 292 G2: 1,081 (study year 1)	Percentage of CHF patients who were adherent to at least 75% of ACE/ARB medications based on 2006 claims data: Measured during 6 months post-MTM enrollment	Calculated OR: 1.088 95% CI: 0.834 to 1.417 P = 0.533
				Percentage of CHF patients who were adherent to at least 75% of beta blocker medications based on 2006 claims data: Measured during 6 months post-MTM enrollment c	Calculated OR: 1.174 95% CI 0.89 to 1.54 P = 0.252
Outcome Type 2: Absolute measure of adherence as percentage of prescribed doses taken	Moczygemba, 2011[33] Moczygemba, 2008[34] Retrospective cohort/ Medium	G1: Opt-in telephone Scott & White Health Plan MTM program G2: No-MTM control group	G1: 60 G2: 60	Percentage prescribed doses taken: Overall average MPR across all medications measured at 6 months before MTM participation (i.e., baseline) and 6 months after MTM (i.e., followup) using pharmacy data	Calculated mean difference: −0.020 95% CI: −0.78 to 0.038 P = 0.502
	Planas et al 2009[71] RCT/high	G1: Collaborative home-based medication review G2: No medication review received	G1: 25 G2: 15	Percent mean adherence (percentage of prescribed doses taken) to antihypertensive medication Measured twice (9 months before and 9 months after baseline visit) and continuously using medication acquisition method, in which days' supply of medication is compared with dates medication was filled using pharmacy refill data.	Calculated mean difference from baseline to 9 months: 0.077 95% CI: −0.127 to 0.281 P = 0.46

Table 20. Medication Adherence: Summary of results by type of adherence outcome (continued)

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 2: Absolute measure of adherence as percentage of prescribed doses taken (continued)	Park, 1996[72] RCT/high	G1: Comprehensive pharmaceutical care G2: Usual care	Visit 1 G1: 7 G2: 5 Visit 2 G1: 21 G2: 23 Visit 3 G1: 23 G2: 20 Visit 4 G1: 21 G2: 22	Mean percent compliance (percentage of prescribed pills taken) from pharmacist report of pill counts 4 month timeframe	Calculated mean difference for change from baseline to Visit 4: -0.023 95% CI: −0.175 to 0.129 p = 0.767
Outcome Type 3: Self-reported Adherence using Morisky Scale	Bernsten, 2001[51]; Sturgess, 2003[52] RCT/ High (pooled data)	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Pooled sample (excluding The Netherlands because no baseline adherence data collected) Baseline G1: 867 G2: 748 18 months G1: 792 G2: 758	Medication adherence: self-reported as assessed by Morisky Scale (Note: Percentage of participants who were adherent defined as patients responded that they “never” experienced any aspects of noncompliance on the 4-item scale with a 4-point response option per item)	Pooled sample (percentage adherent) OR at baseline: 0.82, calculated 95% CI: 0.666 to 1.0, p = 0.050 Calculated OR at 18 months: 1.084, 95% CI: 0.883 to 1.332, p = 0.440
	Volume et al. 2001[69] and Kassam[70] RCT/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	T1: N = 363 G1: 159 G2: 204 T2: N = 317 T3: N = 292 Estimated by group based on overall retention G1: 127 G2: 163 Note: T=time	Self-reported adherence using the Morisky Scale made up of four dichotomous items where summary score is 0-4 with lower scores being better adherence 12 to 13 months after intervention	Calculated mean difference 0.090 95% CI: −0.076 to 0.256 P = 0.289

Table 20. Medication Adherence: Summary of results by type of adherence outcome (continued)

Outcome Type	Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Outcome Type 3: Self-reported Adherence using Morisky Scale (continued)	Jameson et al., 1995[39] RCT/High (Medium for study overall but high for adherence because of poor outcome measure))	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office.	G1: 27 G2: 29	Self-reported composite "understanding and compliance" 0-12 score at baseline and at 6 months (no further information on measure used) Change in self-reported composite score over 6 months with negative score representing improvement	Baseline Means Scale Score (SD not reported) G1: 2.3 G2: 2.3 95% CI: NR p: NS 6 months G1: 0.6 G2: 2.1 95% CI: NR p: NS G1: −1.6 G2: −0.2 95% CI: NR p: NS
Miscellaneous Adherence Outcomes	Hanlon et al., 1996[67] RCT/Medium (Low for study overall but medium for adherence because of lack of information about and precision of adherence measure)	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 86 G2: 83	Self-reported medication compliance with 12- month time frame, assessed by determining whether the way patients said they took their medicine (in terms of number of pills and daily frequency) matched how the medication was prescribed. Compliance was defined as the proportion of medications for which the patients' response agreed with the directions.	Calculated OR: 1.076, 95% CI: 0.527 to 2.197, p: 0.84
	Sidel, 1990[45] RCT/Medium	G1: Received at least 2 pharmacist visits involving medication review, patient-specific education and counseling; follow- up patient telephone calls and contacting of physicians by pharmacists as needed G2: Contacted only to complete the survey.	G1: 92 G2: 104	Change from baseline to 6-month followup in Medication-taking Behavior Subscore (negative scores indicate improvement, which means decreased risk)	G1: −3.47 G2: −4.38 95% CI: NR P < 0.001 for within-group differences p = 0.52 for between-group differences
				Change at 6 months in normative score for Remembering to take Medicine	G1: 0.09 G2: −0.19 95% CI: NR P = 0.52

Abbreviations: ACE = angiotension converting enzyme inhibitor; ARB = angiotension receptor blocker; CHF = congestive heart failure; HbA1C = hemoglobin A1C or glycosolated hemoglobin; MPR = medication possession ratio; MTM = medication therapy management; NR = not reported; RCT= randomized controlled trial.

Of the two studies assessing the proportion of patients who achieved threshold adherence levels, one was a small RCT (medium risk of bias);[68] the other was a relatively large cohort study (high risk of bias).[35] Neither study found statistically significant effects of MTM on adherence. Of the three studies that assessed MTM effects on percentage of prescribed doses taken, two were small RCTs (both high risk of bias);[71,72] the other was a small retrospective cohort study (medium risk of bias).[33] None of these studies found a statistically significant effect of MTM on adherence. All three studies that assessed adherence using self-reported adherence scales were small RCTs (one medium risk of bias[69]; two high risk of bias[39,51]). None found a statistically significant effect of MTM on adherence, although one high risk of bias study,[6] did not account for the marked baseline differences, hence may have missed a statistically signficant difference in change in adherence. This same study (high risk of bias) reported that a statistically significant increase in the percentage of individuals who changed from nonadherent to adherent over 18 months (15.25 percent in the intervention group and 12.2 percent in the control group; p=0.028);[51] however, this assessment did not take into account the percentage in each group that changed from adherent to nonadherent. Finally, the two RCTs (both medium risk of bias) that assessed miscellaneous aspects of adherence found no statistically significant differences between groups in adherence outcomes assessed.[45,67] Hence, none of the 11 studies that assessed effects of MTM on adherence found a statistically significant effect.

Overall, we concluded that evidence is insufficient to draw conclusions about the effectiveness of MTM for improving the proportion of patients who, based on a threshold of 80 percent of prescribed doses taken, were adherent at 6 to 12 months based on direct, imprecise evidence from one small RCT (Table 21). The findings are consistent with the direct but imprecise evidence from one large prospective cohort study with high study limitations. Strength of evidence is also insufficient for improving the absolute percentage of prescribed doses taken at 6 months (mean adherence), based on direct, imprecise evidence from one small retrospective cohort study (Table 22). This conclusion is consistent with findings from two small high risk of bias RCTs that provided direct, imprecise evidence of these effects at 4 to 9 months. Of note, however, is that these two trials had a high level of study limitations and reported opposite directions of effect on absolute percentage of prescribed doses taken, both with nonsignificant differences between groups.

Table 21. Adherence Outcome Type 1—Proportion of Patients Adherent based on a Threshold of Percentage of Pills Taken: Strength of Evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 81 (69)	Medium	Unknown (single study)	Direct	Imprecise	100% of intervention patients and 88.9% of controls were adherent; P = 0.115	Insufficient

Abbreviations: RCT= randomized controlled trial.

Table 22. Adherence Outcome Type 2—Absolute Measure of Adherence as Percentage of Prescribed Doses Taken: Strength of Evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Obser-vational	1;132 (120)	High	Unknown (single study)	Direct	Imprecise	SMD: −0.1226 95% CI: −0.4808 to 0.2355 p = 0.50	Insufficient

Abbreviations: CI = confidence interval; SMD = standardized mean difference

Evidence is also insufficient about improving medication adherence as measured by self-reported scales at 6 to 18 months, based on inconsistent, direct, imprecise evidence from three RCTs (one small, one medium, one large) (Table 23). Finally (Table 24), regarding miscellaneous medications taking behaviors, such as remembering to take medication, a medication-taking behavior subscore, and the proportion of medications matched with instructions, we concluded that evidence was insufficient for the effect of MTM on these outcomes, based on evidence from two RCTs that was direct but imprecise and inconsistent. Although the significant degree of heterogeneity across adherence measures precluded our ability to assess strength of evidence across all adherence studies, we note that considering the body of evidence for the effect of MTM on adherence, taken together, results from all studies were nonsignificant with small magnitudes of effect. Across studies, the direction of effect was inconsistent. Hence, considering the adherence studies as a whole, there appears to be insufficient evidence regarding an effect of MTM on adherence.

Table 23. Adherence outcome type 3--self-reported scales: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2,881 (1,898)	High	Inconsistent	Direct	Imprecise	Three studies; one larger with small and not statistically significant improvement in MTM group and high risk of bias; two with opposite direction of effect, both with non-significant differences between groups	Insufficient

Abbreviations: RCT= randomized controlled trial.

Table 24. Adherence outcome miscellaneous: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 492 (404)	Medium	Inconsistent	Direct	Imprecise	Two studies with opposite direction of effect, both with non-significant differences between groups.	Insufficient

Abbreviations: RCT= randomized controlled trial.

Medication Appropriateness

Five studies (four RCTs,[49,50,67,68] one cohort study[56]) reported on the effects of MTM interventions on medication appropriateness (Table 25 and Table 26). Of these studies, three assessed medication appropriateness across a broad spectrum of regimens;[56,67,68] the other two trials assessed appropriateness for specific medications.[49,50]

For the three broader studies, two trials used the Medication Appropriateness Index (MAI).[67,68]One of these reported results for the full scale and for each item of the index (each item asks about a different aspect of medication appropriateness) individually;[67] the other trial reported results only for each of the individual items.[68] The cohort study of broad regimens used a panel of three pharmacists to rate the appropriateness of the various antihypertensive regimens on a visual analogue scale.[56]

As shown in Table 25, one RCT (low risk of bias)[67] found a statistically significant improvement in the MAI Scale at 3 and 12 months' followup. The small cohort study (high risk of bias) reported no statistically significant improvement in the three appropriateness scores assessed for blood pressure regimens (appropriateness of regimens, of dosing intervals, and of dosages) although it was very underpowered.[56]

Table 25. Medication appropriateness scales: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1196[67] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic	G1: 105 G2: 103	Covariate-adjusted Medication Appropriateness Index assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 17.7 (0.6) G2: 17.6 (0.6) 3 months G1: 13.4 (0.6) G2: 16.5 (0.6) 95%CI: NR p<0.0006 for between- group differences, controlling for baseline and other covariates 12 months G1: 12.8 (0.7) G2: 16.7 (0.7) 95%CI: NR p<0.0006 for between- group differences, controlling for baseline and other covariates

Table 25. Medication appropriateness scales: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1196[67] RCT/Low (continued)		G1: 105 G2: 103	Change in covariate-adjusted Medication Appropriateness Index assessed at baseline, 3, 12 months by blinded research pharmacist	3 months change in outcome G1: -4.3 G2: -1.1 95% CI: NR 24% improvement in intervention group and 6% improvement in control group p= 0.0006 12 months change in outcome G1: -4.9 G2: -0.9 95% CI: NR 28% improvement in intervention group and 5% improvement in control group p=0.0002
Carter et al., 1997[56] Barnette et al. 1996[57] Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: Usual medical care	G1: 25 G2: 26	Appropriateness of BP regimen A blinded review panel of three pharmacists evaluated cases in random order on a visual analog scale, using medical records. The investigators averaged and converted scores to a numerical value by measuring the distance from the best option. Score arranged from 0 to 16.2. Higher scores are better. Appropriateness of daily dosage	BP regimen Baseline G1: 8.7 (4.7) G2: 10.3 (4.8) Follow-up G1: 10.9 (4.5) G2: 10.1 (5.2) p for change scores NR
			Appropriateness of dosing interval	Daily dosage Baseline G1: 11.6 (4.5) G2: 12.6 (4.5) Followup G1: 13.4 (3.7) G2: 13.2 (4.1) p for change scores NR Dosing interval Baseline G1: 13.8 (4.3) G2: 13.4 (4.6) Follow-up G1: 15.1 (2.3) G2: 13.8 (4.1) p for change scores NR

Abbreviations: BP=blood pressure; NR=not reported; RCT=randomized controlled trial.

Of note, one[67] (low risk of bias) of the two trials reporting the effect of MTM on general medication appropriateness scales, also provided descriptive data, by intervention group, regarding the proportion of inappropriate prescriptions for each of 10 items on the MAI (which address different aspects of appropriateness). These findings are reported in Appendix E. While one is unable to draw conclusions regarding the findings because they report percentages with prescriptions (rather than "per patient") as the unit of analysis, they do suggest that some items are likely driving the improvements in MAI in the MTM group more than others. Specifically, six aspects of medication prescription appropriateness: drug indication; dosage; practicality of directions; drug-drug interactions; duplication; duration of therapy seem to show greater improvement in inappropriate prescriptions than do those for four other aspects: effective medication; correctness of directions; drug-disease interactions; expense of medication. Similarly, another study[68] which did not report on the full MAI scale, also reported data regarding the effect of MTM on individual MAI items (Appendix E). The ability to interpret these descriptive findings is not only, like the other study,[67] hampered by the use of prescriptions rather than patients as the unit of analysis, but also is limited by the marked baseline differences that existed between intervention groups.

Two RCTs (both medium risk of bias) assess the appropriateness of regimens for specific medications for specific conditions (Table 26). One assessed, among patients at risk for glucocorticoid-induced osteoporosis, the percentages of patients receiving each of three indicated regimens;[50] the investigators found, at 9-month followup, a statistically significant improvement in the percentage appropriately prescribed calcium supplements among MTM recipients compared with controls but not for bisphosphonate or estrogen drug therapy. The other trial assessed the use of angiotensin-conversion enzyme (ACE) inhibitors among heart failure patients[49]. The pharmaceutical care program had a significant effect on the mean percentage of target dose achieved and on the proportion receiving an appropriate alternative medicine among the subsample; such services did not produce a significant effect on the percentage of patients who received an ACE inhibitor.

Table 26. Medication appropriateness for individual medications: Summary of results

Study Design/Risk of Bias	Study Arms	N analyzed	Outcome and Time Period	Results
McDonough, 2005[50] cluster-randomized RCT/Medium	G1: pharmaceutical care provided by pharmacist in a community pharmacy G2: usual care Patients at risk for glucocorticoid-induced osteoporosis)	Baseline G1: 70 G2: 26 Follow Up G1:61 G2:19	9-month followup Percentage of patients taking calcium supplements	Baseline G1: 38.6 G2: 38.5 p for between-- group differences at baseline presumed not significant[a] Followup G1:55.7 (p<0.05 for within-group difference from baseline) G2: 31.6 p<0.05 for change in outcome between groups from baseline to followup
			Percentage of patients on bisphosphonate drug therapy	Baseline G1: 17.1 G2: 0 p<0.05 for between-group difference at baseline Followup G1: 26.2 (p<0.05 for within-group difference from baseline) G2: 10.5 p: NS for between-group difference at followup; change in outcome between baseline and follow-up was NS between groups
			Percentage of patients on estrogen drug therapy	Baseline G1: 12.9 G2: 0 P NS for between-group difference at baseline Followup G1: 16.4 (p<0.05 for within-group difference baseline) G2: 0 p: NS for between-group difference at followup; change in outcome between baseline and follow-up was NS between groups.

Table 26. Medication appropriateness for individual medications: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N analyzed	Outcome and Time Period	Results
Gattis, 1999[49]Gattis[49] RCT/Medium	G1: Clinical pharmacist intervention G2: Usual medical care Patients with heart failure.	G1: 90 G2: 91	6 month followup Fraction of target ACEI dose at followup median (25^{th} and 75^{th} percentile values)	Follow-up: G1: 1 (25^{th} percentile: 0.5, 75^{th} percentile: 1) G2: 0.5 (25^{th} percentile 0.188, 75^{th} percentile: 1) 95% CI: NR p<0.001
		G1: 12 G2: 19	Of those not on an ACEI at followup, percentage receiving alternative drug therapy	G1: 75 G2: 26 95% CI: NR
		G1: 90 G2: 91	Percentage receiving an ACEI at follow-up	G1: 87 G2: 79 95% CI: p= 0.18

[a]Baseline differences assumed to be nonsignificant because p-value was reported for other outcomes if significantly different between groups.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; NR, not reported; NS. nonsignificant; RCT, randomized controlled trial

Overall, we concluded that the strength of evidence is low for the effect of MTM on medication appropriateness (measured by continuous scores on index) at 3 and 12 months based on indirect, precise evidence from one small RCT (Table 27). The findings are consistent with the direction of effect (indirect, imprecise evidence) from a small prospective cohort study with high study limitations.

Table 27. Medication appropriateness scales: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 208 (208)	Low	Unknown (single study)	Direct	Precise	Improvement in MTM group from score of 17.7 to 13.4 and to 12.8 in 3, 12 months respectively p<0.0006 for between-group differences controlling for baseline and other covariates	Low

Abbreviations: RCT= randomized controlled trial.

Strength of evidence is insufficient for the efficacy of MTM for improving the appropriateness of medication prescriptions for specific medications (Table 28) based on findings from two small RCTs that provided indirect, imprecise evidence of these effects at 6 or

9 months. This evidence based had medium study limitations, but the trials reported opposite directions of effect based on medication type.

Table 28. Medication appropriateness for individual medications: strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2;277 (261)	Medium	Inconsistent	Direct	Imprecise	Significant improvement in appropriateness in the MTM group for some medications but not others.	Insufficient

Abbreviations: RCT= randomized controlled trial.

Intermediate Outcome: Medication Dosing

Two RCTs (medium risk of bias) assessed the effect of MTM on medication dosing (Table 29).[39,48] A third study assessed dose adjustment we excluded it from this analysis because dosing assessed only at baseline.[37]

One trial of renal transplant patients compared the daily doses of three medications (cyclosporine, tacrolimus, and prednisone) for MTM and control groups; it found no statistically significant differences for any of the three medications.[48] The other trial assessed changes in the number of doses that primary care patients received per day at the end of 6 months; patients in the MTM arm received 1.6 fewer doses than at baseline, whereas control patients received 2.2 more doses per day than at baseline (p=0.007).

Table 29. Medication dosing: Summary of findings

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Chisholm, 2002[48] RCT/Medium	G1: Clinical MTM pharmacy services G2: routine clinic services interaction with renal transplant clinic team, but no clinical pharmacist	G1: 13 G2: 10	Timeframe unspecified Mean daily cyclosporine dose (mg/kg)	G1: 6.8 (1.3) G2: 7.1 (1.2) 95% CI: NR P=0.703
			Mean daily tacrolimus dose (mg/kg)	G1: 0.23 (0.05) G2: 0.22 (0.04) 95% CI: NR p=0.823
			Mean daily prednisone dose (mg)	G1: 12.3 (2.8) G2: 13.2 (3.2) 95% CI: NR p=0.705
Jameson et al., 1995[39] RCT/Medium	G1: Consultation with a clinical pharmacist in a primary care office. G2: Standard medical care in a primary care office.	G1: 27 G2: 29	Change in number of doses per day at 6 months' followup.	G1: -1.6 G2: +2.2 95% CI: NR ==0.007

Overall, evidence was insufficient for effect of MTM on medication dosing (Table 30) based on findings from two small RCTs with medium study limitations, but inconsistent, indirect, and imprecise results.

Table 30. Medication dosing: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 79 (90)	Medium	Inconsistent	Indirect	Imprecise	Two RCTs with opposite findings: one showing significant increase in daily doses and the other showing no difference in daily doses of medications	Insufficient

Key Points: Patient-Centered Outcomes

- Evidence was insufficient to draw conclusions about the effect of MTM on adverse drug events (two trials: low study limitations, inconsistent, imprecise); cognitive, affective, and physical function (one trial, medium study limitations, imprecise); mortality (two trials with medium study limitations, one observational study with high study limitations, inconsistent, imprecise); and gastrointestinal bleeding events (one observational study, high study limitations, imprecise).
- With one exception, MTM interventions had no benefit on SF-36 measures (low strength of evidence of no benefit); evidence was insufficient for the SF-36 domain of vitality because of imprecision.
- Evidence was insufficient to determine whether MTM interventions improved patient-reported measures for patients with diabetes (one imprecise medium risk of bias trial).
- MTM interventions did not improve measures of patient satisfaction (low strength of evidence of no benefit).

Adverse Drug Events

Four RCTs[39,55,67,68] and one nonrandomized trial[66] reported on prevalence of adverse drug events (ADEs) following MTM or pharmaceutical care interventions (Table 31). The methods for measuring adverse events differed substantially among included studies. Further, although we assumed that the beneficial direction of effect would be for MTM to decrease ADEs, the nonrandomized trial suggested that MTM services may heighten awareness of potential adverse outcomes by patients and, thus, increase reporting of ADEs by those receiving the intervention.[66] For this outcome, we rated the risk of bias for some studies[39,66,68] as higher than the overall risk of bias because of measurement and detection bias with respect to the measures and methods used to ascertain this outcome.

Table 31. Adverse events: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcomes Reported by Study and Time Period	Results
Hanlon et al., 1996[67] RCT/Low	G1: Clinical pharmacist care within a general medicine clinic. G2: Usual care	G1:86 G2:83	Percentage with an ADE at 12 months	Calculated OR: 0.649, 95% CI: 0.366 to 1.152, p=0.014
Touchette et al., 2012[55] RCT/Low	G1: Basic MTM services (with medication information from patient interview) G2: Enhanced MTM services (pharmacist provided with 2-page clinical summary from patient medical record). G3: Usual pharmacy care	G1: 211 G2: 218 G3: 208	Percentage of patients with an ADE between 0 and 3 months and OR	G1 vs. G3: OR: 1.629 (p = 0.078) G2 vs. G3: OR: 0.726 (p = 0.278)
			Percentage of patients with an ADE between 3 and 6 months and OR	G1 vs. G3: OR: 1.107 (p = 0.717) G2 vs. G3: OR: 0.889 (p = 0.672)
			Mean number (SD) of ADEs per patient between 0 and 3 months	G1 vs. G3: Calculated SMD: 0.165, 95% CI: -0.027 to 0.357 p=0.110 G2 vs. G3: Calculated SMD: -0.010, 95% CI: -0.200 to 0.180 p=0.916
Touchette et al., 2012[55] RCT/Low (continued)			Mean number (SD) of ADEs per patient between 3 and 6 months	G1 vs. G3: Calculated SMD: 0.239, 95% CI: 0.047 to 0.431 p=0.041 G2 vs. G3: Calculated SMD: -0.072, 95% CI: -0.262 to 0.118 p=0.479
Fischer et al., 2000[66] NRCT/High	G1: Comprehensive drug therapy management program G2: Standard community pharmacy practice	G1: 201 G2: 368	OR for likelihood of reporting side effects or problems from prescription medication (95% CI)	1.81 (1.16 to 2.83)
Taylor et al., 2003[68] RCT/High	G1: Pharmaceutical care G2: Standard care	G1: 33 G2: 36	Percentage of patients with at least one medication misadventure at 12 months	G1: 2.8[a] (N=4) G2: 3.0 [a] (N=3) Calculated OR based on reported percent: 0.93, 95% CI, 0.056 to 15.603, p=0.0961 Calculated OR based on reported N: 1.515 (95% CI, 0.312 to 7.344), p= 0.606
Jameson et al., 1995[39] RCT/High	G1: Consultation with a clinical pharmacist in a primary care office. G2: Standard medical care in a primary care office.	G1: 27 G2: 29	Change in mean medication side effect score at 6months.	G1: -3.7 G2: -1.9 p: NS and unable to calculate.

[a] The percent reported by authors cannot be generated based on the reported N and the reported number of events.

Abbreviations: ADE=adverse drug event; CI = confidence interval; DRP=drug-related problems; NRCT = nonrandomized controlled trial; NS=not significant; OR= odds ratio; RCT= randomized controlled trial; SMD = standardized mean difference; vs. = versus

One RCT (low risk of bias) compared clinical pharmacy care within a VA general medicine clinic to usual care;[67] it found no significant difference in the number of subjects reporting an ADE at 12 months. Another RCT (low risk of bias) compared usual care with the provision of basic MTM services designed to mimic conditions similar to a community pharmacy with another study arm that included an enhanced intervention that provided clinical information about the patient to the pharmacist.[55] It reported on outcomes for the period between 0 and 3 months and for the period between 3 and 6 months. The enhanced MTM intervention was superior to the basic MTM intervention at 3 months in the percentage of subjects reporting an ADE; however, the enhanced intervention and usual care at 3 months and three study arms at 6 months did not differ significantly. In addition, the mean number of ADEs per patient was not statistically different between 0 and 3 months across study arms, but both the enhanced MTM and usual care study arms had significantly fewer ADEs per patient than the basic MTM study arm between 3 and 6 months. This RCT found no statistical difference in mean ADEs per patient between the enhanced MTM study arm and usual care between 3 and 6 months.

The other two RCTs were considered high risk of bias for the ADE outcome. One RCT provided pharmaceutical care to patients at high risk for medication-related problems seen in family medicine practices in a rural community;[68] the intervention and control arms did not differ significantly. We rated this trial as high risk of bias because it used a nonstandard measure (medication misadventure) and because the control event rates differed by a factor of 10 relative to those in RCTs with low risk of bias. The other RCT that we rated high risk of bias compared MTM intervention with usual medical care and reported no significant difference between change in medication side effect scores using a scale that the study authors had developed.[39] The nonrandomized trial (high risk of bias for this outcome)compared participants who agreed to participate in a pharmaceutical care program at one of six participating community pharmacies with a group of control patients who received medications at pharmacies that did not provide pharmaceutical care services;[66] study participants were significantly more likely (OR, 1.81; 95% CI, 1.16 to 2.83) to report experiencing symptoms or problems related to prescription medication than control participants, an effect the authors attributed to increased awareness of medication side effects in the intervention group. Without a clear understanding of the hypothesized mechanism of action in each study for influencing ADEs, we cannot interpret the conflicting result presented by the nonrandomized trial relative to the findings from the RCTs.

Overall, we concluded that evidence is insufficient to draw conclusions about the efficacy of MTM for reducing adverse drug events based on direct, but inconsistent and imprecise, evidence from two low-risk-of-bias RCTs (Table 32).

Table 32. Adverse drug events: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 845 (806)	Low	Inconsistent	Direct	Imprecise	Direction and magnitude of effect differs between the two trials.	Insufficient

Abbreviations: RCT= randomized controlled trial.

Cognitive, Affective, and Physical Function

One RCT (medium risk of bias)reported on changes in cognitive, affective, and physical function at 6 weeks;[74] the intervention provided in a general medicine outpatient clinic was designed to simplify medication regimens among cognitively intact patients ages 65 or older at high risk for medication-related adverse events. The investigators measured cognitive function using three different tests (two subtests from the Wechsler Adult Intelligence Scale [digit-symbol and digit span] and modified Randt Memory Test). They measured affective function using the Center for Epidemiological Studies Depression Scale and the Self-Rating Anxiety Scale and physical functioning using the Timed Manual Performance Test, Physical Performance Test, and Functional Reach Assessment. Patients in the intervention arm experienced no significant changes in any of these measures when compared with patients in the control arm. This finding may be explained partly by the fact that although recommendations for medication discontinuation were made in the intervention arm (on average 4.5 drug discontinuation recommendations per participant), the authors stated that intervention participants stopped taking only 1.5 drugs per participant on from their regimen. Evidence was insufficient to draw conclusions about the impact of MTM on these functional outcomes (Table 33).

Table 33. Cognitive, affective, and physical function: Strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 140 (133)	Medium	Consistency unknown-single study	Direct	Imprecise	One study with no significant differences between arms.	Insufficient

Abbreviations: RCT= randomized controlled trial.

Mortality

Two RCTs[49,54] and one cohort study[37] reported all-cause mortality outcomes following MTM interventions at 6 months (Table 34). One RCT (medium risk of bias) of patients after discharge from the hospital for heart failure compared a study arm that added a pharmacist intervention to visiting home nurse services with just the visiting home nurse services.[54] The other RCT (medium risk of bias) in a university general cardiology clinic compared a study arm that included a clinical pharmacist intervention for heart failure patients with usual medical care.[49] These two RCTs reported effect estimates in opposite directions, but neither was statistically significant.

Table 34. All-cause mortality: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome Reported by Study and Time Period	Results
Triller et al., 2007[54] RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: 77 G2: 77	RR for all-cause mortality within 180 days	RR: 1.21 Calculated 95% CI: 0.645 to 2.29 p=0.67
Gattis et al., 1992[49] RCT/Medium	G1: Clinical pharmacist intervention in addition to usual medical care G2: Usual medical care	G1: 90 G2: 91	OR for all-cause mortality within 6 months	OR: 0.59 95% CI: 0.12 to 2.49 p=0.48
Welch et al., 2009[37] Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR for all-cause mortality, within 6 months (adjusted for age, sex, chronic disease score, specific baseline utilization)	Adjusted OR: 0.5 95% CI, 0.3 to 0.9 p=0.044

Abbreviations: CI = confidence interval; G = group; MTM = medication therapy management; OR = odds ratio; RCT= randomized controlled trial; RR = relative risk

The cohort study (Table 34) (medium risk of bias) measured mortality outcomes for beneficiaries who met MTM program eligibility and opted in to a telephone-based MTM program provided through an integrated health care system and for eligible beneficiaries who opted out of the MTM program.[37] This study reported a statistically significant reduction in all-cause mortality at 6 months in the intervention arm, when adjusted for age, sex, and baseline disease and health care utilization levels.

Both RCTs reporting mortality outcomes also reported a composite measure that combined all-cause mortality with another outcome as the primary study endpoint. One RCT reported a composite outcome of all-cause mortality and all-cause hospitalization at 6 months; intervention an control arms did not differ (62 percent versus 61 percent; RR, 0.98; 95% CI, NR; p=1.0).[54] The other RCT reported a composite outcome of all-cause mortality and nonfatal heart failure events at 6 months; patients in the intervention arm experienced a significant benefit from the program (OR, 0.22l; 95% CI, 0.07 to 0.65; p=0.005).[49]

Overall, we concluded that evidence is insufficient for the efficacy of MTM for reducing all-cause mortality at 6 months based on direct, but inconsistent and imprecise, evidence from two RCTs and one observational study, all with medium study limitations (Table 35).

Table 35. All-cause mortality: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 335 (335)	Medium	Inconsistent	Direct	Imprecise	Two studies with opposite direction of effect, both with nonsignificant differences between groups.	Insufficient
Observational	1; 904 (795)	High	Consistency unknown-single study	Direct	Imprecise	OR 0.5 95% CI, 0.3 to 0.9	Insufficient

Abbreviations: CI = confidence interval; NA = not applicable; OR = odds ratio; RCT= randomized controlled trial.

Gastrointestinal Bleeding Events

One cohort study (high risk of bias because of selection bias) reported the relative risk reduction in gastrointestinal bleeding events among patients with a diagnosis of arthritis enrolled in a telephone-based MTM program within a large US integrated health care system.[35] The investigators compared the number of gastrointestinal bleeds after 6 months between patients who did and did not enroll in the MTM program. Enrolled patients had a 60 percent relative reduction in gastrointestinal bleeds; the nonenrolled patients had no change in gastrointestinal bleeds (p=0.001 for between-group difference in change in gastrointestinal bleeds).

Overall, we concluded that evidence is insufficient for the efficacy of MTM for reducing gastrointestinal bleeding events based on direct but imprecise evidence from one cohort study with high study limitations (Table 36).

Table 36. Gastrointestinal bleeding events: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Observational	1; 1,388 (1.373)	High	Consistency unknown-single study	Direct	Imprecise	RRR 60% (p=0.001)	Insufficient

Abbreviations: RCT= randomized controlled trial; RRR = relative risk reduction

Self-Reported Health Status: SF-36 Measures

SF-36 Measures: Overview

Eight RCTs[43,44,51,67-69,72,73] and one cohort study[56] reported health status outcomes using the Medical Outcomes Study Short-Form questionnaire (SF-36) (Table 37). The eight SF-36 domains, which combine into two components, are as follows—*physical health*: physical functioning, physical role functioning, bodily pain, and general health perceptions; and *mental health*: vitality, emotional role functioning, social role functioning, and mental health. Seven trials[43,44,51,67,68,72,73] and the cohort study[56] reported scores for all eight domains. One trial reported only its two component scores (i.e., physical health; mental health).[69] Finally, one trial reported both component and domain scores.[44] The trials differed by overall risk of bias (one, low; four, medium, and three, high); the cohort study was high risk of bias.

Table 37. Scores on SF-36 measures: Summary of effects from meta-analyses

SF-36 Components and Domains	Time Periods and Risk of Bias for Included Trials	Number of Studies	Total Number With/ Without MTM	Mean Difference 95% CI Lower Limit to Upper Limit p-value	Q-value (df for Q) p-value	I-squared
Physical functioning domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	1.171 CI: -3.871 to 6.214 p=0.649	3.873 (2) p=0.144	48.363
	All time periods, all risk of bias	5[43,44,67,68,72]	968/1,038	-0.438 CI: -2.641 to 1.765 p=0.697	4.478 (4) p=0.345	10.669
Physical role functioning domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	3.392 CI: -1.223 to 8.007 p=0.150	0.988 (2) p=0.610	0
	All time periods, all risk of bias	5[43,44,67,68,72]	968/1,038	0.733 CI: -3.429 to 4.895 p=0.730	7.238 (4) p=0.124	44.733
Bodily pain domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	3.320 CI: -0.792 to 7.433 p=0.114	2.765 (2) p=0.251	27.658
	All time periods, all risk of bias	5[43,44,67,68,72]	968/1,038	1.459 CI: -2.793 to 5.711 p=0.501	21.061 (4) p<0.001	81.007
General health perceptions domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	1.916 CI: -0.007 to 3.839 p=0.051	0.856 (2) p=0.652	0
	All time periods, all risk of bias	5[43,44,67,68,72]	968/1,308	2.476 CI: 2.123 to 2.829 p<0.001	1.624 (4) p=0.804	0
Vitality domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	2.797 CI: 0.655 to 4.939 p=0.010	0.965 (2) p=0.617	0
	All time periods, all risk of bias	5[43,44,67,68,72]	9681,038	1.299 CI: -0.305 to 2.904 p=0.112	4.750 (4) p=0.314	15.793
Social functioning domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	2.932 CI: -0.085 to 5.949 p=0.057	1.078 (2) p=0.583	0.000
	All time periods, all risk of bias	5[43,44,67,68,72]	968/1,038	0.631 CI: 0.290 to 0.973 p<0.001	3.407 (4) p=0.492	0
Emotional role functioning domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	5.386 CI: -7.244 to 18.016 p=0.403	7.794 (2) p=0.20	74.341
	All time periods, all risk of bias	5[43,44,67,68,72]	968/1,038	3.441 CI: -4.000 to 10.882 p=0.365	18.742 (4) p=0.001	78.657

Table 37. Scores on SF-36 measures: Summary of effects from meta-analyses (continued)

SF-36 Components and Domains	Time Periods and Risk of Bias for Included Trials	Number of Studies	Total Number With/ Without MTM	Mean Difference 95% CI Lower Limit to Upper Limit p-value	Q-value (df for Q) p-value	I-squared
Mental health domain	All time periods, low or medium risk of bias	3[43,67,68]	566/603	1.615 CI: -0.362 to 3.593 p=0.109	0.968 (2) p=0.616	0
	All time periods, all risk of bias	5[43,44,67,68,72]	968/1,038	1.109 CI: 0.280 to 1.928 p=0.009	1.274 (4) p=0.866	0

Abbreviations: CI = confidence interval; MTM = medication therapy management; SF-36 = 36-Item Short Form Health Survey

One trial (medium risk of bias) focused on patients at high risk of experiencing a drug-related problem.[43] This trial compared an intervention arm that included a clinical pharmacist intervention delivered in an ambulatory care clinic with usual medical care. It reported between-group differences with p-values less than 0.05 for four of the eight SF-36 domains (namely, bodily pain, general health perceptions, vitality, and mental health) and for a question that assessed change in health status. All these differences favored the intervention group. However, to control for multiple comparisons, the investigators set alpha at 0.01 when evaluating statistical significance. Using this more conservative alpha level, they investigators reported that only the bodily pain domain and the item assessing change in health status were statistically significant.

Of the eight remaining studies reporting results for SF-36 domains), four trials (one low risk of bias;[67] three medium risk of bias[44,68,73]) reported no statistically significant between-group differences on any SF-36 score. Two trials[51,72] and the cohort study[56] (all high risk of bias) reported one statistically significant ($p<0.05$) between-group difference, favoring the intervention group—specifically for vitality[72]—among the total of 24 comparisons examined across the three studies. Finally, for one trial (medium risk of bias overall), we rated risk of bias for the SF-36 outcomes as high because of numerous errors in the table reporting these findings (e.g., group mean not contained within 95% CI, group mean not centered within 95% CI);[44] it reported no statistically significant between-group differences on any SF-36 elements.

SF-36 Measures: Meta-analyses

Our analysis focuses on the three trials rated either low or medium risk of bias that provided sufficient data to calculate mean differences for the eight SF-36 domain scores.[1-3] We also conducted sensitivity analyses that included the two high risk-of-bias trials in addition.[44,72] We omitted one trial from the meta-analyses altogether because it reported only that none of the SF-36 domains differed significantly but did not give any precise values.[73] Similarly, we excluded one trial[51] and the cohort study[56] in the meta-analyses because they did not report standard deviations, standard errors, or exact p-values for any of the between-group comparisons; both studies reported that MTM did not produce any significant differences in anySF-36 domain. Finally, we omitted one trial from the domain-specific meta-analyses because it reported only component scores.[69] To correct for the potential inflation of Type I error attributable to multiple comparisons, we used a threshold of α/number of tests (i.e., domains; 0.05/8=0.006) when evaluating statistical significance. Below, we describe our findings for each SF-36 domain, focusing on the meta-analyses of just the low to medium risk of bias trials (i.e., the smaller meta-analysis). We did not conduct a meta-analysis for the SF-36 component scores because only one trial was rated as low to medium risk of bias for these outcomes.

SF-36 Domain Scores

Physical Functioning. Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 1.17; 95% CI, -3.87 to 6.21; p=0.65; I^2=48.36). Adding the two high risk-of-bias studies did not alter this conclusion (mean difference:-0.44; 95% CI, -2.64 to 1.77; p=0.70; I^2=10.67) (Appendix G-4).

Physical role functioning. Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 3.39; 95% CI, -0.79 to 7.43; p=0.11; I^2=27.66). Adding the two other studies did not alter this conclusion (mean difference: 0.73; 95% CI, -3.43 to 4.90; p=0.73; I^2=44.73) (Appendix G-5).

Bodily pain. Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 3.32; 95% CI, -1.22 to 8.01, p=0.15; I^2=0). Adding the two other studies did not alter this conclusion (mean difference: 1.46; 95% CI, -2.79 to 5.71; p=0.50; I^2=81.01) (Appendix G-6).

General health perceptions. Results from the low and medium risk-of-bias analysis showed no benefit for the MTM interventions (mean difference: 1.92; 95% CI, -0.02 to 3.84, p=0.051; I^2=0). With the additional studies, however, results suggested a beneficial effect of MTM interventions on general health perceptions (mean difference: 2.48; 95% CI, 2.12 to 2.83, p<0.001; I^2=0) (Appendix G-7).

Vitality. Results of the smaller meta-analysis showed no benefit for the MTM interventions, after correcting for multiple comparisons (mean difference: 2.80; 95% CI, 0.65 to 4.94; p=0.01; I^2=0). If we had set alpha at the conventional 0.05 level, our findings would demonstrate a beneficial effect of MTM interventions. Adding the two other studies to the analysis did not change the no-benefit results for the MTM interventions, even at the more conventional alpha level (mean difference: 1.30; 95% CI, -0.31 to 2.90; p=0.11; I^2=15.79) (Appendix G-8).

Emotional role functioning. Results from the smaller meta-analysis showed no benefit for the MTM interventions (mean difference: 5.39; 95% CI, -7.24 to 18.02; p=0.40; I^2=74.34). Adding the other two studies did not alter this conclusion (mean difference: 3.44; 95% CI, -4.00 to 10.88; p=0.37; I^2=78.66). However, the high I^2 statistic for both these meta-analyses suggested considerable heterogeneity among the studies for this particular domain (Appendix G-9).

Social role functioning. Results from the low and medium risk-of-bias analysis showed no benefits from MTM interventions (mean difference: 2.93; 95% CI, -0.09 to 5.95; p=0.057; I^2=0). With the additional studies, however, results suggested a beneficial effect of MTM interventions (mean difference: 0.63; 95% CI, 0.29 to 0.97; p<0.001; I^2=0) (Appendix G-10).

Mental health. Results from the smaller meta-analysis showed no benefit for the MTM interventions (mean difference: 1.62; 95% CI, -0.36 to 3.59; p=0.11; I^2=0). Adding the two other studies did not alter this conclusion, after correcting for multiple comparisons (mean difference: 1.11; 95% CI, 0.28 to 1.94, p=0.009; I^2=0) (Appendix G-11).

Two RCTs provided data for the SF-36 physical and mental component scores.[44,69] Although we rated both trials as medium risk of bias overall, we rated one of them[44] as high risk of bias for the SF-36 outcomes because of errors in the table presenting these findings. None of the between-group differences examined in either study were statistically significant with alpha set at 0.05.

SF-36 Strength of Evidence Grades

Based on the evidence from low- and medium risk of bias trials (4 trials; 1,343 randomized, 1,169 analyzed) with medium study limitations, consistent results, precise, and direct evidence,

we graded the strength of evidence for the effect of MTM interventions on seven of the eight SF-36 domains and the overall physical and mental component scores as low for no benefit. For the remaining domain–vitality, we judge the evidence as imprecise and rated the evidence as insufficient.

Condition-Specific Quality of Life

Two small RCTs[58,60] reported condition-specific quality-of-life outcomes (Table 38). One RCT (medium risk of bias) of just patients with diabetes compared patients in a study arm that included a clinical pharmacist intervention delivered in an ambulatory care clinic with those receiving usual medical care.[58] The investigators reported no significant difference in diabetes-specific quality-of-life between the intervention and control arms at the end of 6 months. The other RCT[59,60] (high risk of bias) of patients with renal disease reported a significant difference at 1 year favoring the pharmaceutical care program We graded the strength of evidence, using only the medium risk of bias trial, as insufficient (single study, direct, but imprecise) (Table 39).

Table 38. Condition-specific quality-of-life: Summary of results

Study Design/Risk of bias	Study Arms	N analyzed	Outcome and Time Period	Results
Clifford et al., 2002[58] RCT/ Medium	G1: Collaborative pharmaceutical care program G2: Standard outpatient care for diabetes	G1: 48 G2: 25	Diabetes Quality of Life instrument Scale of 1 to 5 Higher scores indicate greater dissatisfaction, worry, or impact of diabetes	Baseline G1: 2.0 (0.6) G2: 1.9 (0.5) p: NS 6-month followup G1: 1.9 (0.5) G2: 1.9 (0.4) p>0.15
Pai et al., 2009[59]; Pai et al., 2009[60] RCT/High	G1: Pharmaceutical care, consisting of one-on-one care, with in-depth drug therapy reviews conducted by a clinical pharmacist G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	Baseline G1: 61 G2: 44 Year 1: G1: 44 G2: 36 Year 2: G1: 24 G2: 32	Renal Quality of Life Profile Maximum score = 172 Higher scores indicate worsening of HRQOL	Total Score Baseline G1: 71.9 (40) G2: 74.5 (33.5) Year 1 G1: 71.4 (33.6) G2: 87.5 (30.4) p<0.05 for G1 vs. G2 for Y1 Year 2 G1: 56.5 (32.6) G2: 68.8 (35.8)

Abbreviations: HRQOL = health-related quality of life; NS = not significant; RCT= randomized controlled trial.

Table 39. Condition-specific quality of life: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 73 (73)	Medium	Consistency unknown-single study	Direct	Imprecise	Nonsignificant improvement of 0.1 point on a 5-point scale in the intervention group compared to no change in the control group	Insufficient

Patient Satisfaction

Five studies reported on various patient satisfaction measures and outcomes; four were trials (including two cluster randomized trials)[40,51,67,69] and one was a cohort study.[56] All compared patient satisfaction outcomes for patients receiving some form of MTM intervention and patients receiving some type of usual care (Table 40). Of these studies, we rated two RCTs low or medium risk of bias, two cluster randomized trials as medium or high risk of bias; and the cohort study as high risk of bias.

One RCT (low risk of bias) focused on patients age 65 and older who were taking five or more regularly scheduled medications.[67] This study compared patients who receiving clinical pharmacist intervention delivered in an ambulatory care clinic with those receiving usual outpatient care. The study reported non-significant between-group differences for two satisfaction measures (i.e., satisfaction with general health care and satisfaction with pharmacy-related care).

Table 40. Patient satisfaction: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[67] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	General health care satisfaction at 12-month followup (Higher scores indicate greater dissatisfaction)	G1: 1.5 (0.7) G2: 1.6 (0.8) p=0.70
			Pharmacy-related health care satisfaction at 12-month followup (Higher scores indicate greater dissatisfaction)	G1: 5.2 (1.5) G2: 5.4 (1.7) p=0.52
Malone et al., 2000[40]; Ellis et al., 2000[41]; Malone et al, 2001[43]; Ellis et al., 2000[42] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e. no pharmaceutical care)	G1: 447 G2: 484	Patient satisfaction with primary health care provider (Higher scores indicate greater satisfaction)	Time 1 G1: 51.9 (7.5) G2:51.9 (7.5) Time 2 G1: 51.7 (7.3) G2: 51.9 (7.5) p=NS
Bernsten et al., 2001[51]; Sturgess et al., 2003[52] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1,290 G2: 1,164 6 months G1: 1,024 G2: 953 12 months G1: 863 G2: 764 18 months G1: 704 G2: 636	Percentage rating pharmacy services provided as "excellent"	Baseline G1: 66.2 G2: 68.2 p NR 6 months G1: 72.8 G2: 63.7 p <0.05 12 months G1: 73.4 G2: 71.2 p NR 18 months G1: 73.8 G2: 64.6 p<0.05

Table 40. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Bernsten et al., 2001[51]; Sturgess et al., 2003[52] RCT, Cluster-Randomized/High (continued)			Percentage agreeing with statement "I am satisfied with the services provided by the pharmacy that I regularly visit."	Baseline G1: 92.0 G2: NR 6 months G1: 95.1 G2: NR 12 months G1: 93.9 G2: NR 18 months G1: NR G2: NR p=NS for all between-group differences
Carter et al.,1997[56], Barnette et al., 1996[57] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	All results are percentage of patients agreeing or strongly agreeing with a specific statement, as measured at 6-month followup "I am very satisfied with the pharmacy services I receive,"	G1: 100 G2: 96 p=0.065
			"Overall, the program provided a valuable service to me"	G1: 100 G2: 80 p=0.0018
			"The quality of information provided to me by the pharmacist was excellent"	G1: 100 G2: 88 p=0.012
			"My participation in this program helped me to understand high blood pressure better"	G1: 100 G2: 83 p= 0.011
			"The area was private enough for me to feel comfortable talking about my high blood pressure"	G1: 96 G2: 96 p=0.036
			"I felt comfortable talking with the pharmacist about my health problems"	G1: 100 G2: 96 p=0.052
			"I am confident the pharmacist is able to help me control my high blood pressure"	G1: 100 G2: 92 p=0.340
			"I am confident the information provided by the pharmacist to the physician improved my health care."	G1: 87 G2: 83 p=0.325
			"There are things about the high blood pressure program that could be better."	G1: 9 G2: 0 p=0.157

Table 40. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997[56], Barnette et al., 1996[57] Cohort/High (continued)			"I am very willing to continue to see the pharmacist for help with my high blood pressure control."	G1: 95 G2: 88 p=0.459
			"I think the pharmacist should provide this type of service for everyone."	G1: 77 G2: 75 p=0.890
			"I think the pharmacist should be paid for this type of service."	G1: 91 G2: 82 p=0.379
Volume et al., 2001[69]; Kassam et al., 2001[70] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N=363 G1: 159 G2: 204 Time 2: N=317 G1: NR G2: NR Time 3: N=292 G1: NR G2: NR	General satisfaction (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.59 (0.77) G2: 1.56 (0.73 Time 2: G1: 1.51 (0.84) G2: 1.57 (0.72) Time 3: G1: 1.53 (0.77) G2: 1.62 (0.88) p=NS for all between-group differences
			Interpersonal skills (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.36 (0.48) G2: 1.37 (0.53) Time 2: G1: 1.37 (0.59) G2: 1.35 (0.57) Time 3: G1: 1.31 (0.50) G2: 1.45 (0.72) p=NS for all between-group differences
			Evaluation and goal setting (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 2.58 (1.12) G2: 2.74 (1.09) Time 2: G1: 2.46 (0.98) G2: 2.98 (1.24) Time 3: G1: 2.49 (1.10) G2: 2.90 (1.08) p<0.05 for between-group differences in score changes from Time 1 to Time 2 and Time 1 to Time 3

Table 40. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001[69]; Kassam et al., 2001[70] RCT-Cluster Randomized/Medium (continued)			Trust (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.62 (0.66) G2: 1.46 (0.57) Time 2: G1: 1.40 (0.54) G2: 1.39 (0.58) Time 3: G1: 1.43 (0.58) G2: 1.51 (0.75) p<0.05 for between-group differences in score changes from Time 1 to Time 2 p<0.05 for group x measure interaction over all three time periods
			Helping patients (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 2.25 (1.31) G2: 2.22 (1.14) Time 2: G1: 1.98 (1.17) G2: 2.23 (1.15) Time 3: G1: 2.07 (1.22) G2: 2.37 (1.21) p= S for all between-group differences
			Explanation (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.34 (0.55) G2: 1.34 (0.63) Time 2: G1: 1.39 (0.67) G2: 1.30 (0.56) Time 3: G1: 1.38 (0.73) G2: 1.35 (0.61) p= NS for all between-group differences

Table 40. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001[69]; Kassam et al., 2001[70] RCT-Cluster Randomized/Medium (continued)			Pharmacy finances (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 3.08 (1.82) G2: 2.85 (1.80) Time 2: G1: 2.89 (1.89) G2: 2.86 (1.75) Time 3: G1: 3.08 (1.80) G2: 3.16 (1.88) p= NS for all between-group differences
			Drug plan finances (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 3.31 (1.70) G2: 3.41 (1.75) Time 2: G1: 3.45 (1.96) G2: 3.39 (1.83) Time 3: G1: 3.65 (1.67) G2: 3.56 (1.83) p= NS for all between-group differences
			Communicates with doctor (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.50 (0.77) G2: 1.60 (0.89) Time 2: G1: 1.36 (0.63) G2: 1.72 (1.00) Time 3: G1: 1.36 (0.65) G2: 1.74 (0.97) p<0.05 for between-group differences in score changes from Time 1 to Time 3

Abbreviations: NR = not reported; NS = not significant; RCT= randomized controlled trial

The other RCT (medium risk of bias) focused on patients at high risk of experiencing a drug-related problem.[43] This study compared patients receiving a clinical pharmacist intervention delivered in an ambulatory care clinic with those in usual medical care. The study reported a nonsignificant between-group difference on a measure assessing patient satisfaction with the primary care provider.

One cluster trial (medium risk of bias) focused on patients ages 65 and older who were taking three or more medications concurrently.[69] This study evaluated a community pharmacy-based intervention and assessed nine different measures of satisfaction at baseline, at 6-7 months

following baseline, and at 12-13 months following baseline. This study reported statistically significant between-group change in a measure labeled, *Evaluation and Goal Setting*. This measure included six items assessing the extent to which the pharmacist involved the patient in setting therapeutic goals. However, none of the items asked directly about patient satisfaction with the goal setting process. This study also reported a statistically significant between-group change from baseline to the 12-13 month follow-up on a measure labeled, *Communicates with Doctor*. This measure included two items asking about whether the patient's pharmacist and doctor work together to determine the most appropriate therapy for the patient. Neither item asked directly about patient satisfaction with the level of pharmacist-doctor communication. Finally, this study reported a statistically significant between-group change in a measure labeled, *Trust*. At baseline, patients in the intervention group reported lower trust in their pharmacist. Over the course of the study, their level of trust improved to the level reported by patients in the control group at baseline, accounting for the between group differences reported. The study reported no statistically significant between-group changes on the remaining six satisfaction measures, including a measure that directly assessed overall satisfaction with pharmacy services.

When grading strength of evidence, we did not consider the results from the remaining cluster trial RCT[51] and the cohort study[56] because they were rated as high risk of bias. We also did not consider findings from three other studies (one RCT,[58] one nonrandomized clinical trial,[38] and one cohort study[35]) because they assessed only changes in satisfaction over time in the intervention arm and did not make any between-group comparisons. Overall, we concluded that the strength of evidence for MTM interventions with respect to patient satisfaction was low for no benefit (Table 41).

Table 41. Patient satisfaction: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 1,625 (1,543)	Medium	Consistent	Direct	Precise	17 of 21 between- group differences small and not statistically significant; 4 statistically significant differences ranged in magnitude from -0.15 to -0.36, favoring MTM	Low for no benefit

Abbreviations: MTM = medication therapy management; RCT = randomized controlled trial; SD = standard deviation

Resource Utilization

Key Points: Resource Utilization

- Effective MTM interventions might plausibly lead to either an increase or a decrease in resource utilization, depending on the baseline status of the patient and intended goals of the intervention. When studies did not present a clear hypothesis or expected direction of effect, we were unable to interpret changes in resource utilization outcomes as either a benefit or a harm of MTM interventions.
- Evidence was insufficient to assess the effectiveness of MTM in changing numerous measures of use of health care resources. These included the number of medications, use of generic medications for telephone-based MTM, and several different measures of medication costs; outpatient visits and costs; laboratory tests and costs; emergency

department visits and costs; and risk of hospitalization, hospital costs, and length of hospital stay.

- Community pharmacy-based MTM interventions increase the weighted generic substitution ratio when compared with educational mailings, but the effect size is low (one cohort study, high study limitations, low strength of evidence of benefit).
- MTM interventions among patients with a variety of clinical conditions do not change in the number of hospitalizations when compared with usual care (three trials, medium study limitations, consistent, direct, precise, low strength of evidence of no benefit).
- MTM interventions in the home reduce the rate of hospitalizations for patients with heart failure (one cohort, high study limitations, direct, precise, low strength of evidence of benefit).

Detailed Synthesis: Resource Utilization

Number of Medications

Understanding whether a change in the number of medications taken following an MTM intervention is a measure of appropriate resource utilization requires knowledge of the goal of drug therapy. A decrease in the number of medications can represent regimen simplification and resolution of therapeutic duplication; thus, it can be interpreted as a measure of appropriate resource utilization. The converse—that is, an increase in number of medications—cannot, however, be interpreted as a measure of inappropriate resource use. An increase in number of medications can in fact represent appropriate use of resources when it resulted from identifying and resolving an inadequate drug regimen.

Numerous studies provided information on the number of medications at followup in intervention and control arms or on the change in number of medications between baseline and followup.[31,38-40,44,46,48,51,59,60,65,67-69] Only one study, however, offered any context to interpret the results in the context of benefits and harms.[63] In this cohort study (high risk of bias), the investigators found that those eligible for the intervention who received MTM services had a significant decrease in the prevalence of high-risk medication use that was not seen in the control group of patients eligible for the intervention but who did not receive it (-10.8 percentage points [$p<0.05$] versus -1.4 percentage points [no significant change]). The investigators noted, however, that the intervention arm had a higher prevalence of use of high- risk drugs at baseline and that pharmacists may have targeted these patients selectively for the intervention, suggesting confounding. Based on study limitations and unknown consistency, we graded the body of evidence as insufficient to evaluate the effect of MTM interventions on the number of medications taken (Table 42).

Table 42. Number of medications: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 2,211 (2211)	High	Consistency unknown-single study	Direct	Precise	-10.8 percentage points (p0<.05) vs. -1.4 percentage points (not significant)	Insufficient

Use of Generic Medications

Two cohort studies examined the use of generic medications (Table 43); both studies evaluated telephone-based MTM[35,46] and one also compared community pharmacy-based MTM with educational mailings.[46] We assessed both studies as high risk of bias owing to lack of adjustment for potential confounding from study design (intervention refusers versus acceptors)[35] or lack of capacity of pharmacists or inability to reach patients.[46]

Table 43. Use of generic medications: Summary of results

Study Design/Risk of Bias	Study Arms	N analyzed	Outcome and Time Period	Results
Pindolia et al., 2009[35] Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (refusers)	G1: 292 G2: 1081	Increase in the overall use of generic drugs	G1: 6% G2: 3% p not calculated because baseline percentages not provided
Winston et al., 2009[46] Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed call center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Weighted generic substitution ratio: 30-day equivalent claims divided by total number of claims	Calculated mean differences for G1 vs. G3: 1.2 (95% CI: 0.724 to1.676; p<0.001) Calculated mean difference for G2 vs. G3: 0.80 (95% CI: -0.246 to 1.846; p=0.134)

Abbreviations: CI = confidence interval; G = group; MTM = medication therapy management; RCT = randomized controlled trial.

With respect to telephone-based MTM services, we graded the body of evidence as insufficient (high study limitations, inconsistent, and imprecise) to evaluate their effect on number of generic medications (Table 44). Regarding the effect of pharmacy-based MTM intervention on the generic substitution ratio (Table 45), we graded the strength of evidence as low; the evidence was direct and precise, but a small standardized mean difference (0.04), study limitations and uncontrolled confounding limited our confidence that the estimate of effect is close to the true effect for this outcome.

Table 44. Use of generics for telephone-based MTM versus usual care or educational mailings: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	2; 97,124 (75,166)	High	Inconsistent	Direct	Imprecise	Calculated mean difference from one study: 0.80 (95% CI: -0.246 to 1.846; p=0.134)	Insufficient

Abbreviations: CI = confidence interval; NA = not applicable; SMD = standardized mean difference.

Table 45. Use of generics for community pharmacy-based MTM versus educational mailings: Strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 95,736 (73,793)	High	Consistency unknown-single study	Direct	Precise	Calculated mean difference: 1.2 (95% CI: 0.724 to1.676 to; p<0.001) (Standardized mean difference: 0.04)	Low for benefit for the community pharmacy arm

Abbreviations: CI = confidence interval; SMD = standardized mean difference.

Medication Costs: Overview

Eighteen studies reported data on costs of prescription medications (Table 46). We use the same language as the authors in describing their measures; they varied in study design and risk of bias and used a wide range of measures that cannot all be meaningfully combined. We categorized these outcomes in four groups; patient out-of-pocket costs (copayments), health plan costs, combined expenditures by patients and insurers, and combinations of medications and other costs. Table 46 lists studies in order by outcome category (or outcomes in some cases) and then alphabetically by author name. Later sections offer a detailed synthesis by these four categories of costs and describe the relevant studies in more detail. We were unable to categorize one high-risk-of-bias cohort study[56,57] because it did not offer sufficient information on how "charges" were calculated. We note that several studies use the term "costs" although the specific measure used may not reflect true costs if they do not account for profits or subsidies. We use the same language as the authors in describing their measures.

Table 46. Measures used in studies of costs of medications

Study	Prescription Costs to Patients	Total Expenditures on Medications by Health Plan	Total Outlays on Medication	Medication and Other Costs Combined
Christensen et al., 2007[38]	Difference in patient copayment for prescriptions over 6 months	Difference in insurer payment for prescriptions over 6 months		
Fox et al., 2009[31]	Mean Medicare Part D copayment costs per patient per month Mean Medicare Part D and non- Part D copayments	NA	Mean Medicare Part D drug costs (total Medicare Part D drug costs (patient copays + insurance plan medication costs + dispensing fees)	NA
Pindolia et al., 2009[35]	Out-of-pocket prescription costs per health plan member	NA	Total prescription drug costs per health plan member (2006)	NA
Chrischilles et al., 2004 [63]	NA	Mean amount billed per patient for active drugs (based on Medicaid claims)	NA	NA

Table 46. Measures used in studies of costs of medications (continued)

Study	Prescription Costs to Patients	Total Expenditures on Medications by Health Plan	Total Outlays on Medication	Medication and Other Costs Combined
Jameson et al., 1995[39]	NA	Cost of prescription drugs over 6 months, based on maximum allowable cost for Medicaid reimbursement	NA	NA
Moczygemba et al., 2011[33] Moczygemba et al., 2008[34]	NA	Total Part D drug costs (based on prescription claim records, excludes non-Part D drug costs	NA	
Sellors et al., 2003[44]	NA	Mean daily medication costs to the Ontario Drug Benefit Program	Mean daily medication costs	Mean cost of health care resources per senior (total costs, including all hospital stays)
Krska et al., 2001[73]	NA	NA	Average monthly costs of prescribed medication per patient (excluding costs of prescribed medicines not taken)	NA
Malone et al., 2000[40]; Ellis et al., 2000[41]; Malone et al., 2001[43]; Ellis et al., 2000[42]	NA	NA	Mean drug costs (calculated from Denver VAMC pharmacy department, individual sites, or the VA Pharmacy Benefits Management group)	NA
Pai, 2009[59]; Pai, 2009[60]	NA	NA	Mean drug costs (calculated from average wholesale price)	NA
Staresinic et al., 2007[36]	NA	NA	Total prescription cost per MTM program beneficiary per month ([gross drug cost=ingredient cost paid + dispensing fee + sales tax]/member months in Part D contract)	NA
Welch et al., 2009[37]	NA	NA	Mean medication costs per day (from data on study beneficiaries' purchases of ambulatory prescription medications)	NA
Williams, 2004[74]	NA	NA	Average monthly wholesale price of prescription and non-prescription drugs	NA
Winston et al., 2009[46]	NA	NA	Mean drug cost per patient per month (based drug claims processing data, total allowed charges, including ingredient cost paid, dispensing fee, and sales tax, before subtracting any patient cost-sharing amounts)	NA

Table 46. Measures used in studies of costs of medications (continued)

Study	Prescription Costs to Patients	Total Expenditures on Medications by Health Plan	Total Outlays on Medication	Medication and Other Costs Combined
Bernsten et al., 2001[51]; Sturgess et al., 2003[52]	NA	NA	NA	Mean total cost per patient including (1) cost associated with additional time spent by pharmacists; (2) cost associated with contacts with GPs, specialists and nurses; and (3) cost of hospitalizations and drugs
Fischer et al., 2002[65]	NA	NA	NA	Change in total charges for inpatient care, outpatient care, and pharmacy charges
Triller et al., 2007[54]	NA	NA	NA	Aggregate health system costs Home care agency costs

Abbreviations: GPs = general practitioners; MTM = medication therapy management; NA = not applicable; VA = Veterans' Administration; VAMC = Veterans' Administration Medical Center

Medication Costs: Patient Copayments

Three nonrandomized studies (one nonrandomized controlled trial [NRCT] of medium risk of bias[38] and two cohort studies of high risk of bias[31,35]) studies compared the copayments for patients who refused MTM with patients who accepted MTM enrollment. These studies provided inconsistent evidence that patient medication co-payments increased following MTM. Table 47 documents the main findings; results are denominated in US dollars ($) unless specifically identified as Canadian dollars or as another currency. We calculated mean differences between groups when the original authors did not provide those data; all currencies are rounded to two decimals (i.e., for US currency, cents).

The NRCT compared patients in the MTM arm with controls within and outside the intervention county; the control arms had declines in copayments and the MTM had increases in copayments. The two cohort studies had inconsistent and imprecise estimates of effect; one study showed an increase in copayments for the MTM arm and a decline for the control arm,[35] and the other reported a smaller increase in the MTM arm than in the control arm.[31] None of these studies explained whether the increase in copayment was a result of an appropriate change in medication therapy or the desired effect of the intervention. Although the results were precise in the NRCT and suggested an increase in medication copayments following MTM, the lack of directness in interpreting this outcome as a measure of appropriate resource utilization and the absence of other low and medium risk-of-bias studies to assess consistency of findings suggests insufficient evidence to judge the effect of MTM interventions on patient medication co-payment (Table 48).

Table 47. Patient copayments: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Christensen et al., 2007[38] NRCT/Medium	G1: Patients receiving pharmacist-provided-MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in patient copayment for prescriptions over 6 months in $ (SD)	Calculated mean difference for G1 vs. G2: $80.40; 95% CI, $10.43 to $150.37 p=0.024 Calculated mean difference for G1 vs. G3= $88.60; 95% CI, $24.61 to $152.59 p=0.007
Fox et al., 2009[31] Cohort/High	G1: MTM program (acceptors) G2: Opt-out from MTM program (refusers)	G1: 247 G2: 50	Mean difference in Medicare Part D medication copayment costs per patient per month	Calculated mean difference: -$3.92, 95% CI, -$25.71 to $17.87 p=0.724
			Mean difference in all medication copayments (Medicare Part D and not Part D) per patient per month	Calculated mean difference: -$1.71 95% CI, -$24.53 to $21.11 p=0.883
Pindolia et al., 2009[35] Cohort/High	G1: Telephone-based MTM program (acceptors) G2: Usual medical care (refusers)	G1: 292 G2: 1,081	Mean out-of-pocket prescription costs per health plan member in $ (assumed per year, as NR in study) (SD)	Calculated mean difference: $77.00; 95% CI, -#71.82 to $225.82 p=0.311

Abbreviations: CI =confidence interval; G = group; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; RCT= randomized controlled trial; SD = standard deviation; SMD: standardized mean difference.

Table 48. Patient copayments: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
NRCT	1; 1,639 (1,606)	High	Consistency unknown, single study	Indirect	Precise	Calculated mean difference for MTM vs. same country control: $80.40; 95% CI, $10.43 to $150.37 p=0.024 Calculated mean difference for MTM vs. different county control: $88.60; 95% CI, $24.61 to $152.59 p=0.007	Insufficient

Abbreviations: NRCT = nonrandomized controlled trial.

Medication Costs: Expenditures by Insurers

Two RCTs (both medium risk of bias),[39,44] the NRCT reported on above,[38] and two cohort studies (one medium[33,34] and one high risk of bias[63]) measured the net effect of MTM on expenditures incurred by insurers on medications (Table 49). Changes in health plan drug expenditures attributable to MTM depend on the net effect of MTM activities, which can entail adding clinically needed drugs, increasing doses or frequency, substituting therapeutically equivalent lower cost drugs, and simplifying regimens (singly or in combination). For individual

patients, a net increase in expenditures may be the outcome of a more appropriate drug regimen. Included studies provided only the net effect on expenditures at the study arm level. All demonstrated that MTM either reduced health plan expenditures or limited the increase in expenditures over time for patients receiving the MTM intervention when compared with patients in the control or comparison arm. These results were not precise, however; confidence intervals included the null effect for all but one trial

Table 49. Total expenditures on medications by insurers: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Insurers	Results
Jameson et al., 1995[39] RCT/Medium	G1: Pharmacotherapy consultation G2: Usual care	G1: 27 G2: 29	Change in cost of prescription drugs over 6 months, based on maximum allowable cost for Medicaid reimbursement	Calculated mean difference: -$293.00 95% CI: -$501.50 to -$84.50 p<0.01
Sellors et al., 2003 [44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient to the Ontario Drug Benefit Program (assumed CAD) at 5 months	Calculated mean difference: $0.19 95% CI: -$1.52 to $1.14 p = 0.78 Calculated mean difference over 6 months=0.19*30*6=34
Christensen et al., 2007[38] NRCT/Medium	G1: Patients receiving pharmacist-provided MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in amount insurer paid for prescriptions over 6 months	Calculated mean difference for G1 vs. G2: -$54.70 95% CI: -$287.59 to $178.19 p=0.645 Calculated mean difference for G1 vs. G3: -$7.20; 95% CI: -$230.80 to $216.40 p=0.950
Moczygemba et al., 2011[33] Moczygemba et al., 2008[34] Cohort/Medium	G1: MTM-eligible patients who opted into a telephone MTM program G2: MTM-eligible patients who did not opt-in to the MTM program.	G1: 60 G2: 60	Mean Part D drug costs (based on prescription claim records, excludes non-Part D drug costs) (SD) at baseline and 6 months	Calculated mean difference: -$276.00 95% CI: -$751.25 to $199.25, p=0.26
Chrischilles et al., 2004 [63] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Mean amount billed per patient for active drugs (based on Medicaid claims) (SD) at baseline and at 9 months	Calculated mean difference: -$0.95 95% CI: -$58.67 to $56.77 P=0.974

Abbreviations: CAD = Canadian dollar; CI = confidence interval; MTM = medication therapy management; PCM = pharmaceutical case management; RCT = randomized controlled trial; SMD = standardized mean difference.

We did not pool estimates of effect for the two trials because of heterogeneity in outcomes and setting; one trial was conducted in Canada and presented average daily costs, whereas the US-based study presented change over time. The nonrandomized studies were less heterogeneous but the pooled estimates had wide confidence intervals; the mean difference,

without the high risk-of-bias study was -$97.55 over 6 months (95% CI, -$306.68 to 111.58; p=0.361; I^2: 0) (Appendix G-12). These results continued to be imprecise when we included a comparison of the intervention arm from one county versus a control arm from another county in the Christensen et al. study.[38]

Based on the lack of precision and directness, we rated the evidence from medium risk-of-bias studies as insufficient to evaluate the effect of MTM on expenditures by insurers (Table 50).

Table 50. Health plan expenditures: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 953 (835)	Medium	Consistent	Indirect	Imprecise	Mean difference varies from -$34 CAD to -$293 USD over 6 months	Insufficient
NRCT and Cohort	2; 1,771 (1,746)	High	Consistent	Indirect	Imprecise	-$97.55; 95% CI, -$306.68 to 111.58; p=0.361; I^2, 0	Insufficient

Abbreviations: CAD= Canadian dollar; CI = confidence interval; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial; SD= standard deviation, USD= US dollar

Medication Costs: Total Outlays on Medications

Three RCTs (medium risk of bias),[40-44,74] two RCTs (high risk of bias),[59,60,73] and five cohort studies (high risk of bias)[31,35-37,46] measured the effect of MTM on total outlays on medications. As with other data on resource use, the failure to specify the expected mechanism of action on the outcome and the predicted direction makes interpreting inconsistent results challenging. An additional challenge relates to the wide variation in data sources and degree of clarity on how investigators calculated outlays. In some studies, the specific measure used includes the combination of expenditures incurred by insurers and patients for prescription medications (Table 51). In other studies, the measure is based on wholesale costs, but whether and how the cost is split between the insurer and the patient is unclear. Results in Table 51 are denominated in US dollars unless otherwise specified, and calculated differences are rounded to two decimals.

Table 51. Total outlays on medications: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outlays on prescriptions	Results
Malone et al., 2000[40]; Ellis et al., 2000[41]; Malone et al., 2001[43]; Ellis et al., 2000[42] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual drug costs in (calculated from Denver VAMC pharmacy department, individual sites, or the VA Pharmacy Benefits Management group)	Calculated mean difference: $63.00 95% CI: -$5.08 to $131.078; p=0.07 Calculated mean difference per month: $63/$12=$5.25
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient at 5 months (assumed CAD)	Calculated mean difference: $0.19 (assumed CAD) 95% CI: -$0.85 to $1.23 p=0.72

Table 51. Total outlays on medications: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outlays on prescriptions	Results
Williams, 2004[74] RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary medication adjustment team G2: Usual medical care	G1: 57 G2: 76	Average monthly wholesale price of prescription and nonprescription drugs	Reported mean difference: -$20.16 95% CI: $5.78 to $34.54 p: 0.006
Krska et al., 2001[73] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Average monthly costs of prescribed medication per patient in British pounds (£) (SD) at 3 months (calculated using information from patients on actual use)	Calculated mean difference: -£.0.19, 95% CI:- £6.69 to £6.49 p=0.956.
Pai, 2009[59]; Pai, 2009[60] RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	Mean drug costs (calculated from average wholesale price) over 2 years	Pharmaceutical care reduced mean drug costs by $6.21 compared with the usual care group, p=NS, no absolute costs or other details reported
Fox et al., 2009[31] Cohort/High	G1: MTM program (acceptors) G2: Opt-out from MTM program (refusers)	G1: 247 G2: 50	Mean difference in annual Medicare Part D drug costs (patient copayment + insurance plan medication costs + dispensing fee)	Calculated mean difference: -$27.78, 95% CI -%125.82 to %26.60 p=0.57
Pindolia et al., 2009[35] Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (refusers)	G1: 292 G2: 1,081	Total annual prescription drug cost per health plan member in USD	Calculated mean difference: -62.22, 95% CI -112.469 to -11.971; p=0.015
Staresinic et al., 2007[36] Cohort/High	G1: MTP program (acceptors) G2: Usual care (refusers)	G1: 282 G2: 1,544	Total prescription cost per MTM program beneficiary per month (gross drug cost=ingredient cost paid + dispensing fee + sales tax per member-months in Part D contract)	Participants spent less on prescription medications on average (described as per member per month drug spending) than nonparticipants. Figure provided suggested a decrease in spending of between $100 and $150 in the intervention group, but exact numbers not reported.

Table 51. Total outlays on medications: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outlays on prescriptions	Results
Welch et al., 2009[37] Cohort/High	G1: MTM program provided to home-based beneficiaries G2: Opt-out among home-based patients eligible for MTM	G1: 459 G2: 336	Mean change in medication costs per day at 6 months. (Estimates come from data on study beneficiaries' purchases of ambulatory prescription medications)	Difference in difference: $3.62, SD NR, adjusted p=0.203 NOTE: Age, sex, chronic disease score, and preperiod drug cost included in multivariate regression modeling for adjusted P
			Mean percentage increase in medication costs per day at 6 months (No SD reported,)	Adjusted OR : 1.4 95% CI: 1.1 to 1.9 NOTE: Model adjusted for age, sex, chronic disease score, and baseline medication cost
Winston et al., 2009[46] Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed, call-center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Mean (SD) drug cost per patient per month after 8 months of services (based on drug claims processing data, total allowed charges, including ingredient cost paid, dispensing fee, and sales tax, before subtracting any patient cost-sharing amounts)	Calculated mean difference for G1 vs. G3: -$35.00, 95% CI -43.390 to -26.610; P<0.001 Calculated mean difference for G2 vs. G3: -15.0, 95% CI -33.411 to 3.411; P=0.11

Abbreviations: CAD = Canadian dollar; CI = confidence interval; MTMP = Medication Therapy Management Program; RCT= randomized controlled trial; SMD = standardized mean difference; USD = US dollar, VAMC = Veterans Affairs Medical Center

We did not pool the three medium risk-of-bias studies because of the heterogeneity of measures.[40-44,74] Two suggested an increase in outlays in the intervention arm[40-44] (although estimates were imprecise and confidence intervals contained the null effect), and one suggested a reduction.[74] The high risk-of-bias studies similarly demonstrated inconsistent results; some reported reduced outlays[35,36,46] and others showed increased outlays[31,37] or no effect[59,60,73] following MTM.

Based on the lack of consistency, directness, and precision, we rated the evidence from three medium risk-of-bias trials as insufficient to evaluate the effect of MTM on total outlays on medications (Table 52).

Table 52. Total outlays on medications: Strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2,083 (1,975)	Medium	Inconsistent	Indirect	Imprecise	Mean difference varies from -26 USD to +5.25 USD per month	Insufficient

Abbreviations: RCT=randomized controlled trial; USD= US dollar

Medication Costs: Combined Medication and Other Costs

Three trials (two medium risk-of-bias; [44,54] one high risk-of-bias[51,52]) and one NRCT (medium risk of bias[65]) provided consistent evidence that MTM does not reduce combined medication and other costs (variably defined in each study) (Table 53). Studies did not report their results in sufficient detail to allow pooling. Based on available information, we judged the evidence to be insufficient to evaluate the effect of MTM on combined medication and other costs (Table 54).

Table 53. Medication and other costs: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Medication and other costs	Results
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of health care resources per patient, including all hospital stays at 5 months (CAD assumed)	Calculated mean difference: $249.41 (assumed CAD), 95% CI: -$338.39 to $837.21; p=0.406
			Mean cost of health care resources per patient, including only drug (i.e., medication)-related hospital stays at 5 months (CAD assumed)	Calculated mean difference: -$8.10 (assumed CAD), 95% CI: -$386.72 to 4350.52; p=0.923
Triller et al., 2007[54] RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: NR G2: NR	Aggregate health system costs (not defined in detail) Home care agency costs (not defined in detail)	Values not reported, but authors stated that costs did not differ significantly between the two groups.
Bernsten et al., 2001[51,52] RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 867 G2: 748 6 months G1: NR G2: NR 12 months G1: NR G2: NR 18 months G1: NR G2: NR	Mean total cost per patient including (1) cost associated with additional time spent by pharmacists; (2) cost associated with contacts with GPs, specialists and nurses; and (3) cost of hospitalizations and drugs	Cost data not pooled and analyzed for costs because health care systems differed between 7 countries included in the study. However, authors reported no significant between-group differences in any country (p=NS)
Fischer et al., 2002[65] NRCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Change in total charges for inpatient care, outpatient care, and pharmacy charges	G1: -900 G2: -2000 95% CI: NR P: NS, no details reported Calculated mean difference: $1,100.

Abbreviations: CAD = Canadian dollar; CI = confidence interval; GP = general practitioner; NR = not reported, NS = not significant; RCT = randomized controlled trial.

Table 54. Medication and other costs: Strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; >889, N NR in 1 study (>779)	Medium	Consistent	Indirect	Imprecise	Variable estimates	Insufficient
NRCT	1; 675 (675)	Medium	Consistency unknown, single study	Indirect	Imprecise	Difference in mean costs of $1100 favoring control group, but results not statistically significant.	Insufficient

Abbreviations: N = number; NR = not reported; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial

Number of Outpatient Visits

Nine studies examined the effect of MTM interventions, when compared with usual care, on outpatient visits. These studies varied in geographic setting (seven Western European countries,[51,52] the United States,[40-43,45,55-57,63,65] the United Kingdom,[73] Canada[44]), period of evaluation (3 months to 36 months), specific outcome measure (ranging from a focus on visits with physicians to total ambulatory care visits or contacts with physicians and nurses), and risk of bias. They are described in Table 55. No study indicated whether the intervention was specifically designed to increase or to decrease outpatient visits; as a result, the directionality of the results cannot be interpreted as a benefit or a harm.

Table 55. Number of outpatient visits: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone, 2000[40]; Ellis, 2000[41]; Malone, 2001[43]; Ellis, 2000[42] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in number of clinic visits (including visits with the pharmacists in the intervention arm) over 12 months	Calculated mean difference: 2.0, 95% CI: -0.415 to 4.415, p= 0.104
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Number of clinic visits over 5 moths	Calculated mean difference: -0.02, 95% CI: -1.274 to 1.234, p=0.975
Sidel, 1990[45] RCT/Medium	G1: Patients received at least 2 pharmacist visits involving medication review, patient-specific education and counseling; follow-up patient telephone calls and contact of physicians as needed G2: Patients contacted only to complete the survey.	G1: 92 G2: 104	Change in number of ambulatory visits over past 3 months, measured at baseline and again at 36 months	Calculated mean difference: -1.41, 95% CI: -2.98 to 0.160, p=0.078

Table 55. Number of outpatient visits: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012[55] RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 183 G2: 190 G3: 183	3-6 months G1: 183 G2: 190 G3: 183	G1 vs. G3 Calculated mean difference: 0.50, 95% CI: -0.388 to 0.488, p=0.823 G2 vs. G3 Calculated mean difference: -0.50, 95% CI: -0.383 to 0.483, p=0.821
Bernsten et al., 2001[51,52] RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	G1: 1024 G2: 953	Mean number of contacts with primary care providers, including home visits and office appointments at 6 months	Calculated mean difference: 0.120 95% CI: -0.461 to 0.701, p=0.686
Krska et al., 2001[73] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: NR G2: NR	Hospital clinic attendance, use of social services or contacts with district nurses and health visitors before and after the pharmacist review	No differences; details NR
Fischer et al., 2002[65] NRCT/High	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Changes in number of clinic visits over 1 year	Intention-to-treat analysis Adjusted between-group difference not significant, details NR
Carter et al., 1997[56,57] Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Number of distinct dates of service over 6 months	G1: 2.2 (2.4) G2: 1.0 (1.0) 95% CI: NR, p=0.07
Chrischilles et al., 2004[63] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Number of outpatient facility claims at 12 months	Results NR, p=0.121

Abbreviations: CI = confidence interval; DRP, drug-related problems; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; PCM = pharmaceutical care management; QOL = quality of life; RCT = randomized controlled trial

Three RCTs (all medium risk of bias) provided sufficient data on outpatient visits within the first year to pool results.[40-44,55] A meta-analysis of these studies, including results for the basic MTM arm for Touchette et al. (rather than the "enhanced MTM" arm),[55] across outcomes from 5 to 12 months yielded an estimated standardized mean difference of 0.049 (95% CI, -0.034 to 0.133, p=0.247; I^2=0) (Appendix G-13). Including the results of the "enhanced MTM" arm instead of the basic MTM arm did not change the direction or precision or results (standardized mean difference: 0.27, 95% CI: -0.036 to 0.91, p=0.40, I^2=0). Likewise, adding one trial with high risk of bias (stemming primarily from attrition bias[51,52]) to the meta-analysis did not alter the direction or precision of the estimate of effect (standardized difference in means: 0.032; 95% CI, -0.032 to 0.095, p=0.326, I^2=0). A fifth study (medium risk-of-bias) found fewer outpatient visits in the intervention arm at 3 years, but confidence intervals spanned the null.[45] A sixth medium risk-of-bias RCT noted "no differences in hospital clinic attendance, use of social services or contacts with district nurses and health visitors before and after the pharmacist

review" but did not indicate whether this observation extended to the control arm and offered no statistics.[73] The single nonrandomized controlled study found no differences between study arms in an intention-to-treat analysis.[65]

Two high risk-of-bias cohort studies,[56,57,63] reported no statistically significant differences between study arms in the number of outpatient facility claims but offered no additional information.

Based on the lack of consistency and precision, we graded the body of evidence of medium risk-of-bias trials as insufficient to evaluate the effect of MTM interventions on outpatient resource utilization (Table 56).

Table 56. Number of outpatient visits: Strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2227 (2038)	Medium	Inconsistent	Direct	Imprecise	Standardized mean difference: 0.049; 95% CI, -0.034 to 0.133, p=0.247; I^2=0	Insufficient

Abbreviations: RCT= randomized controlled trial

Cost of Outpatient Visits

Four studies examined the effect of MTM interventions, when compared with usual care, on the costs of outpatient visits (Table 57). These studies included three set in the United States[40-43,56,57,63] and one set in Canada.[44] The period of evaluation ranged from 5 months to 12 months. As with studies on the number of outpatient visits, no study indicated that the intervention was designed specifically to raise or lower the costs of outpatient visits; as a result, the directionality of the results cannot be interpreted as a benefit or a harm. As with other costs analyses, the data are in US dollars unless otherwise specified and rounded to nearest two decimals.

Two trials (medium risk-of-bias) offered inconsistent evidence on the effect of MTM interventions on outpatient costs. One U.S.-based VA study found a significantly smaller increase in annual costs of clinic visits in the intervention group than in the usual care group.[40-43] The Canadian study found no significant differences by study arm.[44] One cohort study (high risk of bias from selection bias) evaluated two measures of costs; the intervention arm had significantly higher costs for hypertension-related services than the usual care arm.[56,57] Another US-based cohort study of the Medicaid program in Iowa (high risk of bias) found no statistically significant differences in cost of outpatient visits by intervention arm.[63]

Table 57. Costs of outpatient visits: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone, 2000[40]; Ellis, 2000[41]; Malone, 2001[43]; Ellis, 2000[42] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual cost of clinic visits	Calculated mean difference: -$102.00 95% CI: -$187.81 to -$16.20 p=0.02
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of physician visits (assumed CAD) at 5 months	Calculated mean difference: $5.66, 95% CI: -$24.22 to $35.54, p=0.71
			Mean cost of clinic visits (assumed CAD) at 5 months	Calculated mean difference: -$2.13, 95% CI: -$20.46 to $16.20, p=0.82
			Mean cost of other health care services and visits to health care professionals (assumed CAD) at 5 months	Calculated mean difference: -$4.70 95% CI: -$140.22 to $130.82; p=0.95
Carter et al., 1997[56,57] Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Hypertension-related charges (SD) at 6 months	Calculated mean difference: $70.00, 95% CI: $15.97 to $124.03, p=0.011
			Mean visit charges at 6 months	Calculated mean difference: $487.00, 95% CI: $44.87 to $929.14, p=0.031
Chrischilles et al., 2004[63] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Outpatient facility claims at 12 months	Results NR, p=0.107

Abbreviations: CAD = Canadian dollar; CI = confidence interval; NR = not reported; RCT = randomized controlled trial; SD = standard deviation

Based on the lack of consistency and precision, we graded the body of evidence from the two trials as being insufficient to evaluate the effect of MTM interventions on the costs of outpatient visits (Table 58).

Table 58. Costs of outpatient resource utilization: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1,943 (1,842)	Medium	Inconsistent	Indirect	Imprecise	Variable	Insufficient

Abbreviations: RCT= randomized controlled trial.

Number of Laboratory Tests

Understanding whether a change in the number and costs of laboratory tests as a result of an MTM intervention measures appropriate resource use requires knowledge of the goals of drug therapy. MTM could raise numbers and costs of laboratory tests by identifying patients who should be receiving more frequent laboratory monitoring or by starting patients on new drugs that require laboratory monitoring based on their clinical situation. However, MTM could also lower numbers and costs of laboratory tests if it produces better coordination of care and

prevents duplicative testing. Included studies did not specify the expected direction of effect from MTM on the number and costs of laboratory tests.

Two trials (both medium risk of bias; one set in the United States[40-43] the other in Canada[44]) reported on the number laboratory tests following MTM interventions (Table 59). The Canadian study included the number and costs of imaging procedures over a 5-month period;[44] the US-based study did not specify the inclusion of imaging procedures and evaluated tests and costs over a 12-month period. The US-based found statistically significant differences; the Canadian study failed to find any significant differences.

Table 59. Number of laboratory tests: Summary of results

Study Design/Risk of bias	Study Arms	N analyzed	Outcome and Time Period	Results
Malone, 2000[40]; Ellis, 2000[41] (interventions); Malone, 2001[43] (detailed QOL outcomes); Ellis, 2000[42] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual number of laboratory tests	Calculated mean difference: -1.6, 95% CI: -2.550 to -0.650, p=0.001
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of laboratory tests and imaging procedures at 5 months	Calculated mean difference: 0.15, 95% CI: -0.959 to 1.259, p=0.791

Abbreviations: RCT= randomized controlled trial.

The small number of studies limits our ability to explore causes for the observed heterogeneity. Factors such as differences in health systems, period of evaluation, and definition of the outcome could explain differences in results. Based on lack of consistency, we graded the body of evidence from these two medium risk of bias trials as insufficient to evaluate either the effect of MTM interventions on the number of laboratory tests (Table 60).

Table 60. Number of laboratory tests: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1,943 (1,842)	Medium	Inconsistent	Indirect	Imprecise	Differences range from +0.15 to -1.6 tests	Insufficient

Abbreviations: RCT= randomized controlled trial.

Costs of Laboratory Tests

The two studies reporting data on number of laboratory tests also provided information on costs.[40-43] The challenges associated with interpreting evidence on number of laboratory tests apply to costs as well (Table 61).

Table 61. Costs of laboratory tests: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone, 2000[40]; Ellis, 2000[41]; Malone, 2001;[43] Ellis, 2000[42] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual costs for laboratory tests	Calculated mean difference: -$33.00 95% CI: -$65.96 to -$0.04, p=0.05
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all lab and imaging procedures at 5 months (assumed CAD)	Calculated mean difference: $6.24 (assumed CAD) 95% CI: -$46.34 to $58.88 p=0.816

Abbreviations: CAD = Canadian dollar

Based on lack of consistency, we graded the body of evidence from these two medium risk of bias trials as insufficient to evaluate either the effect of MTM interventions on the costs of laboratory tests (Table 62).

Table 62. Costs of laboratory tests: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1943 (1842)	Medium	Inconsistent	Indirect	Imprecise	Differences range from +0.62 CAD to -33 USD	Insufficient

Abbreviations: CAD, Canadian dollars; RCT= randomized controlled trial; USD, US dollars.

Emergency Department Visits

Four studies in all reported changes in emergency department (ED) visits following MTM interventions: three trials (two medium risk of bias[44,55] and one high risk-of-bias[44,68]) and one cohort study (medium risk of bias)[37] (Table 63). With the exception of one arm from the Touchette et al. trial,[55] the confidence intervals for the effects from the medium risk-of-bias studies spanned the null effect.[37,44] One trial, rated high risk of bias for this outcome, reported a decline in ED visits in the intervention arm and no change in the control arm;[68] it did not, however, provide patient-level means. As a result, we are unable to judge the variance within the sample.

Table 63. Emergency department visits: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of ED or urgent care visits and ambulance use at 5 months	Calculated mean difference: -0.03 95% CI: -0.113 to 0.053 p=0.48
Touchette et al., 2012[55] RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 183 G2: 190 G3: 183	Mean number of ED visits per participant between 3-6 months after intervention	G1 vs. G3 calculated mean difference: -0.138 95% CI: -0.258 to -0.018 p=0.025 G2 vs. G3 calculated mean difference: -0.118, 95% CI: -0.242 to 0.006 p=0.062
Taylor et al., 2003[68] RCT/High	G1: Pharmaceutical care group G2: Standard care	G1: 33 G2: 36	Change in number of ED visits from 12 months before baseline through 12 months after	G1: -12 G2: 0 p=0.044
Welch et al., 2009[37] Cohort/medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR of ED visit from 6 month before MTM through 6 months after MTM (adjusted for age, sex, chronic disease score, specific baseline utilization)	Reported adjusted OR: 0.9 95% CI: 0.6 to 1.3, p NR

Abbreviations: CI = confidence interval; DRP = drug related problems; ED = emergency department; MTM = medication therapy management; NR = not reported; OR = odds ratio; RCT = randomized controlled trial.

Given the lack of consistency and precision, evidence is insufficient to draw conclusions about the effectiveness of MTM in reducing ED visits (Table 64).

Table 64. Emergency department visits: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1,526 (1,344)	Medium	Inconsistent	Direct	Imprecise	Mean difference ranges from -0.03 to -0.138	Insufficient
Observational	1; 904 (795)	High	Consistency unknown-single study	Direct	Imprecise	Adjusted OR: 0.9 (0.6 to 1.3)	Insufficient

Abbreviations: OR = odds ratio; RCT= randomized controlled trial.

Emergency Department Costs

One trial (medium risk of bias)[44] and one cohort study (high risk of bias)[63] reported on costs of ED visits following MTM interventions (Table 65). Despite differences in geographic setting and health care delivery systems (Canada[44] and the United States[63]), period of evaluation (5 months,[44] and 12 months[63]), and risk or bias, neither study demonstrated an effect of any MTM-type intervention (Table 65).[44,63] Based on lack of precision, we graded the medium risk-of-bias study as being insufficient evidence to evaluate the effect of MTM interventions on the cost of ED visits (Table 66).

Table 65. Costs of emergency department visits: Summary of results

Study Design/Risk of bias	Study Arms	N analyzed	Outcome and Time Period	Results
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of ED or urgent care visits and ambulance use at 5 months in $ (assumed CAD) (SE)	Calculated mean difference: -$5.60 (assumed CAD) 95% CI:-$23.06 to $11.86 p=0.53
Chrischilles et al., 2004[63] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Charges for ED claims at 12 months	Results NR P=0.513

Abbreviations: CAD: Canadian dollar, CI = confidence interval; ED= Emergency department; NR = not reported; PCM = pharmaceutical care management; SE = standard error

Table 66. Cost of emergency department visits: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 889 (779)	Medium	Consistency unknown-single study	Direct	Imprecise	Mean difference: -$5.60 (assumed CAD) 95% CI:-$23.06 to $11.86, p=0.53	Insufficient

Abbreviations: CAD = Canadian dollar; RCT = randomized controlled trial

Hospitalizations

Nine studies measured hospitalizations as an outcome following MTM interventions.[37,40-44,51,52,54,55,59,60,62,73] Of these, we have excluded data from one study in the analysis below because it reported total number of events by each intervention arm rather than by patients within intervention arm. As a result, we are unable to assess variance.[73] We report on the mean number of hospitalizations, the risk of hospitalization, and the rates of hospitalization (Table 67).

Table 67. Hospitalizations: Mean number, risk and rates

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone, 2000[40]; Ellis, 2000[41] (interventions); Malone, 2001[43] (detailed QOL outcomes); Ellis, 2000[42] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in number of hospitalizations	Calculated mean difference: 0.06, 95% CI: -0.051 to 0.171, p=0.29
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of all-cause hospitalizations	Calculated mean difference: -0.03 95% CI: -0.085 to 0.025, p=0.289
			Mean drug-(medications) related hospitalizations	Calculated mean difference: 0 95% CI: -0.28 to 0.28 p=1.0

Table 67. Hospitalizations: Mean number, risk and rates (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012[55] RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	Time One G1: 180 G2: 190 G3: 193 Time Two G1: 183 G2: 190 G3: 183	Percentage of participants with at least one hospital visit at 3 to 6 months	G1 vs. G3: Calculated OR: 2.069, 95 % CI: 1.104 to 3.878 p=0.02 G2 vs. G3: Calculated OR: 1.345 95 % CI: -0.9=693 to 2.609 p=0.381
			Mean number of hospital visits per participant	G1 vs. G3: Calculated mean difference: 0.039, 95 % CI: -0.047 to 0.125, p=0.37 G2 vs. G3: Calculated mean difference: 0.045, 95 % CI: -0.037 to 0.127, p=0.28
Triller et al., 2007[54] RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: 77 G2: 77	Percentage with any hospitalization, all causes	RR 0.93, Calculated 95% CI: 0.707 to 1.232 p: 0.63
			Percentage with any hospitalization related to heart failure	RR: 0.82, Calculated 95% CI: 0.581 to 1.581 p: 0.26
Bernsten et al., 2001[51,52] RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 867 G2: 748 6 months G1: NR G2: NR 12 months G1: NR G2: NR 18 months G1: NR G2: NR	Percentage with ≥1 hospitalization in the prior 18 months	Pooled sample Baseline (during 18 months before study) Overall: NR G1: 41.7 G2: 41.3 p=NS 18 months Overall: NR G1: 35.6 G2: 40.4 p=NS, cannot be calculated without N
Pai, 2009[59]; Pai, 2009[60] RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	Mean number of all-cause hospitalizations over 2 years	G1: 1.8 (2.4) G2: 3.1 (3) 95% CI: NR, cannot be calculated without N p: 0.02
			Cumulative hospitalized time in days (SD)	Cumulative hospital time G1: 9.7 days (14.7) G2: 15.5 days (16.3) 95% CI: NR, cannot be calculated without N p=0.06

Table 67. Hospitalizations: Mean number, risk and rates (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Roughead, 2009[62] Cohort/Medium	G1: Collaborative home-based medication review G2: No medication review received	G1: 273 G2: 5,444	Rate of hospitalization for heart failure at any time during study	Adjusted HR (): 0.55 95% CI: 0.39 to 0.77 p: NR NOTE: Model adjusted for age, sex, comorbidity, SES, season, region of residence, and numbers of prescriptions, prescribers, pharmacies, changes in medications, hospitalizations, occupational therapy visits, and speech therapy visits
Welch et al., 2009[37] Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR of hospitalization from 6 month before MTM through 6 months after (adjusted for age, sex, chronic disease score, specific baseline utilization)	Reported adjusted OR: 1.4 95% CI) 1.1 to 2.0 ; p values NR NOTE: Model adjusted for age, sex, chronic disease score, specific baseline utilization

Abbreviations: CI = confidence interval; DRP = drug-related problems; HR = hazard ratio MTM = medication therapy management, NR = not reported; NS = not significant; OR = odds ratio; RCT = randomized controlled trials; RR = relative risk; SES = socioeconomic status

Three trials (medium risk-of-bias) reported on the change in number of hospitalizations or mean number of hospitalizations following MTM interventions (Table 67).[40-44,55] Using a random-effects model, we pooled these results for all-cause hospitalizations and obtained a mean difference of 0.038 (95% CI, -0.005 to 0.080; p=0.085; I^2=0) (Appendix G-14). We obtained similarly small effect sizes and wide confidence intervals spanning the null when including each arm of the Touchette et al. study separately[55] or including the single high risk-of-bias trial.[60] One study also provided data to calculate an effect size and confidence intervals for drug-related hospitalizations that also overlapped the null effect.[44]

Four studies (two medium-risk-of-bias RCTs,[54,55] one high risk-of-bias RCT,[51,52] and one medium risk-of-bias cohort study[37]) reported on the percent hospitalized following MTM (Table 67), based on percentages of patients hospitalized or odds or hazard ratios of hospitalization. Not all studies provided sufficient data to allow the generation of a summary estimate of effect with confidence intervals. The results are inconsistent; two studies suggested an higher hospitalizations with MTM rather than usual care[37,55] and two suggested lower hospitalizations (but with confidence intervals overlapping the null).[51,52,54] The inconsistency in results may be a consequence of the wide range of included populations, from a relatively homogenous group of home care patients with heart failure[54] to veterans in ambulatory care.[51,52]

One cohort study (medium risk-of-bias) reported a decreased rate of hospitalization for heart failure at any time during study. This study of home medications review was designed specifically to delay the next hospitalization among patients with heart failure in Australia.[62]

Based on consistent results from studies with medium study limitations that we rated as precise because of their narrow confidence intervals around the null, we rated MTM as having no effect on the mean number of hospitalizations (low strength of evidence, Table 68). We rated the evidence on the percent hospitalized as insufficient based on inconsistent and imprecise evidence

(Table 69). By contrast, we rated the evidence on the rate of hospitalization as low based on a precise estimate from a large cohort study (Table 70); we note that the findings from a single study of a very specific intervention (home medicines review) of heart failure patients limits its applicability to patients with other morbidities and settings. Together, the lack of consistency across these measures of hospitalization likely reflects heterogeneity in numerous factors in this evidence base.

Table 68. Mean number of hospitalizations: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	3; 2,580 (2,398)	Medium	Consistent	Direct	Precise	Mean difference of 0.038 (95% CI -0.005 to 0.080	Low for no benefit

Abbreviations: CI = confidence intervals; RCT = randomized controlled trial

Table 69. Percentage of patients hospitalized: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 791 (710)	Medium	Inconsistent	Direct	Imprecise	Direction and magnitude varies	Insufficient
Cohort	1; 904 (795)	High	Consistency unknown, single study	Direct	Precise	Adjusted OR (95% CI): 1.4 (1.1 to 2.0)	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio; RCT= randomized controlled trial

Table 70. Rate of hospitalization: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 5,717 (5,717)	High	Consistency unknown, single study	Direct	Precise	Adjusted HR (95% CI): 0.55 (0.39 to 0.77)	Low

Abbreviations: CI = confidence interval; HR = hazard ratio

Hospitalization Costs

Two trials (medium risk-of-bias)[40-44] and one cohort study (high risk-of-bias)[63] reported changes in costs of hospitalization following MTM interventions (Table 71). Although two studies were set in the United States, one evaluated outcomes from Veteran Affairs Medical Centers[40-43]and the other evaluated claims from the Iowa Medicaid program.[63] The third study was set in Canada.[44] The period of evaluation of outcomes ranged from 5 months[44] to 12 months.[40-43,63] All were consistent in demonstrating no effect of MTM interventions on the costs of hospitalization. Based on lack of consistency in direction of effect and lack of precision, we graded the body of evidence as being insufficient to evaluate the effect of MTM interventions on the cost of hospitalization (Table 72).

Table 71. Costs of hospitalization: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sellors et al., 2003[44] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all admissions to hospital (assumed CAD) over what time period	Calculated mean difference: $159.74 (assumed CAD) 95% CI: -$281.99 to $601.47 p=0.478
Malone, 2000[40]; Ellis, 2000[41] Malone, 2001[43] (Ellis, 2000[42] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual hospitalization costs	Calculated mean difference: -$221.00 95% CI: -$566.33 to $124.33 p=-0.21
Chrischilles et al., 2004[63] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Inpatient claims within 9 months of becoming eligible for PCM	Results NR, p= 0.937

Abbreviations: CAD = Canadian dollar; NR = not reported; PCM = pharmaceutical care management; RCT= randomized controlled trial.

Table 72. Cost of hospitalization: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	2; 1,943 (1,842)	Medium	Inconsistent	Direct	Imprecise	Inconsistent direction of effect but consistent in lack of significant effect	Insufficient

Abbreviations: RCT= randomized controlled trial.

Hospital Length of Stay

One trial (high risk of bias) [59,60] reported that MTM interventions reduced length of hospital stay by 21 percent. Based on study limitations and lack of precision, we graded this outcome as having insufficient evidence to evaluate the effect of MTM interventions on the length of hospital visits (Table 73).

Table 73. Length of hospital stay: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
RCT	1; 107 (46)	High	Consistency unknown-single study	Direct	Imprecise	MTM reduced length of stay by 21%	Insufficient

Abbreviations: RCT= randomized controlled trial.

Key Question 3: Outcomes of Medication Therapy Management by Intervention Features

Key Points

- Studies do not routinely report outcomes of MTM by intervention features.

- We found evidence on four intervention features informed by a single study for each feature: access to patient data,[55] pharmacy intensity of adoption of the intervention,[63] community pharmacy versus call-center pharmacy,[46] and private versus Medicaid coverage of pharmaceutical care.[47] With the exception of the investigation reporting on access to patient data, these studies had a high risk of bias.
- Evidence was insufficient on access to patient data, pharmacy intensity of adoption of the intervention, community pharmacy versus call-center pharmacy, and private versus Medicaid coverage of pharmaceutical care for most outcomes.
- MTM programs with pharmacist access to patient records reduces the number of adverse drug events (low strength of evidence) when compared basic MTM programs.
- Community pharmacists increase the generic dispensing ratio more than call-center-based pharmacists (low strength of evidence).

Detailed Synthesis: Intervention Features

Access to Patient Records

A single trial (medium risk-of-bias) of 556 patients overall (373 in the two MTM arms) evaluated differences between two MTM intervention arms; one without access to patient records (denoted "basic" MTM and one specifically with such access in the form of a two-page clinical synopsis containing basic data on a patient's medical history, laboratory values, and current medications, including over-the-counter and herbal medications (denoted "enhanced MTM").[55] Table 74 provides the effect size and strength of evidence for the seven outcomes assessed in this trial. In all instances, we rated the trial as medium for study limitations and unknown for consistency; we do not repeat these ratings in the table. With the exception of mean number of adverse drug events, which suggested benefit for enhanced MTM when compared with basic MTM (low strength of evidence), we found insufficient evidence to evaluate the comparative effectiveness of the two arms.

Table 74. Access to patient records (basic MTM versus enhanced MTM): Strength of evidence

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Percentage with ≥ 1 ADE	Direct	Imprecise	Calculated OR: 1.294, 95% CI: 0.768 to 2.180, p=0.333	Insufficient
Percentage with ≥ 1 emergency department visit	Direct	Imprecise	Calculated OR: 1.222, 95% CI: 0.795 to 1.878, p=0.360	Insufficient
Percentage with ≥ 1 hospitalization	Direct	Imprecise	Calculated OR: 1.539, 95% CI: 0.862 to 2.746 , p=0.145	Insufficient
Mean number of ADEs	Direct	Imprecise	Calculated mean difference: 0.346, 95% CI: 0.112 to 0.580, p=0.004	Low for benefit
Mean number of emergency department visits	Direct	Imprecise	Calculated mean difference: -0.001 , 95% CI: -0.119 to 0.117, p=0.987	Insufficient
Mean number of hospitalizations	Direct	Imprecise	Calculated mean difference: 0.055 , 95% CI: -0.038 to 0.148, p=0.244	Insufficient
Mean number of physician visits	Indirect	Imprecise	Calculated mean difference: 0.100 , 95% CI: -0.322 to 0.522 , p=0.643	Insufficient

Abbreviations: ADE = adverse drug event; OR = odds ratio.

Pharmacy Intensity of Adoption

One cohort study (high risk of bias) of 2,211 patients evaluated eight outcomes based on pharmacy intensity of adoption of the MTM intervention (Table 75).[63] Specifically, the authors categorized pharmacies that completed recommendations in at least one quarter into four groups: (1) for at least 50 percent of patients, high-intensity pharmacy (2) 25 to 49 percent as moderate intensity; (3) 1 to 24 percent as low intensity; and (4) no recommendations study as no intensity. For all outcomes, we rated this study as high for study limitations and unknown for consistency (not repeated in table). Outcomes for which we can infer a benefit or a harm from the effect are rated as direct outcomes. We found insufficient evidence to judge the effectiveness of MTM by intensity of adoption on all reported outcomes.

Table 75. Pharmacy intensity of adoption: Strength of evidence

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Number of emergency department claims	Direct	Imprecise	Findings NR, p=0.330	Insufficient
Number of inpatient institutional claims	Direct	Imprecise	Findings NR, p=0.839	Insufficient
Number of outpatient facility claims	Indirect	Imprecise	Findings NR, p=0.112	Insufficient
Number of pharmacy, institutional, and medical services	Indirect	Imprecise	Findings NR, p=0.616	Insufficient
Emergency department claims	Direct	Imprecise	Findings NR, p=0.652	Insufficient
Inpatient institutional claims	Direct	Imprecise	Findings NR, p=0.862	Insufficient
Outpatient facility claims	Indirect	Imprecise	Findings NR, p=0.212	Insufficient
Pharmacy, institutional, and medical services	Indirect	Imprecise	Findings NR, p=0.166	Insufficient

Abbreviation: NR = not reported

Community Pharmacy Versus Call Center

One large cohort study (high risk of bias) of the MirixiaPro platform (95,736 patients enrolled, 73,793 analyzed) compared patients using a community pharmacy, which included both face-to-face and telephone interactions, with patients using a call center pharmacy (Table 76).[46] The investigators measured three diverse outcomes. In all instances, we rated the study as high for study limitations and unknown for consistency (not repeated in table).Outcomes for which we can infer a benefit or a harm from the effect are rated as direct outcomes. We found insufficient evidence for drug cost and drug use outcomes, which we rated as indirect evidence with high study limitations. MTM delivered by community pharmacists increases the weighted generic dispensing ratio (GDR) when compared with MTM delivered by call-center pharmacists (low strength of evidence). The study defines the weighted GDR as the number of generic 30-day equivalent claims divided by the total number of claims, and then weighted for each patient by a factor equal to the individual's total prescription volume multiplied by a constant to hold sample size unchanged.

Table 76. Community pharmacy versus call center: Strength of evidence

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Drug cost per patient per month (USD)	Indirect	Precise	Calculated mean difference: -20.0, 95% CI: -32.826 to -7.174, p=0.002	Insufficient
Drug use per patient per month	Indirect	Precise	Calculated mean difference: -0.370, 95% CI: -0.477 to -0.263, p<0.001	Insufficient
Weighted generic dispensing ratio	Direct	Precise	Calculated mean difference: 9.710, 95% CI: 9.583 to 9.837, p<0.001	Low

Abbreviations: CI = confidence interval; USD = United States dollar

Type of Payer

One cohort study (high risk of bias, N=615) compared outcomes for patients with Medicaid and patients with private insurance (Table 77).[47] The investigators reported on three diverse outcomes. In all instances, we rated the study as high for study limitations and unknown for consistency (not repeated for each outcome in the table). We found insufficient evidence to judge the effectiveness of MTM by type of payer on all reported outcomes.

Table 77. Type of payer: Strength of evidence

Outcome	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Per-patient Medication Appropriateness Index at followup	Direct	Precise	Calculated mean difference: 0.81, 95% CI: -1.303 to 2.923, p=0.452	Insufficient
Proportion of patients for whom cost was a problem at followup	Direct	Precise	Calculated OR: 1.498, 95% CI: 0.807 to 2.778, p=0.20	Insufficient
Drug therapy problems identified	Direct	Precise	2.6 in both arms, p=1.0	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio

Key Question 4. Outcomes of MTM by Patient Characteristics

We did not identify any studies that analyzed outcomes of MTM by patient characteristics.

Key Question 5. Harms of Medication Therapy Management Interventions

Key Points

- Studies do not routinely report harms that result from MTM interventions. One study reported on confusion from information received through an MTM intervention. Study limitations and lack of precision of these results suggested that evidence was insufficient to evaluate the effect of MTM interventions on harms.

Detailed Synthesis: Confusion

A single cohort study (high risk of bias) compared patients who accepted a home medicines review with those who did not have a home medicines review.[61] The investigators reported a five-fold increase in the odds of being confused by information received (22 percent versus 5 percent; calculated OR, 5.57; 95% CI, 1.03 to 30.1; p=0.04). However, the sample size does not meet optimal information size criteria, suggesting lack of precision of the results.

Table 78. Confusion: Strength of evidence

Study design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 149 (68)	High	Consistency unknown-single study	Direct	Imprecise	Calculated OR: 5.57, 95% CI: 1.03 to 30.1, p=0.04	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio

Detailed Synthesis: Inconvenience

A single cohort study (high risk of bias) compared pharmaceutical care with usual care.[56,57] The investigators reported that patients in the intervention arm were less likely to agree or strongly agree with the statement that they were inconvenienced by monthly appointments with the pharmacists (40 percent versus 69 percent; calculated OR, 0.278; 95% CI, 0.088 to 0.875; p=0.029). As with the information on confusion, the sample size does not meet optimal information size criteria, suggesting lack of precision of the results.

Table 79. Confusion: Strength of evidence

Study Design	Number of Studies; Subjects (Analyzed)	Study Limitations	Consistency	Directness	Precision	Findings and Direction [Magnitude] of Effect	Strength of Evidence
Cohort	1; 55 (51)	High	Consistency unknown-single study	Direct	Imprecise	Calculated OR: 0.278, 95% CI: 0.088 to 0.875; p=0.029	Insufficient

Abbreviations: CI = confidence interval; OR = odds ratio

Discussion

We conducted a systematic review of benefits and harms of medication therapy management (MTM) programs. Because of the wide variation in types of interventions classified as MTM, we first catalogued intervention components and implementation features of MTM interventions (Key Question [KQ] 1). We then evaluated the effect of MTM on intermediate, patient-centered, and resource utilization outcomes (KQ 2). We also reviewed the evidence to identify how these effects might vary by specific intervention components and features (KQ 3) and patient characteristics (KQ 4). Finally, we reviewed the evidence on harms associated with MTM (KQ 5).

Below, we summarize the main findings and strength of evidence, where applicable. We then discuss the findings in relationship to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions.

This evidence base consisted of 36 studies (19 randomized controlled trials [RCTs] trials and 17 observational studies) reported in 42 articles. Most RCTs compared an MTM intervention with usual care rather than with a different active intervention; most observational studies were cohort studies. Numerous studies had methods problems that led us to rate them as having a medium or high risk of bias; only a few studies were of low risk of bias. When possible (enough studies similar in intervention, populations, and outcomes measured), we conducted meta-analyses of data from RCTs; in some cases, we did two sets, one with and one without the high risk-of-bias trials.

Key Findings and Strength of Evidence

KQ 1: Intervention Components and Implementation Features

Nearly two-thirds of included studies were broadly focused on patients with a wide-ranging collection of conditions; the remaining studies were narrowly focused on patients with a specific condition. All studies used a pharmacist as the interventionist. Services were provided face-to-face in just over half of included studies. Included studies provided interventions in a variety of clinical settings, including community pharmacies, centralized pharmacies or pharmacy call centers, and outpatient medical clinics, and some used home visits; half of the narrowly focused interventions were delivered exclusively in an outpatient medical clinic.

Whether termed “pharmaceutical care” or “MTM,” studies did not describe intervention components and features in a consistent manner or in sufficient detail. These drawbacks were especially prevalent for intervention intensity and frequency, method of patient enrollment for services, level of integration with usual care, and reimbursement characteristics for rendered MTM services. KQ 1 was descriptive in nature, so we did not grade strength of evidence.

KQ 2: Overall Effectiveness

Of the 36 studies included in this review, we rated 14 as high risk of bias overall; that is, concerns about randomization failure, confounding, or overall attrition increased the risk of bias for all outcomes. In addition, we rated some studies that were otherwise of low or medium risk of bias as high for individual outcomes, chiefly because of measurement bias. These instances are specified in the relevant results section in Chapter 3.

We rated the strength of evidence for each outcome from low- or medium risk-of-bias studies when available. MTM significantly improved medication appropriateness assessed in general

(Table 80). However, we did not find evidence of benefit for any other intermediate outcomes on which we had data. No studies addressed either goals of therapy or patient engagement.

Table 80. Summary of findings and strength of evidence for intermediate outcomes of MTM interventions

Intermediate Outcome	Study Design: No. Studies (N Analyzed)	Results	Strength of Evidence
Anticoagulation	RCT: 1 (10)	Imprecise	Insufficient
Hemoglobin A1C	RCT: 2 (102)	Inconsistent, imprecise	Insufficient
Low density lipoprotein cholesterol	RCT: 1 (38)	Imprecise	Insufficient
Hypertension: achieving blood pressure goals	RCT: 1 (44)	Imprecise	Insufficient
Hypertension: systolic blood pressure	RCT: 1 (23)	Imprecise	Insufficient
Hypertension: diastolic blood pressure	RCT: 1 (23)	Imprecise	Insufficient
Drug therapy problems identified	RCT: 1 (332) Cohort: 2 (668)	Indirect, imprecise, high study limitations	Insufficient
Drug therapy problems resolved	Cohort: 1 (120)	Indirect, imprecise, high study limitations	Insufficient
Medication adherence	RCT: 8 (2,415) Cohort: 2 (1,493)	Inconsistent, imprecise	Insufficient
Medication Appropriateness General Index Scores	RCT: 1 (208)	Improvement in MTM group from score of 17.7 to 13.4 and to 12.8 at 3 and 12 months, respectively	Low for benefit
Medication-specific appropriateness	RCT: 2 (261)	Indirect, imprecise, inconsistent	Insufficient
Medication dosing	RCT: 2 (90)	Inconsistent, imprecise	Insufficient
Goals of therapy	0	NA	NA
Patient engagement	0	NA	NA

Abbreviations: CI = confidence interval, MTM = medication therapy management; N = number; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial.

Similarly, we did not have evidence of benefit for most patient-centered outcomes (Table 81). MTM did not improve most measures of health-related quality of life (low strength of evidence for no benefit). We graded the "vitality" domain of the Medical Outcomes Study Short-Form (SF36) questionnaire as insufficient for this domain. For the SF-36, neither the other seven domains nor the two component scores (physical health, mental health) showed significant benefit from MTM interventions. The various patient satisfaction items also showed no impact from MTM programs (low strength of evidence for no benefit).

Table 81. Summary of findings and strength of evidence for patient-centered outcomes of MTM interventions

Patient-Centered Outcome	Study Design: No. Studies (N Analyzed)	Results	Strength of Evidence
Adverse drug events	RCT: 2 (806)	Inconsistent, imprecise	Insufficient
Cognitive, affective, and physical function	RCT: 1 (133)	Imprecise	Insufficient
Mortality	RCT: 2 (335) Cohort: 1 (795)	Inconsistent, imprecise	Insufficient
Gastrointestinal bleeding events	Cohort: 1 (1,373)	High study limitations	Insufficient
General health-related quality of life domains other than vitality	RCT: 4 (1,169)	Variable mean difference with confidence intervals consistently spanning the null effect	Low for no benefit
General health-related quality of life vitality domain	RCT: 4 (1,169)	Imprecise	Insufficient
Condition-specific health-related quality of life (diabetes)	RCT: 1 (73)	Imprecise	Insufficient
Patient satisfaction	RCT: 3. (1,625)	No differences on 17 or 21 items of patient satisfaction	Low for no benefit
Activities of daily living	0	NA	NA
Work or school absenteeism	0	NA	NA
Patient and caregiver participation in medical care and decisionmaking	0	NA	NA

Abbreviations: CI = confidence interval, MTM = medication therapy management; N = number; NA = not applicable; RCT = randomized controlled trial.

Outcomes related to using health resources were similarly not much influenced by MTM interventions (Table 82). Two exceptions may merit attention: (1) the use of generic medications for patients receiving MTM from community pharmacy when compared with educational mailings (low for benefit from the community pharmacy approach) and (2) the rate of hospitalization among heart failure patients with home medicines review when compared with usual care. When MTM was implemented in settings with a broad range of patients, it did not reduce the number of hospitalizations (low strength of evidence).

Table 82. Summary of findings and strength of evidence for resource-utilization outcomes of MTM interventions

Use of Resources Outcomes	Study Design: No. Studies (N Analyzed)	Results	Strength of Evidence
Number of high-risk medications	Cohort: 1 (2,211)	High study limitations	Insufficient
Use of generic medications for call-center pharmacy-based MTM vs. educational mailings	2; 97,124 (75,166)	High study limitations, inconsistent	Insufficient
Use of generic medications for community pharmacy-based MTM vs. educational mailings	Cohort: 1 (73,793)	Calculated mean difference in weighted generic dispensing ratio: 1.2 (95% CI: 0.724 to1.676 to; p<0.001)	Low for benefit for community pharmacy
Medication costs: patient copayments	NRCT: 1 (1,626)	High study limitations, indirect	Insufficient
Medication costs: health plan expenditures	RCT: 2 (835); NRCT & Cohort: 2 (1,746)	Indirect, imprecise	Insufficient
Medication costs: total outlays	RCT: 3 (1,975)	Inconsistent, indirect, imprecise	Insufficient
Medication costs: medication costs plus other expenditures	RCT: 2 (>779); NRCT: 1 (675)	Indirect, imprecise	Insufficient
Number of outpatient visits	RCT: 2 (2,038)	Inconsistent, imprecise	Insufficient
Outpatient costs	RCT: 2 (1,842)	Inconsistent, indirect, imprecise	Insufficient
Number of laboratory tests	RCT: 2 (1,842)	Inconsistent, indirect, imprecise	Insufficient
Costs of laboratory tests	RCT: 2 (1,842)	Inconsistent, indirect, imprecise	Insufficient
Number of emergency department visits	RCT: 2 (1,344) Observational: 1 (795)	Inconsistent, imprecise	Insufficient
Costs of emergency department visits	RCT: 1 (779)	Imprecise	Insufficient
Hospitalization: number	RCT: 2 (2,398)	Mean difference of 0.038 (95% CI −0.005 to 0.080)	Low for no benefit
Hospitalization: percentage	RCT: 2 (710)	Inconsistent. Imprecise	Insufficient
Hospitalization: rate (patients with heart failure and home medicine review)	Cohort: 1 (5,717)	Adjusted HR (95% CI): 0.55 (0.39 to 0.77)	Low for benefit
Costs of hospitalization	RCT: 2 (1,842)	Inconsistent, imprecise	Insufficient
Length of hospital stay	RCT: 1 (46)	High study limitations, imprecise	Insufficient

Abbreviations: CI = confidence interval, HR = hazard ratio; MTM = medication therapy management; N = number; NA = not applicable; NRCT = nonrandomized controlled trial; OR = odds ratio; RCT = randomized controlled trial.

Over all three categories of outcomes, each of which had a substantial number of individual measures, MTM improved outcomes in only a couple of instances. Study limitations and lack of precision of the estimates of effects limited the strength of evidence considerably. As discussed later, even the minimal findings of effectiveness are at best only narrowly applicable.

KQ 3: Effectiveness of MTM by Intervention Features

We found evidence from one study each on four intervention features: (1) access of pharmacists to patient records,[55] (2) community pharmacy versus call center,[63] (3) level of intensity of intervention,[46] and (4) type of payer (private vs. Medicaid).[47] With the exception of the study on pharmacists' access to patient records, we rated these studies as high risk of bias. Evidence was insufficient for most outcomes for the first two intervention features, with two exceptions. First, MTM delivered by community pharmacists increased the weighted generic dispensing ratio when compared with call-center pharmacists (low strength of evidence). Second, enhanced MTM with pharmacists' access to patient records reduced the mean number of adverse

drug events; this finding suggested benefit when compared with basic MTM (low strength of evidence). We found insufficient evidence for all outcomes for intensity of intervention and type of payer.

KQ 4: Effectiveness of MTM by Patient Characteristics

We did not identify any studies that analyzed outcomes of MTM by patient characteristics.

KQ 5: Harms of MTM Interventions

Lack of precision and the limitations of a single high risk-of-bias study meant that evidence was insufficient to judge whether MTM resulted in greater confusion[61] or inconvenience[56,57] than usual care. We found no evidence on other prespecified harms, specifically including care fragmentation, patient decisional conflict, patient anxiety, increased (actual) adverse drug events, prescriber confusion, and prescriber dissatisfaction.

Findings in Relation to What Is Already Known

Our findings contrast with conclusions that Chisholm-Burns and colleagues reached in a recent systematic review.[75] In that review, the authors concluded that "Pharmacist-provided direct patient care has favorable effects across various patient outcomes, health care settings, and disease states."[75, p. 923] Several differences between the Chisholm-Burns review and the current review may account for the discrepant conclusions. First, the Chisholm-Burns review included all studies that cited evidence of pharmacist involvement in direct patient care. The interventions examined included chronic disease management and prospective and retrospective drug utilization review; we excluded these types of efforts because our intended focus was on the MTM intervention itself. Notably, the Chisholm-Burns review did not use the term "medication therapy management" to categorize the interventions in the articles they reviewed. Second, approximately 30 percent of the papers in the Chisholm-Burns review were conducted entirely in institutional settings. In contrast, we did not identify any studies within institutional settings that met our MTM intervention definition criteria. Third, the Chisholm-Burns review included a total of 298 articles and did not omit from their analyses studies with a high risk of bias; by contrast, we based our strength-of-evidence grades in this review on only those studies with no more than medium risk of bias.

The striking differences between the conclusions reached in these two reviews emphasize two important needs for both conceptual and practical efforts to systematically review MTM programs. The first is to create a systematic system for classifying the different types of direct patient care services that pharmacists can provide. The second is to develop consensus guidelines for describing intervention features in publications reporting findings from evaluation studies. Progress on these two steps would enable systematic reviews to differentiate better between different types of services and avoid the problem of overgeneralizing review results.

The Centers for Medicare & Medicaid Services (CMS) supported a large evaluation of MTM programs that we were unable to include in this draft because of the timing of the release of that report.[28] We will include it in our final report along with our update of the published and grey literature. Although we have not yet incorporated the findings of this large evaluation into our systematic review, we note that the report finds that MTM improved patient adherence to medication regimens and the quality of prescribing. Our review did not find sufficient evidence to evaluate the effect of MTM on improved adherence, but we did find low strength of evidence

that MTM improves medication appropriateness, which is conceptually similar to "quality of prescribing." The discrepancy between the CMS findings regarding adherence and findings of studies included thus far in our review may reflect the greater precision that the CMS investigators might have had in their use of pharmaceutical prescription refill records to assess adherence when compared with other studies that primarily used self-report to assess adherence. The report also found some reduction in resource use, but these results were for patients with diabetes or congestive heart failure. Our review found that for patients with heart failure, MTM was likely to reduce hospitalization rates, but we found no effect on mean number of hospitalizations for broadly defined populations.

Applicability of the Findings

This body of evidence has significant clinical and methodological heterogeneity, which limits the ability to make any universal statements about effectiveness.[76] However, the range of study designs, which includes RCTs, nonrandomized trials, and cohort studies, enhances the applicability of findings for real-world settings. Included studies ranged from relatively small interventions in single clinics provided by a single interventionist to evaluations of MTM services delivered on a large scale through integrated health systems or health plans as a Medicare Part D or other drug plan benefit. This diversity of studies enhanced the applicability of findings to a wide variety of settings, including outpatient clinics, community pharmacies, and centralized pharmacy call centers. A few studies conducted outside the United States included MTM as part of a home visits program; findings from this model may not be directly applicable within the United States.

The studies in this review are broadly applicable to a range of chronically ill, adult patient populations. The majority of interventions were directed at populations with multiple and common chronic conditions, such as diabetes, chronic heart failure, and hypertension. Several specifically targeted adults aged 65 years or older. Few studies reported sociodemographic characteristics beyond age and sex; thus, the applicability of findings to specific populations (e.g., rural, low socioeconomic status, cognitively impaired, uninsured) is unknown. The nature of the MTM intervention, which includes involving patients as active participants in the process, limits the extent to which findings can be generalized beyond patients who agreed to participate in such interventions. Patients who agree to participate may be systematically different from those who decline to be in such a program. For that reason, the impact of such interventions at a population or health-plan level may be limited by the degree of uptake among interested patients.

The intervention used across most studies can be characterized as complex and moderately resource intensive. Components involve identifying applicable patients; initially assessing patients; providing counseling, education, and care coordination; and following patients over time. These services were provided per protocol in some studies and as needed or ad hoc in others. Most studies described intervention components in terms of "pharmaceutical care model" components or Medicare Part D MTM program criteria, but few provided detailed descriptions or measurement of implementation fidelity.

The comparator arm in all studies was usual medical care. This does not typically include distinct MTM services by health care providers other than prescribing providers (not common for the time period covered by most of the studies). Models of collaborative health care delivery are evolving, and the changing roles and training of pharmacists increase the potential applicability of MTM interventions in future models of health care.

The broad sets of outcomes evaluated across this body of evidence spanned a substantial range of both intermediate and health outcomes as well as outcomes related to resource use. Proximal and intermediate outcomes included number of drugs, identification of drug therapy problems, appropriateness of medication prescribing, and laboratory or biometric markers of disease control (e.g., hypertension, hemoglobin A1c, low-density lipoprotein cholesterol). Patient-centered outcomes focused on numerous measures of quality of life as well as adverse drug events. Many studies also reported outcomes involving health care resource use and expenditures (e.g., number and costs of hospitalizations, emergency department visits, outpatient visits).

Most studies did not, however, clearly indicate the expected, desired, or intended direction of effect on most resource use outcomes, making the applicability of using these interventions to reduce drug-related health care costs or expenditures difficult to assess. For example, whether one should expect the number of medications prescribed for heart failure to increase or decrease under the careful scrutiny of an MTM intervention is not clear.

The focus of outcome measurement in many studies was the short-term identification and characterization of drug therapy problems and their resolution; these endpoints are thought to be the outcomes most sensitive to change as a result of receiving MTM services. However, by design, because identification of drug therapy problems is a part of the MTM intervention itself, differences between the nature of the intervention and that of the control programs mean that measuring these outcomes cannot be as rigorous in a usual care comparison group as it is in the intervention group. In fact, many studies were able to measure only changes in this outcome in the intervention group. Hence, many studies failed to demonstrate a direct analytic link between the resolution of drug therapy problems as a result of MTM and impact on intermediate outcomes, patient-centered outcomes, and resource utilization. Thus, the applicability of studies that demonstrate an impact on the resolution of drug therapy problems is limited.

Implications for Clinical Practice and Policymakers

Although we found the evidence insufficient in general to draw definitive conclusions about the comparative effectiveness of MTM for most outcomes that we evaluated, our findings do suggest some implications for practice and policy. MTM is already in widespread practice and is now shaped in the United States largely by Medicare Part D policy: this presents both challenges and opportunities. MTM programs of the future, sponsored and administered by Part D drug benefit plans, may be less integrated into routine health care for Medicare beneficiaries than many of the pharmaceutical care interventions included in our review. We were unable to answer definitively whether level of integration matters for effectiveness, but policymakers may need to consider expectations about the impact that MTM might have on patient-centered outcomes and resource use in the context of other health care delivery transformation activities or quality improvement initiatives that are also occurring. More integration of MTM services with other activities may be effective; however, the more integrated MTM becomes within routine medical care, the more difficult it becomes to isolate it as a discrete intervention for evaluation.

Policymakers could thus consider whether MTM services should be positioned as a *contributor* to overall improvement in processes of care, health status, and costs or positioned as an intervention to which effects can be discretely *attributed*. Improvements in medication appropriateness or drug therapy regimens may not always translate into improvements in health or costs, and even if they do, secular improvements in other areas of quality improvement may make measuring outcomes attributable to MTM very challenging.

Future training of MTM providers would benefit from a better understanding of which MTM components really matter. At the moment, such information is lacking. Policymakers and funders who wish to understand the comparative effectiveness of different MTM components could encourage rigorous program evaluation designs that fit within the context of the real-world implementation of these programs. For example, positive deviance analyses[77] with rigorous measurement of implementation features or stepped wedge trial designs[78] may be useful approaches.

A typical approach for evaluating complex interventions is to identify the "core" components for standardization, while allowing for flexibility for peripheral components or variations in implementation. In complex practice-based innovations, such flexibility may reflect desirable (or unavoidable) adaptations to local circumstances. Policy governing MTM programs may warrant modifications to permit investigators to conduct rigorous and innovative evaluative designs to identify core components or effectiveness-enhancing modifications. As future research and evaluation elucidates these components or enhancements, policy will need to evolve to keep pace with best practices.

Finally, considering both patients' and prescribers' perspectives in future design and delivery of MTM services may be needed. In our current analytic framework, MTM interventions require a significant element of engagement by both patients and prescribers if the interventions are to have a reasonable likelihood of improving outcomes. Although "opt in" strategies may increase the reach of such interventions, keeping patients (and their prescribing providers) engaged in the intervention over a reasonable amount of time may be the key to translating the potential of MTM interventions into actual improvements.

Limitations of the Comparative Effectiveness Review Process

The constraints for populations, interventions, and settings that we imposed on this systematic review may limit its applicability as discussed above. During topic refinement and based on technical expert panel inputs and public comment, we expanded the scope by removing an exclusion criterion that would have required MTM interventions to have been directed at a patient population with two or more chronic conditions. As a result, we did include studies that focused on one chronic condition. Because of the prevalence of certain chronic conditions in the adult population, and particularly among Medicare beneficiaries, we think this decision was sensible and permitted us to examine a broader evidence base than would otherwise have been the case.

Although we tried to distinguish MTM from disease or case management interventions, making this distinction was challenging. We created a threshold for what intervention components were required to be present for this distinction. Specifically, we elected to emphasize whether the intervention entailed a comprehensive review of all medications; for that reason, we did not constrain studies of interest to those that targeted a single medication or drug regimen or that focused on a single condition such as diabetes or hypertension.

As described in Chapter 2 on Methods, when we were unable to determine which medications the interventionist had reviewed, we wrote to the authors for additional information. We chose to pursue authors in an effort to permit us to use studies that had been designed as MTM but did not describe the comprehensive medication review component in detail.

Our approach may have been overly inclusive because it led us to include studies that addressed a single disease, as long as the pharmacist reviewed all medications. For example, 12

of the 36 studies were relatively narrowly focused; four of these addressed patients with chronic heart failure and two addressed patients with either hypertension or hypertension and diabetes. The remaining six studies focused on post-transplant patients (kidney, lung), diabetes, glucocorticoid-induced osteoporosis, and hemodialysis. The fact that we drew the line at only one intervention component criterion resulted in an approach that was inclusive of these more narrowly focused (albeit often termed "MTM") studies and may render our results less applicable to MTM interventions targeted to patients with a wide range of chronic conditions.

Also based on feedback during the process of setting out the scope of this review, we chose to include interventions that were broader than the Medicare Part D MTM-defined interventions. Put another way, we broadened our view of patient populations and intervention criteria, and we allowed studies not conducted in the United States into the evidence base. This decision led us to include interventions described as "pharmaceutical care," which were generally based on the pharmaceutical care model as described and refined by Strand and associates;[10] it also permitted us to examine investigations with elements of pharmaceutical care or MTM that did not specifically label the intervention as either MTM or pharmaceutical care. These studies were often described as "clinical pharmacist interventions."

Furthermore, all the non-U.S. studies involved interventions within single-payer health systems. Hence, the interventions in this review constitute a more heterogeneous group than if we had allowed only those labeled as Medicare Part D MTM programs. This is both a limitation and a strength. Although our approach makes results more challenging to interpret, it enhances our ability not to miss interventions that include MTM components but lack the descriptor term MTM.

Studies did not often explicitly describe certain MTM components. In cases when we could not determine whether investigators had provided certain MTM components (such as patient education and counseling, medication action plan, or coordination with other health care providers), we again contacted the authors to gain additional information that would allow us to make an informed decision. We were fairly permissive in interpreting the presence of the MTM intervention components other than comprehensive medication review (e.g., medication action plan). The main reason is that we recognized that terms describing some components have evolved over time and may have been absent from the lexicon in earlier years or implicitly conveyed by authors by simply using the terms "MTM" or pharmaceutical care to describe their intervention.

Our approach to categorizing interventions for KQ 1 relied primarily on the short descriptions in published manuscripts and those we were able to obtain via email inquiries. Their similarities or differences substituted for any overarching taxonomy, because none that we considered seemed to fit our purpose. Thus, we have introduced intervention labels that, admittedly, do not fully describe or account for clinical heterogeneity among interventions. This approach limits our ability to make definitive statements about the effectiveness of various intervention components. We believe that the clusters and categorizations we used are useful heuristics, but some may regard them more as hypothesis generating than as reflecting settled principles of classification.

Finally, our search process was complicated by having to ensure coverage of all terms that could be used to describe MTM interventions over time. Adding to this challenge was our effort to examine the gray literature, where we thought we might find studies tilted toward effectiveness and real-world program evaluation. As it turned out, studies of these types of interventions were not indexed similarly; for that reason, we needed to rely heavily on hand

searches of citation lists from key background articles to identify possibly relevant studies for inclusion. Thus, we may have missed some studies that might have qualified for inclusion. Given the considerable diversity in the evidence base we did have, however, and the general lack of data supporting effectiveness of MTM, we do not think that any potential missed studies would have changed our conclusions in any material way. No meta-analyses included more than five studies; as a result, we did not examine included studies for publication bias quantitatively.

Limitations of the Evidence

As a body of evidence, the MTM literature evaluated in this review has measured numerous outcomes. As indicated in previous sections, very few outcomes, with the exception of harms, remain completely unexamined. Of the 36 studies in this review, we rated 22 as having medium or low risk of bias. The 36 studies included 19 trials and 3 nonrandomized controlled studies. In other words, the literature on this topic is not marked by failure to consider important outcomes; neither is it universally of high risk of bias, and it does not reflect pervasively weak designs.

Despite these advantages, we were unable to identify sufficient evidence on the majority of hypothesized outcomes of MTM. In several instances, our inability to rate evidence as higher than insufficient came from indirect, inconsistent, and imprecise evidence. The choice of outcome measures in this body of evidence limited our ability to come to conclusions in some instances. For example, some studies did not focus on changes that proponents might expect MTM services to produce. Because effective MTM can either increase or decrease expenditures or use of services based on the needs of the patient, studies that did not prespecify the expected direction of change had no way to interpret their results as an appropriate change. Studies that demonstrated inconsistent results in direction of change (i.e., some showing an increase in resource use and others showing a decrease) may well have been consistent in terms of appropriate change, but because they generally failed to establish a priori the direction in which they expected to find an effect, we rated such evidence as indirect and inconsistent.

Similarly, studies often used nonstandardized or idiosyncratic measures for outcomes such as adverse events, adherence, and expenditures or costs; this tendency limited our ability to meta-analyze results. When studies focused on specific outcomes, they were often significantly underpowered to detect differences between groups (that is, they did not meet optimal information size criteria). As a result, we rated several studies as imprecise.

MTM intervention studies are largely practice based and incorporate substantial heterogeneity in specific intervention elements and in patient populations targeted. Yet the evidence is sharply constrained in its ability to inform questions of the effectiveness of specific MTM components or intervention features (KQ 3 in our review) because study designs did not often capitalize on variants in MTM programs for a prospective evaluation of outcomes by those variants. Neither did they measure fidelity to intended MTM elements for post-hoc evaluation. Similarly, the relatively untargeted nature of the MTM interventions meant that, in many studies, only small numbers of patients had any one specific condition, and most studies did not measure patient characteristics beyond age and sex, thus limiting our ability to address KQ 4 in our review. For this reason, the evidence we identified for this review was most relevant for KQ 2.

Research Gaps

In many bodies of research, questions regarding the *comparative* effectiveness of specific intervention components or implementation features are best answered after clear evidence of the effectiveness of the intervention relative to usual care has been established. Our review largely

indicates insufficient evidence on the primary question of effectiveness relative to usual care. By definition, this limited what we could say about comparative effectiveness.

Nonetheless, the widespread implementation of MTM coexists with the urgent need for actionable information for policy, program policies, and training. This clinical and policy environment means that new research cannot afford to address causal claims relative to usual care first, followed by comparative effectiveness of the intervention elements in a relatively controlled environment, and finally, program evaluation of real-world implementation, all in sequential order.

In choosing among various research goals, therefore, funders may wish to consider the relative value of new evidence on overall effectiveness, effectiveness of implementation features, and program implementation and accountability. Trial research in narrow clinical settings can address questions of effectiveness but may lack applicability to real-world implementation. Likewise, evaluations of real-world programs with variable fidelity to interventions can answer questions about process and implementation, but they offer limited information on effectiveness.

For new studies focusing on causal claims, a critical gap relates to the failure to specify the expected direction of effect. New research requires a strong theoretical foundation to help specify causal mechanisms and hypothesized effects. Without such an edifice, future research will continue to produce inconsistent and uninterpretable results.

Heightened attention to causal mechanisms will also help researchers convey their understanding of what outcomes these types of interventions are likely to influence. For instance, how should researchers wishing to establish direct causal links between MTM programs and outcomes evaluate distal outcomes such as patient-centered outcomes and resource utilization? This effort requires a better understanding of the relationship between proximal outcomes like "drug therapy problems identified and resolved" and distal outcomes. For instance, MTM may reduce outpatient visits to address side effects. MTM may also result in the need for further testing and evaluation for some patients, which could, in turn, result in more rather than fewer outpatient visits. Unless the nature of change resulting from MTM is specified in relation to goals of drug therapy, studies cannot assert benefit or harm. Further, drug therapy problems are diverse and may not all have the same causal relationship to health, quality of life, patient satisfaction, or resource use outcomes. Furthermore, a causal model of these distal outcomes may need to take into account the competing or complementary contributions of MTM, new models of health care delivery (e.g., patient-centered medical homes), and other quality improvement interventions.

Investigators embarking on new studies focusing on causal links between MTM and outcomes may wish to consider the limitations of studies based on secondary data from existing MTM programs that use opt-in/opt-out patient enrollment mechanisms. Although these studies may provide invaluable information on process measures such as patient engagement, underlying issues of confounding severely limit the validity of causal claims from such studies.

Regardless of the goal of their future research, investigators should consider issues of sample size to ensure precision of their results. This issue is particularly relevant when evaluating outcomes likely to occur in smaller subgroups of patients. Innovative designs (e.g., stepped wedge trials) can permit both rigor and adequate sample size within the context of real-world implementation. With careful attention to fidelity, such designs may also inform questions of the effectiveness of intervention components and implementation features. Such designs may also help inform our understanding of critical training elements for MTM service providers.

Regarding research gaps for specific outcomes such as patient satisfaction, measures specific to the types of services provided through MTM (e.g., patient education about medications) or to the proximal outcomes that MTM is intended to achieve (e.g., reduced medication side effects, improved disease control) may offer better insights into the effects of MTM. Similarly, a medication-related instrument may better measure patients' concerns that are directly related to medication use (e.g., experience of side-effects, intrusiveness of the medication regimen) than generic tools.

Conclusions

We identified 36 studies (14 that we rated as high risk of bias) that offered information on a range of intermediate outcomes, patient-centered outcomes, and resource utilization. Evidence was insufficient on the effect of MTM on most outcomes. For a limited number of outcomes, we found enough evidence to show that MTM results in improvement when compared with usual care (low strength). Specifically, these outcomes include medication appropriateness, the rate of hospitalization among heart failure patients with home medicines review when compared with usual care, and the use of generic medications for patients receiving MTM from community pharmacies when compared with educational mailings. Similarly, we found sufficient evidence to conclude that MTM conferred no benefit for a limited number of outcomes. When MTM is implemented in settings with a broad range of patients, it does not reduce the number of hospitalizations (low strength of evidence). MTM does not improve most measures of health-related quality of life (low strength of evidence). We found evidence on four intervention components and intervention features: one study provided information on each feature and yielded insufficient evidence for most outcomes with two exceptions. MTM programs with pharmacist access to brief clinical summaries from the medical records reduce the mean number of adverse drug events when compared with basic MTM programs without such access (low strength of evidence). Community pharmacists increase the generic dispensing ratio more than call-center–based pharmacists (low strength of evidence). Similarly, the evidence on harms associated with MTM was limited to one study each on confusion and inconvenience and was rated as insufficient.

Investment in new research should be preceded by a careful consideration of goals of research. Studies focusing on causal claims require a strong theoretical foundation, an a priori statement of expected direction of effect that accounts for goals of therapy for each patient, and the use of designs that avoid confounding. Studies focusing on comparative effectiveness of intervention components and implementation features in real-world settings require a careful assessment of fidelity to the intervention components.

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Appendix A. Literature Search Strategies

Published Literature

PubMed. Total of 1521 records retrieved; 1425 records imported after removing duplicates.

PubMed search revision 6-27-13: added British terms for MTM to account for the MEDMAN study.

149 additional results; all imported

Search String	Search Terms	Number of Results
#1	Search “medicine management”[tiab] OR “medicines management”[tiab] Filters: Humans; English	149

PubMed search revision 2-27-13: search re-run while keeping “wildcard” search terms.

26 additional results; all imported

Search String	Search Terms	Number of Results
#1	Search "Medication Therapy Management"[Mesh]	475
#2	Search "medication therapy management"	622
#3	Search "comprehensive medication review"	18
#4	Search "personal medication record"	13
#5	Search ("medication" AND "action plan")	139
#6	Search "medication therapy review"	10
#7	Search "Medication Reconciliation"[Mesh]	168
#8	Search (med* AND reconciliation)	27
#9	Search "medication-related problems"	197
#10	Search MTMP	31
#11	Search prescriber intervention*	223
#12	Search "drug utilization management"	5
#13	Search "chronic care improvement "	13
#14	Search "drug therapy services"	4
#15	Search ("utilization management strategies" OR "utilization management strategy")	17
#16	Search "optimized treatment outcomes"	6
#17	Search ((patient OR patients) AND "medication understanding")	12
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	33
#19	Search "medication counseling"	122
#20	Search "pharmaceutical case management"	11
#21	Search “drug therapy management”	97
#22	Search ("drug therapy problem" OR “drug therapy problems")	82
#23	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)	1694
#24	Search #23 Filters: Humans	1491
#25	Search #23 Filters: Humans; English	1387
#26	Search (#25 AND (2012/10:2013/12[edat]))	26

PubMed search revision 2-18-13: updated final PubMed/Medline "specific" MTM-and-MTM-components search conducted on 11/26/12 by using Entrez date limit of October 2012 to February 2013, which is the date each record was entered into PubMed, as opposed to limiting by publication date.

17 additional results; all imported

Search String	Search Terms	Number of Results
#1	Search "Medication Therapy Management"[Mesh]	472
#2	Search "medication therapy management"	621
#3	Search "comprehensive medication review"	18
#4	Search "personal medication record"	13
#5	Search ("medication" AND "action plan")	139
#6	Search "medication therapy review"	10
#7	Search "Medication Reconciliation"[Mesh]	162
#8	Search (med* AND reconciliation)	27
#9	Search "medication-related problems"	197
#10	Search MTMP	31
#11	Search prescriber intervention*	223
#12	Search "drug utilization management"	5
#13	Search "chronic care improvement "	13
#14	Search "drug therapy services"	4
#15	Search ("utilization management strategies" OR "utilization management strategy")	17
#16	Search "optimized treatment outcomes"	6
#17	Search ((patient OR patients) AND "medication understanding")	12
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	33
#19	Search "medication counseling"	122
#20	Search "pharmaceutical case management"	11
#21	Search "drug therapy management"	97
#22	Search ("drug therapy problem" OR "drug therapy problems")	82
#23	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)	1687
#24	Search #23 Filters: Humans	1476
#25	Search #23 Filters: Humans; English	1372
#26	Search (#25 AND (2012/10:2013/02[edat]))	17

PubMed primary search 11-26-12 – 1190 results, all imported

Search String	Search Terms	Number of Results
#1	Search "Medication Therapy Management"[Mesh]	433
#2	Search "medication therapy management"	582
#3	Search "comprehensive medication review"	17
#4	Search "personal medication record"	13
#5	Search ("medication" AND "action plan")	134
#6	Search "medication therapy review"	10
#7	Search "Medication Reconciliation"[Mesh]	135
#8	Search (med* AND reconciliation)	27
#9	Search "medication-related problems"	193
#10	Search MTMP	31
#11	Search prescriber intervention*	217
#12	Search "drug utilization management"	5
#13	Search "chronic care improvement "	13
#14	Search "drug therapy services"	4
#15	Search ("utilization management strategies" OR "utilization management strategy")	17
#16	Search "optimized treatment outcomes"	6
#17	Search ((patient OR patients) AND "medication understanding")	9
#18	Search ("drug therapy outcome" OR "drug therapy outcomes")	33
#19	Search "medication counseling"	120
#20	Search "pharmaceutical case management"	11
#21	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)	1473
#22	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20) Filters: Humans	1280
#23	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20) Filters: Humans; English MTM terms and specific component terms.	1190

Cochrane Library. Total of 359 records retrieved; 250 imported after removing duplicates.

Cochrane Library search revision 6-27-13: added British terms for MTM to account for the MEDMAN study.

21 additional results; all imported

Search String	Search Terms	Number of Results
#1	"medicine management":ti or "medicine management":ab or "medicines management":ti or "medicines management":ab	21

Cochrane Library search revision 2-27-13: search re-run while removing "wildcard" search terms and conference papers and abstracts.

338 additional results; 337 imported

Search String	Search Terms	Number of Results
#1	MeSH descriptor: [Medication Therapy Management] explode all trees	19
#2	"medication therapy management"	30
#3	"comprehensive medication review"	3
#4	"personal medication record"	1
#5	"medication" and "action plan"	81
#6	"medication therapy review"	0
#7	MeSH descriptor: [Medication Reconciliation] explode all trees	5
#8	"medication reconciliation"	21
#9	"medication-related problems"	32
#10	MTMP	0
#11	"prescriber intervention" or "prescriber interventions"	0
#12	"drug utilization management"	0
#13	"chronic care improvement"	0
#14	"drug therapy services"	0
#15	"utilization management strategies" or "utilization management strategy"	0
#16	"optimized treatment outcomes"	0
#17	(patient or patients) and "medication understanding"	3
#18	"drug therapy outcome" or "drug therapy outcomes"	142
#19	"medication counseling"	19
#20	"pharmaceutical case management"	1
#21	"drug therapy problem" or "drug therapy problems"	16
#22	"drug therapy management"	8
#23	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	338
#24	MeSH descriptor: [Congresses] explode all trees	4
#25	MeSH descriptor: [Congresses as Topic] explode all trees	38
#26	congresses:pt	45
#27	#24 or #25 or #26	83
#28	#23 not #27	338

Cochrane Library primary search 2-18-13: run concurrently with revised PubMed search, but eventually replaced with 2-27-13 search described above.

534 additional results; 532 imported

Search String	Search Terms	Number of Results
#1	MeSH descriptor: [Medication Therapy Management] explode all trees	19
#2	"medication therapy management"	30
#3	"comprehensive medication review"	3
#4	"personal medication record"	1
#5	"medication" and "action plan"	81
#6	"medication therapy review"	0
#7	MeSH descriptor: [Medication Reconciliation] explode all trees	5
#8	med* and reconciliation	47
#9	"medication-related problems"	32
#10	MTMP	0
#11	prescriber intervention*	180
#12	"drug utilization management"	0
#13	"chronic care improvement"	0
#14	"drug therapy services"	0
#15	"utilization management strategies" or "utilization management strategy"	0
#16	"optimized treatment outcomes"	0
#17	(patient or patients) and "medication understanding"	3
#18	"drug therapy outcome" or "drug therapy outcomes"	142
#19	"medication counseling"	19
#20	"pharmaceutical case management"	1
#21	"drug therapy problem" or "drug therapy problems"	16
#22	"drug therapy management"	8
#23	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	534

International Pharmaceutical Abstracts (IPA): total of 684 records retrieved; 454 imported after removing duplicates.

IPA search revision 6-27-13: added British terms for MTM to account for the MEDMAN study.
19 additional results; 18 imported

Search String	Search Terms	Limiters/Expanders	Last Run Via	Number of Results
#1	TI ("medicine management" OR "medicines management") AND AB ("medicine management" OR "medicines management")	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	19

IPA search revision 2-27-13: search re-run while removing "wildcard" search terms.

673 additional results; 666 imported

Search String	Search Terms	Limiters/Expanders	Last Run Via	Number of Results
S22	S21	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	673
S21	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	1,558
S20	"drug therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	243
S19	"drug therapy problem" OR "drug therapy problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	145
S18	"pharmaceutical case management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	14
S17	"medication counseling"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	232
S16	"drug therapy outcome" OR "drug therapy outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	72
S15	(patient OR patients) AND "medication understanding"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International	4

Search String	Search Terms	Limiters/Expanders	Last Run Via	Number of Results
			Pharmaceutical Abstracts	
S14	"optimized treatment outcomes"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	0
S13	"utilization management strategies" OR "utilization management strategy"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S12	"drug therapy services"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	2
S11	"chronic care improvement"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	3
S10	"drug utilization management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	16
S9	"prescriber intervention" OR "prescriber interventions"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	4
S8	MTMP	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10
S7	"medication-related problems"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	199
S6	"medication reconciliation"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	341
S5	"medication therapy review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	10
S4	"medication" AND "action plan"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	80
S3	"personal medication record"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search	12

Search String	Search Terms	Limiters/Expanders	Last Run Via	Number of Results
			Database - International Pharmaceutical Abstracts	
S2	"comprehensive medication review"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	12
S1	"medication therapy management"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - International Pharmaceutical Abstracts	289

IPA primary search 2-18-13: run concurrently with revised PubMed search, but eventually replaced with 2-27-13 search described above.

739 additional results; 679 imported

Search String	Search Terms	Limiters/Expanders	Number of Results
S23	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Limiters - Language: English; Articles about Human Studies Search modes - Boolean/Phrase	739
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Search modes - Boolean/Phrase	1,803
S21	"drug therapy management"	Search modes - Boolean/Phrase	243
S20	"drug therapy problem" OR "drug therapy problems"	Search modes - Boolean/Phrase	145
S19	"pharmaceutical case management"	Search modes - Boolean/Phrase	14
S18	"medication counseling"	Search modes - Boolean/Phrase	232
S17	"drug therapy outcome" OR "drug therapy outcomes"	Search modes - Boolean/Phrase	72
S16	(patient OR patients) AND "medication understanding"	Search modes - Boolean/Phrase	4
S15	"optimized treatment outcomes"	Search modes - Boolean/Phrase	0
S14	"utilization management strategies" OR "utilization management strategy"	Search modes - Boolean/Phrase	4
S13	"drug therapy services"	Search modes - Boolean/Phrase	2
S12	"chronic care improvement"	Search modes - Boolean/Phrase	3
S11	"drug utilization management"	Search modes - Boolean/Phrase	16
S10	prescriber intervention*	Search modes - Boolean/Phrase	95
S9	MTMP	Search modes - Boolean/Phrase	10
S8	"medication-related problems"	Search modes - Boolean/Phrase	199
S7	med* AND reconciliation	Search modes - Boolean/Phrase	508
S6	"medication reconciliation"	Search modes - Boolean/Phrase	341
S5	"medication therapy review"	Search modes - Boolean/Phrase	10
S4	"medication" AND "action plan"	Search modes - Boolean/Phrase	80
S3	"personal medication record"	Search modes - Boolean/Phrase	12
S2	"comprehensive medication review"	Search modes - Boolean/Phrase	12
S1	"medication therapy management"	Search modes - Boolean/Phrase	289

Gray Literature

Search revision 6-28-13: added British terms (“medicine management” OR “medicines management”) for MTM to account for the MEDMAN study.

Total of 14 records retrieved, 13 imported after initial screening.

Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
ClinicalTrials.gov Expert Search Strategy	“medicine management” OR “medicines management”	[ALL-FIELDS] AND (NOT NOTEXT) [FIRST-RECEIVED-RESULTS-DATE]	2 (2)
WHO ICTRP	“medicine management” OR “medicines management”	None	10 (10)
HSRProj Advanced search	“medicine management” OR “medicines management”	None	0
NIH RePORTER Advanced search	“medicine management” OR “medicines management”	None	0
DOPHER (Database of Promoting Health Effectiveness Reviews)	“medicine management” OR “medicines management”	None	0
New York Academy of Medicine Gray Literature Report (greylit.org)	“medicine management” OR “medicines management”	None	0
CMS.gov	“medicine management” OR “medicines management”	“allintitle”, which limited results to those in which “medication therapy management” appeared in title of retrieved websites	2 (1)

Primary searches 3-4-13: 750 records retrieved, 596 imported after removing duplicates.

Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
ClinicalTrials.gov Expert Search Strategy	(“medication therapy management” OR “comprehensive medication review” OR “Medication Reconciliation” OR “pharmaceutical case management” OR “drug therapy management” OR “drug therapy problem” OR “drug therapy problems”)	[ALL-FIELDS] AND (NOT NOTEXT) [FIRST-RECEIVED-RESULTS-DATE]	119 (119)
WHO ICTRP	Title search: medication therapy management OR comprehensive medication review OR Medication Reconciliation OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems Intervention search: was either 41,000+, with the shorter search (see Search Strings #1c and #1d), or no results for “medication therapy management” by itself.	None	5 (5) (Title search); 0 (Intervention search)
HSRProj Advanced search	“medication therapy management” OR “comprehensive medication review” OR “personal medication record” OR (medication AND “action plan”) OR “medication therapy review” OR “Medication Reconciliation” OR “medication-related problems” OR “prescriber intervention” OR “drug utilization management” OR “chronic care improvement” OR “drug therapy services” OR “utilization management strategies” OR “utilization management strategy” OR “optimized treatment outcomes” OR ((patients OR patient) AND “medication understanding”) OR “drug therapy outcome” OR “drug therapy outcomes” OR “medication counseling” OR “pharmaceutical case management” OR “drug therapy management” OR “drug therapy problem” OR “drug therapy problems” [Limited to Ongoing/Completed status]	None	87 (82)
NIH RePORTER Advanced search	medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems	None	234 (85)
DOPHER (Database of Promoting Health Effectiveness Reviews)	1) medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy	None	0 for all search strings

Source	Search Terms	Limits or Adjustments	Number of Results Retrieved (Imported)
	problems 2) “MTM” or “Medication Therapy Management”		
New York Academy of Medicine Gray Literature Report (greylit.org)	1) medication therapy management OR comprehensive medication review OR personal medication record OR (medication AND action plan) OR medication therapy review OR Medication Reconciliation OR medication-related problems OR medication relation problems OR prescriber intervention OR drug utilization management OR chronic care improvement OR drug therapy services OR utilization management strategies OR utilization management strategy OR optimized treatment outcomes OR (patients OR patient) AND medication understanding) OR drug therapy outcome OR drug therapy outcomes OR medication counseling OR pharmaceutical case management OR drug therapy management OR drug therapy problem OR drug therapy problems 2) “MTM” or “Medication Therapy Management”	None	0 for search string #1; 1 (1) for search string #2
CMS.gov	1) “medication therapy management” OR “comprehensive medication review” OR “personal medication record” OR (medication AND “action plan”) OR “medication therapy review” OR “Medication Reconciliation” OR “medication-related problems” OR “prescriber intervention” OR “drug utilization management” OR “chronic care improvement” OR “drug therapy services” OR “utilization management strategies” OR “utilization management strategy” OR “optimized treatment outcomes” OR ((patients OR patient) AND “medication understanding”) OR “drug therapy outcome” OR “drug therapy outcomes” OR “medication counseling” OR “pharmaceutical case management” OR “drug therapy management” OR “drug therapy problem” OR “drug therapy problems” 2) allintitle: "medication therapy management" site:cms.gov	“allintitle”, which limited results to those in which “medication therapy management” appeared in title of retrieved websites	304 (304) total: 295 through CMS.gov directly; 9 indirectly through Google

Appendix B. Abstract and Full-Text Review Form Templates

Abstract Review Form

Ref ID	Author	Year	Include or Exclude? (separate exclusion codes for publication type, PICOTS, and study design)	If ineligible, is manual review or hand search of full-text needed?	If ineligible, potential background reference?	NOTE: The following columns apply only to studies meeting our inclusion criteria	Study Design (RCT, NRCT, Other Study Design)	If "Other Study Design", which specific design does it use? (Cohort, Case-Control, Nonconcurrent Time Series, Other – describe in Comments column)	Comments (e.g., if reviewer included an abstract due to a lack of clarity within the abstract)

Full-text Review Form

Ref ID	First author's last name	Year	Study name (if applicable)	Include or Exclude? (separate exclusion codes for publication type, PICOTS, and study design)	Hand search references? (If so, marked with an "X")	BKG? (If so, marked with an "X")	Comments for INELIGIBLE studies (e.g., additional detail about exclusion reasons)	NOTE: The following columns apply only to studies meeting our inclusion criteria	Study Design (Dropdown list options: RCT, NRCT, Cohort, Case-Control)	KQ(s) (separate sub-columns for KQs 1, 2a, 2b, 2c, 3, 4, and 5, and relevant questions marked with an "X")	Comments for ELIGIBLE studies (e.g., for reviewers to describe "Other" study designs)

Appendix C. List of Studies Excluded after Full-Text Level Review

Ineligible Publication Type (n = 71)

1. Author names not provided. MTM program increased statin use. Dis Manag Advis. 2008 Oct;14(10):suppl 1-3, 1. PMID: 19031586.

2. Author names not provided. What's expected for med reconciliation? OR Manager. 2008 Mar;24(3):21, 3. PMID: 18438074.

3. . Hospitals collaborate to reduce ED overuse. Hosp Case Manag. 2012 Oct;20(10):151-3. PMID: 23091842.

4. Altman JS. Medication therapy management and the new practitioner. Am J Health Syst Pharm. 2007 Mar 15;64(6):590-2. PMID: 17353567.

5. Avery AJ, Rodgers S, Cantrill JA, et al. Correction: Protocol for the PINCER trial: a cluster randomised trial comparing the effectiveness of a pharmacist-led IT-based intervention with simple feedback in reducing rates of clinically important errors in medicines management in general practices. Trials; 2010. p. 23.

6. Bates DW. Role of pharmacists in the medical home. Am J Health Syst Pharm. 2009 Jun 15;66(12):1116-8. PMID: 19498128.

7. Bell JS, Vaananen M, Ovaskainen H, et al. Providing patient care in community pharmacies: practice and research in Finland. Ann Pharmacother. 2007 Jun;41(6):1039-46. PMID: 17504836.

8. Bratcher CR, Bello E. Traditional or centralized models of diabetes care: the multidisciplinary diabetes team approach. J Fam Pract. 2011 Nov;60(11 Suppl):S6-11. PMID: 22336928.

9. Brown EV. Reconcilable differences. Health Manag Technol. 2008 Jan;29(1):12-4, 6. PMID: 18286931.

10. Brusig E, Davies W. PSTAC survey in 2006 was instrumental in obtaining permanent (category I) CPT codes for MTM services performed by pharmacists. J Manag Care Pharm. 2008 Jan-Feb;14(1):86-7. PMID: 18240887.

11. Butler CD. Medication therapy management for adverse drug event preventive care. J Am Pharm Assoc (2003). 2010 Jul-Aug;50(4):449. PMID: 20621858.

12. Cahill JA, Manasse Jr HR. Medication therapy management programs: to optimize pharmacy outcomes. J Manag Care Pharm. 2005 Mar;11(2):179. PMID: 15766326.

13. Cantwell KM. Collaborating for successful medication therapy management programs. Am J Health Syst Pharm. 2005 Mar 15;62(6):583. PMID: 15757878.

14. Carter BL, Malone DC, Billups SJ, et al. Interpreting the findings of the IMPROVE study. Am J Health Syst Pharm. 2001 Jul 15;58(14):1330-7. PMID: 11471481.

15. Carter BL, Zillich AJ, Elliott WJ. How pharmacists can assist physicians with controlling blood pressure. J Clin Hypertens (Greenwich). 2003 Jan-Feb;5(1):31-7. PMID: 12556651.

16. Cauchi R. Medication therapy management: catching errors, saving lives and money. NCSL Legisbrief. 2010 Jan;18(4):1-2. PMID: 20196247.

17. Centers for Medicare & Medicaid Services. Medicare Part D Medication Therapy Management (MTM) Programs: 2009 Fact Sheet. 2009.

18. Centers for Medicare & Medicaid Services. 2010 Medicare Part D Medication Therapy Management (MTM) Programs Fact Sheet. 2010.

19. Centers for Medicare & Medicaid Services. 2012 Medicare Part D Medication Therapy Management (MTM) Programs Fact Sheet. 2012.

20. Cotterell CC, Dombroske L, Fischermann EA. Comprehensive drug-use evaluation program in a health maintenance organization. Am J Hosp Pharm. 1991 Aug;48(8):1712-7. PMID: 1897551.

21. Degnin FD. Difficult patients, overmedication, and groupthink. J Clin Ethics. 2009 Spring;20(1):64-74. PMID: 19385324.

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Ineligible Study Design (n = 44)

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Ineligible Comparator (n = 6)

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Ineligible Outcomes (n = 8)

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Ineligible Setting (n = 7)

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Appendix D. List of Studies on Hold

Articles awaiting author response for final inclusion/exclusion decision (n = 7)

1. Borges AP, Guidoni CM, Ferreira LD, et al. The pharmaceutical care of patients with type 2 diabetes mellitus. Pharm World Sci. 2010 Dec;32(6):730-6. PMID: 20734138.

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5. Kliethermes MA. Adherence in an MTM clinic. 2009. p. 204.

6. Marrufo G, Dixit A, Perlroth D, et al. Medication Therapy Management in a Chronically Ill Population: Interim Report (Prepared by Acumen LLC under Contract #HHSM-500-2011-00012I/TOT#0001.) Baltimore, MD: Services CfMM; 2013.

7. Nguyen J, Matsuoka B, Morodomi L, et al. EVALUATING THE MEDICATION THERAPY MANAGEMENT PROGRAM IMPACT. 2011. p. 11.

Appendix E. Evidence Tables

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Bernsten et al., 2001[1]; Sturgess et al., 2003[2]	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	To identify actual and potential DRPs using a structured approach, and to resolve those problems in collaboration with PCPs using pharmacy-based interventions	1) Aged ≥65 2) Taking ≥4 prescribed medications 3) Oriented with respect to self, time, and place 4) Community-dwelling 5) Regular visitors to recruited community pharmacy	Housebound or resident in nursing/ residential home	RCT: cluster-rando-mized	18	Multiple (Government, foundation, professional organizations, pharmaceutical companies)	NR	Pooled sample Median (IQR) Overall: NR G1: 74 (8) G2: 74 (8) Northern Ireland Mean (SD) Overall: NR G1: 73.1 (5.0) G2: 74.2 (6.3)	Pooled sample Overall: NR G1: 57.9 G2: 57.3 Northern Ireland Overall: NR G1: 63.6 G2: 61.0	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Blenner-hassett et al., 2007[3]	Implementation of a Home Medication Review (HMR) into a chronic heart failure collaborative care model. HMRs were conducted by accredited pharmacists. G2: No HMR	To help implementation of home medicine review and improve medication management	(1) Patient lives at home or in unfunded self-care; (2) At risk for medication mismanagement (e.g., taking five or more medications; suspected non-compliance; taking more than 12 doses per day; difficulty managing because of literacy, language, dexterity, impaired vision, confusion or cognitive difficulties; many changes to their medication regimen; attending multiple doctors; taking medications with a narrow therapeutic index; recent discharge from hospital; symptoms suggestive of an adverse drug reaction; and other (e.g. loss of spouse, recurrent falls).	NR	Cohort	NR	Professional organization	NR	Overall: NR G1: 80.6 G2: 79.9	Overall: NR G1: 59 G2: 46	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Carter et al., 1997[4]; Barnette, Murphy, and Carter, 1996[5]	G1: Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. G2: Usual care	To train community pharmacists to provide HTN monitoring and direct consultation to physicians and nurses	(1) Greater than 18 years of age, with essential HTN (one of the following: average diastolic blood pressure 90 mm Hg or above, average systolic blood pressure 140 mm Hg or above, or current therapy with antihypertensive drugs [controlled or uncontrolled blood pressure]); (2) Receiving care from a physician in the medical center or annex and prescriptions from the clinic pharmacy	(1) Secondary causes of HTN; (2) Unwilling or unable to return to clinic pharmacy for scheduled appointment; (3) Spouse or sibling enrolled in study; (4) BP >210 mm Hg systolic or >115 mm Hg diastolic; (5) Serious complicating disease so disabling that BP control was secondary or minor concern (e.g., terminal cancer, New York Heart Association class III or IV CHF)	Cohort	6 months	Unspecified	Overall: NR, but likely 100% rural G1: NR G2: NR	Mean (range) Overall: NR G1: 67.3 (47-80) G2: 68.5 (40-92)	NR	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Chisholm et al., 2002[6]	G1: Clinical pharmacy services, including reviewing patients' medication therapy with emphasis on controlling BP, and preventing or resolving DTPs. Pharmacists counseled patients about their regimen, including desired clinical responses and possible adverse reactions. G2: Routine transplant clinic services, but without clinical pharmacist interaction. Routine clinical services here entailed meeting a renal transplant clinic team that consisted of 2 nephrologists, a clinical pharmacist, PAs and a nurse.	To improve blood pressure control among African-American renal transplant patients.	African-American patients who received a renal transplant at the Medical College of Georgia (MCG) from November 1996 through March 1998 and met the following criteria: 1) be a minimum of 1 years of age; 2) have received only one renal transplant (primary renal transplant); and 3) have received post-transplant care at the MCG renal transplant clinic. Patients were included in the study regardless of whether or not they had HTN.	See inclusion criteria	RCT: parallel, not clustered	Approximately 30 months	Foundation or non-profit	NR	Overall: NR G1: 51 (16.8) G2: 47 (12.7)	Overall: NR G1: 38.5 G2: 30.0	Overall: 100% African-American

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Chris-chilles et al., 2004[7]	G1: PCM provided by pharmacists G2: Did not receive PCM services	Avoid adverse drug events and the health system costs associated with these adverse events in a Medicaid population at high risk for adverse effects	Noninstitutionalized Iowa Medicaid patients taking four or more long-term medications, including at least one medication representing 1 of specified 12 diseases, were eligible (the 12 diseases were congestive heart disease, ischemic heart disease, diabetes mellitus, HTN, hyperlipidemia, asthma, depression, atrial fibrillation, osteoarthritis, gastroesophageal reflux, pep- tic ulcer disease, and chronic obstructive pulmonary disease) with pharmacy claims at one (or more) of the 117 participating pharmacies.	All patients who were not continuously eligible for Medicaid from 6 months before through 12 months after the date on which they became eligible for PCM.	Cohort	21 months	Multiple (Government and foundation funding)	NR	Overall: 52.5 (20.2) G1: 54.1 (0.8) G2: 48.4 (0.5)	Overall: 71.4 G1: 80.0 G2: 69.3	Overall: NR White G1: 89.1 G2: 90.0 Black G1: 5.9 G2: 5.5 Other G1: 1.0 G2: 2.1 Unknown G1: 4.0 G2: 2.4

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Christen-sen et al., 2007[8]	G1: MTM services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	To assess the feasibility of a pharmacist based medication therapy management service for North Carolina State Health Plan enrollees.	(1) Residence in Orange or Durham County, NC; (2) Among the 1,000 highest number of prescriptions used during the first 6 months of 2004.	NR	NRCT	6 months	Multiple (Third-party payor and foundation)	NR	G1: 67.7 (11.4) G2: 67.6 (12.2) G3: 66.0(12.1)	G1: 62.3 G2: 68.9 G3: 71.3	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Clifford et al., 2002[9]	G1: Pharmaceutical care provided by a clinical pharmacist , which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. G2: Standard outpatient care for diabetes	To improve glycemic control in diabetic patients without adversely affecting QOL or satisfaction with health care provided	Adult patients ≥18 years with type 1 or type 2 diabetes and at least one of the following features indicating high risk for development of diabetes complications: 1) Random blood glucose levels >11 mmol/L on ≥2 occasions in tertiary care setting within previous 12 months; 2) HbA1C >8% on ≥2 occasions in previous 12 months; 3) HTN (SBP >160 mm Hg and/or DBP >90 mm Hg) and/or taking drug therapy; 4) Dyslipidemia (total serum cholesterol >5.5 mmol/L and/or serum triglycerides >4.0 mmol/L); 5) Polypharmacy (>3 drugs)	See inclusion criteria	RCT: parallel, not clustered	6 months	Multiple (Pharmaceutical, professional organization)	NR	Overall: NR G1: 60 (12) G2: 61 (12) p=NS	Overall: NR G1: 42 G2: 52 p=NS	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Fischer et al., 2000[10]	G1: Pharmaceutical care based on Encara Practice System provided by onsite health maintenance organization staff pharmacists G2: Standard community pharmacy practice G3: Patients at eligible clinics who declined to receive intervention but were included in some analyses.	(1) To improve the amount of information patients received; (2) To improve the way patients self-administer medication; (3) To enhance awareness of side effects.	(1) HMO enrollees enrolled in a participating clinic; (2) Had asthma, COPD or heart disease identified via pharmacy or hospital data base medication records.	NR	NRCT	6 months	Foundation or non-profit	NR	Overall: NR G1: 67.2 G2: 68.3 G3: 58.9	Overall: NR G1: 54 G2: 52 G3: 50	% White Overall: NR G1: 98 G2: 96 G3: 92
Fischer et al., 2002[11]	Pharmaceutical care based on Encara Practice System provided by pharmacists. Pharmacist-physician communication about pharmacist-identified DTPs. G2: Usual care with no additional interventions	To assess whether pharmaceutical care program decreases health care utilization, medication use, or charges	(1) Age ≥18; (2) Enrolled in participating HMO for ≥2 years with active prescriptions treating heart or lung disease; (3) Obtained prescriptions from participating pharmacy; (4) Must have filled prescriptions for one of several pre-specified medication types for heart or lung disease in 6 months before study	Died, disenrolled, or discontinued pharmacy benefit before end of study period	NRCT	2 years (1997-98) [one year before intervention initiation and one year after]	Multiple (Pharmaceu-tical companies, third-party payors)	NR	Overall: NR G1: 57 G2: 58	Overall: NR G1: 50 G2: 51	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Fox et al., 2009[12]	G1: Florida Health Care Plans MTM program, consisting of a medication therapy review and evaluation by a clinical pharmacist that was documented and sent to the patient's physician through health plan review G2: Opt-out from MTM program	To reduce LDL-C and improve HEDIS goal attainment among patients with diabetes on lipid-lowering medications	FHCP enrollees who: 1) Were Medicare Part D members; 2) Were diagnosed with ≥3 chronic diseases; 3) Used ≥4 maintenance medications; 4) Were likely to have Part D medication costs ≥$4000 per year; 5) Were eligible for inclusion in 2008 HEDIS comprehensive diabetes care (CDC) administrative dataset	None specified	Cohort	21 months	Unspecified	NR	Overall: NR G1: 67.6 (7.2) G2: 68.3 (6.1)	Overall: NR G1: 45.5 G2: 57.9	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Gattis et al., 1999[13]	G1: Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. G2: Usual medical care	To improve outcomes in outpatients with heart failure.	Patients with a diagnosis of heart failure with LVEF < 45% in a general cardiology clinic at a University Medical Center.	Life expectancy < 6 months; currently participating in a drug trial, primary residence was a skilled nursing facility, marked dementia or other psychological disorder that prevented participation in patient education or follow-up.	RCT: parallel, not clustered	24 weeks	Multiple (Foundation and academic)	NR	Overall: G1: 71.5 (25%: 60, 75% : 77) G2: 63.0 (25%: 55, 75% : 72)	Overall: NR G1: 31 G2: 33	White Overall: NR G1: 80 G2: 79

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Hanlon et al., 1996[14]	G1: Pharmaceutical care provided by a clinical pharmacist G2: Usual care in the General Medicine Clinic	To evaluate the effect of sustained clinical pharmacist interventions involving elderly outpatients with polypharmacy and their primary care physicians on: prescribing appropriateness, health-related quality of life, adverse drug events, medication compliance and knowledge, number of medications used, patient satisfaction, and physician receptivity	(1) Age ≥65; (2) Had evidence of polypharmacy operationally defined as prescribed 5+ regularly scheduled medications by a VA physician; (3) Receiving primary care in the General Medicine Clinic.	1) Nursing home residence; 2) Patients with cognitive impairment, as determined by the Mental Status Questionnaire; 3) No caregiver available to be involved in the intervention	RCT: parallel, not clustered	One year	Government	NR	Overall: NR G1: 69.7 (3.5) G2: 69.9 (4.1)	Overall: NR G1: 1.9 G2: 0	White Overall: NR G1: 79 G2: 74.8

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Harrison et al., 2012[15]	G1: Pharmaceutical care provided by a clinical pharmacist for the purpose of identifying and resolving actual and potential drug therapy problems, medication teaching, adherence optimization, medication reconciliation, and provision of drug information. G2: Retrospective historical control of matched patients who received standard care at a routine medical visit within 8 months prior to study period	Primarily focused on reducing DTPs, but study also assessed recommendations made and patient satisfaction with service.	(1) All new lung transplant recipients; (2) Referrals for medication-related concerns were also accepted from interprofessional team or at patient's request; (3) Control group patients identified from the 8 months before study period were matched with study patients for time post-transplant.	NR	Cohort	NR	Unfunded	NR	Mean or median age NR. Only % within 3 specified ranges reported. Ages 18-39 G1: 12% G2: 30% Ages 40-59 G1: 51% G2: 47% Ages >60 G1: 37% G2: 23%	Overall: 44 G1: 44 G2: 44	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Isetts et al., 2008[16]	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM	(1) To provide MTM services to patients; (2) to measure clinical effects associated with MTM, (3) to measure percent of patients achieving goals for HTN and hyperlipidemia in MTM vs. comparison; and 4) to compare patients' total health expenditures for the year before and after MTM	Patients in intervention group: 1) Enrolled in Blue Plus insurance product of Blue Cross BlueShield of Minnesota; (2) Age ≥18 years; (3) Receiving medical care at one of 6 clinics in Fairview, MN where MTM services provided; (4) Diagnosed with ≥1 of 12 study medical conditions, (5) ≥2 health care claims related to 12 study conditions in 6-month period before the start of the study.	NR	Cohort	12	Academic	NR	Overall: NR G1: 14% were age 65 or older G2: NR	Overall: NR G1: 66 G2: NR	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Jameson, VanNoord, and Vanderwoud, 1995[17]	Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	To simplify the pharmacologic regimen, improve effectiveness of the regimen, and decrease side effects. Secondary goal to decrease cost without adversely affecting the first three goals. Improved clinical outcomes (decreased number of medications, decreased number of doses per day, monthly cost of medications, patient self-reported compliance, drug regimen convenience, fewer side effects and problems).	All patients at a Family Health Center seen during a 1 year period with 2 or more risk factors: 5 or more medications, 12 or more daily doses, 4 or more medication changes in last 12 months, more than 3 disease states, documented medication noncompliance, medications that require therapeutic monitoring.	Active alcohol or illicit drug use, unwilling or unable to return for a pharmacotherapy consultation, medication regimen primarily managed by an outside provider, terminally ill, less than 18 years of age.	RCT: parallel, not clustered	6 months	Multiple (Foundation or non-profit, academic, and pharmaceutical)	NR	Overall: 60.5 G1: NR G2: NR	Overall: 80 G1: NR G2: NR	African American Overall: 28 G1: NR G2: NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Jeong et al., 2007[18]	G1: Pharmacist-managed MTMP provided by ambulatory care pharmacists and healthcare support staff G2: Eligible for Part D MTMP but declined enrollment G3: Patients without Part D as their primary drug benefit	NR	Patients who: 1) Were likely to incur >$4,000 in drug costs per year 2) Received ≥2 Part D medications 3) Had ≥2 chronic conditions 4) Had a diagnosis of hyperlipidemia, diabetes, or CAD for LDL-C analysis 5) Had a diagnosis of diabetes for HbA1c analysis 6) Had a lab (LDL-C or HbA1c) within 6 months before and 6 months after index date	See inclusion criteria	Cohort	12 months	Integrated health care system (Kaiser Permanente)	NR	Overall: NR G1: 72 (10) G2: 71 (11) G3: 74 (7)	Overall: NR G1: 53 G2: 55 G3: 52	NR
Krska et al., 2001[19]	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	To study the effect of medication review led by a pharmacist on resolution of pharmaceutical care issues medicine costs, use of health and social services and health-related quality of life	Patients aged at least 65 years with at least two chronic disease states, taking at least 4 prescribed medicines regularly	Dementia, being considered by the GP to be unable to cope with the study	RCT: parallel, not clustered	3 months	Government	NR	Overall: NR G1: 74.8 (6.2) G2: 75.2 (6.6) p=0.972	Overall: NR G1: 56.5 G2: 64.6 p=0.132	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al., 2001[22]; Ellis et al., 2000[23] IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities. G2: Usual care without pharmaceutical care	Determine if clinical pharmacists could change resource use and humanistic outcomes among Veterans identified at high risk for medication-related problems.	1) High risk for drug-related problems (were taking 5 or more drugs, 12 or more doses/day, had 3 or more chronic medical conditions, 4 or more changes in their drug regimen over the past year, history of nonadherence or taking an agent that required therapeutic drug monitoring); 2) Received care at the VA within the past 12 months and anticipated continued VA care for the duration of the study; 3) Lived close/had transportation to VA.	1) Participation in a pharmacist managed clinic within previous 12 months; 2) Terminal condition/poor life expectancy; 3) Required mental health services; 4) Poor spoken or written English; 5) Visually impaired.	RCT: parallel, not clustered	12 months	Pharmaceutical	Overall: 67 (10.1) G1: 66.8 (10.2) G2: 66.6 (10.0)	Overall: NR G1: 3.6 G2: 3.8	NR	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
McDonough et al., 2005[24]	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of does, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	To reduce risk of glucocorticoid osteoporosis.	Patients 18 years of age or older who had been on the equivalent of at least 7.5 mg of prednisone for at least 6 months	NR	RCT: cluster-randomized	9 months	Multiple (Pharmaceutical company and academic)	NR	NR	Overall: NR G1: 57.7 G2: 74.3	Caucasian or Asian Overall: NR G1: 92.3 G2: 84.3

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Moczygemba et al., 2011[25]; Moczygemba et al., 2008[26]	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. G2: No-MTM control group	To identify and resolve medication and health-related problems	Medicare Part D beneficiaries of the Scott & White Health Plan with: 1) ≥2 chronic diseases 2) ≥2 Part D drugs 3) ≥$4000 in Part D drug costs 4) Received ≥1 MTM consultation	Patients ≥90 years of age due to patient privacy concerns	Cohort	9	Foundation or non-profit	NR	Mean (SD) Overall: NR G1: 71.2 (7.5) (range: 53-86) G2: 73.9 (8.0) (range: 46-88) p: 0.06	Overall: NR G1: 48.3 G2: 71.7 p: 0.009	White Overall: NR G1: 78.3 G2: 91.7 p: 0.29

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Pai et al., 2009[27]; Pai et al., 2009[28]	G1: Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	To investigate the impact of a pharmaceutical care program managed by clinical pharmacists on drug use, drug costs, hospitalization rates, and drug-related problems (DRPs) in ambulatory patients undergoing hemodialysis.	To participate in the study, patients had to speak English, and be older than 18 years and undergoing a stable hemodialysis regimen for at least 3 months. Informed consent was obtained from each patient before starting the study, with a consent rate of 70%.	If patients elected not to consent or were unable to provide informed consent, they continued to receive the care that their shift was assigned; however, no data from these patients were collected or analyzed.	RCT: cluster-randomized	2 years	Foundation or non-profit	NR	Overall: 59.0 (15.0) G1: 56.3 (15) G2: 60.5 (14.7)	Overall: 48.1% G1: 38.6% G2: 59.6%	Caucasian Overall: 27.9% G1: 22.8% G2: 34.0% Hispanic Overall: 30.8% G1: 29.8% G2: 31.9% Native American Overall: 17.3 G1: 22.8% G2: 10.6% Other Overall: 24.0% G1: 24.6% G2: 23.4%
Park et al., 1996[29]	G1: Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. G2: Usual care	Improve blood pressure and quality of life for patients with HTN.	Patients with HTN either currently taking anti-hypertensive medication or with a BP > 140/90.	Bedridden; non-English speaking; had another family member enrolled in the study.	RCT: parallel, not clustered	4 months	Unspecified	NR	Overall: NR G1: 57.3 (range 29-82) G2: 63.0 (Range 23-88)	Overall: NR G1: 44 G2: 41	% white G1: 81 G2: 69

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Pindolia et al., 2009[30]	G1: Telephone-based MTM services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors). G2: Usual medical care (refusers)	To 1) ensure that safest, most efficacious, and cost-effective drug therapy is provided by collaborating with physicians and patients/care givers in the development of an optimal drug regimen that meets both medical and patient needs; (2) educate patients on all aspects of their drug therapy; and (3) improve adherence to drug therapy regimens	In 2006: 1) Diagnosed with 2 of 26 selected chronic diseases; 2) Filled ≥2 prescriptions as identified by pharmacy claims data; 3) Likely to incur annual costs of ≥$4000 for all Medicare Part D-covered medications based on quarterly prescription drug expenditures of $1000 In 2007: 1) Diagnosed with 3 of 21 selected chronic diseases; 2) Filled ≥4 prescriptions as identified by pharmacy claims data; 3) Likely to incur annual costs of ≥$4000 for all Medicare Part D-covered medications based on monthly prescription drug expenditures of $334	NR	Cohort	2 years	Unspecified	NR	2006 Mean (SD) [range] Overall: NR G1: 73.5 (9.7) [42-92] G2: 74.2 (9.8) [32-96] p: 0.229 2007 Mean (SD) [range] Overall: NR G1: 73.0 (9.1) [39-93] G2: 73.9 (9.8) [33-98] p: 0.168	2006 Overall: NR G1: 64 G2: 60 p: 0.175 2007 Overall: NR G1: 54 G2: 63 p: 0.01	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Planas et al., 2009[31]	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	To improve BP and antihypertensive medication adherence in patients with both diabetes and HTN	Members of managed care organization (MCO) already enrolled in concurrent study of community pharmacy-based diabetes management program. Criteria for diabetes study: (1) Lack of diabetes control (i.e., most recent A1C within last 6 months >7.0%) (2) ≥18 years old (3) Currently insured by MCO (4) Able and willing to come to periodic visits during a 9-month period Criteria for HTN study: (1) Present at baseline diabetes study visit (2) BP ≥130/80 mm Hg or currently taking antihypertensive therapy	(1) Pregnant; (2) Currently enrolled in another diabetes program	RCT: parallel, not clustered	9 months	Multiple (Foundation and pharmacy chain)	NR	Overall: NR G1: 64.2 (10.5) G2: 65.2 (14.1)	Overall: NR G1: 65.6 G2: 60.0	White Overall: NR G1: 75.0 G2: 90.0 Black Overall: NR G1: 21.9 G2: 10.0 Hispanic Overall: NR G1: 3.1 G2: 0

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Roughead et al., 2009[32]	G1: Home Medication Reviews (HMR), a collaborative model of pharmaceutical care, conducted by accredited pharmacists. G2: No medication review received	To reduce time to next hospitalization for heart failure (HF) among Australian war veterans and war widows with HF	Community-dwelling elderly who: 1) Had all health services fully subsidized by Australian Government's Department of Veterans' Affairs (DVA); 2) Were dispensed beta-blocker subsidized for HF in 6 months before the HMR; 3) Were aged ≥65 years at the time of home review	1) Residents in aged-care facilities	Cohort	40 months	Government	Region of residence Remote Overall: NR G1: 0 G2: 1 Outer regional Overall: NR G1: 12 G2: 9 Inner regional Overall: NR G1: 29 G2: 31	Median (SD) Overall: G1: 81.6 (4.8) G2: 81.6 (4.8)	Overall: NR G1: 30 G2: 26	NR
Sellors et al., 2003[33]	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes	Reducing regimen complexity and improving patient outcomes	1) Community dwelling; 2) 65 years or older; 3) taking 5 or more medications; 4) had been seen by their physician within the past 12 months; 5) had no evidence of cognitive impairment; and 6) could understand English	1) Had planned surgery, 2) were on a nursing home waiting list or 3) were receiving palliative care	RCT: cluster-randomized	3 months	Multiple (Government and hospital)	NR	Overall: NR G1: 74.0 (6.1) G2: 74.0 (6.0)	Overall: NR G1: 277 (64.3) G2: 281 (61.4)	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Sidel et al., 1990[34]	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	To determine the prevalence of use of prescription and OTC medications and home remedies, to characterize medication taking behaviors and practices, and to assess the impact of in-home pharmacist intervention in identifying and correcting problems with medication use	(1) All Medicare recipients 65 years or older living in the Norwood area eligible; (2) Patients who were considered "high risk" by baseline RAP questionnaire	(1) Patients considered reluctant or difficult; (2) Those who died or moved during identification and assignment	RCT: parallel, not clustered	6-11 months	Government	Overall: 0	65-74 years G1: 48.4% G2: 48.1% 75-84 years G1: 38.5% G2: 41.4% 85 years and older G1: 13.2% G2: 10.6%	Overall: NR G1: 76.9 G2: 77.9	Non-White G1: 7.7 G2: 6.7 Hispanic G1: 4.4 G2: 7.7

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Staresinic et al., 2007[35]	G1: MTM services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist G2: Usual care provided to MTM-eligible enrollees who chose not to participate	To ensure that drugs prescribed to beneficiaries are appropriately used to optimize therapeutic outcomes and lower the risks of adverse drug events and drug interactions.	(1) PDP beneficiaries who fill at least two Part D covered drugs for ≥2 chronic diseases of interest, including, but not limited to, asthma, CD, CHF, diabetes, dyslipidemia, and HTN (specific disease states varied by PDP); (2) Additional independent eligibility criteria included an extrapolated annual drug cost (set by the Secretary of DHHS) of $4000 or more by the end of the plan year. Long-term care residents eligible.	CMS-mandated exclusions including any one of following: use of OTC drugs, vitamins, drugs for cosmetic use, medications to treat cold or cough symptoms, fertility agents, DESI drugs, and drugs not covered under Part D.	Cohort	NR	Unspecified	NR	<45 years Overall: 6.8% G1: 2.1% G2: 7.7% 45-64 years Overall: 29.2% G1: 25.9% G2: 29.9% ≥65 years Overall: 63.9% G1: 72.0% G2: 62.4%	Overall: 61.3 G1: 58.2 G2: 61.9	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Taylor, Byrd, and Krueger, 2003[36]	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	Prevention, detection and resolution of medication-related problems in high-risk patients in a rural community.	(1) Age ≥18 years; (2) Receiving care at participating clinic; (3) Identified as high risk for medication-related adverse event (defined as ≥3 of following risk factors: 5+ medications, 12+ doses per day, 4+ medications changes in the previous year, 3+ concurrent diseases, history of medication noncompliance, presence of drugs that require therapeutic monitoring)	(1) Significant cognitive impairment; (2) History of missed office visits; (3) Scheduling conflicts; (4) Life expectancy of <1 year	RCT: parallel, not clustered	12 months	Foundation or non-profit	Overall: 100	Overall: NR G1: 64.4 (13.7) G2: 66.7 (12.3)	Overall: NR G1: 63.6 G2: 72.2	White Overall: NR G1: 60.6 G2: 61.1

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Touchette et al., 2012[37]	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	To improve the safety of medication by reducing ADEs and DRPs; Also to reduce health care, especially ED visits.	1) Age ≥65 years; (2) Primary use of English for written and oral communication; (3) Telephone access for the study's duration; (4) Presence of ≥3 comorbid chronic conditions associated with increased health care use; (5) >2 visits to clinic provider during previous year; (6) >6 chronic prescription medications during 6 months before enrollment; (7) >1 recent situations placing patient at higher risk of DRP (i.e., ≥3 different health care providers visited in the last 12 months; any medication change, new physician visit, ED visit, hospitalization; or invasive procedure [requiring stopping medications] in previous 30 days).	1) Presence of a terminal condition with life expectancy of 6 months or less; 2) Previous enrollment in MTM program involving comprehensive medication review in previous 12 months.	RCT: parallel, not clustered	6 months	Government	NR	Overall: 74.6 (6.7) G1: 74.5 (6.6) G2: 74.8 (6.8) G3: 74.6 (6.8)	Overall: 66.2 G1: 63.0 G2: 67.0 G3: 68.3	Black Overall: 51.2 G1: 48.3 G2: 49.1 G3: 56.3 Hispanic Overall: 4.4 G1: 6.2 G2: 2.3 G3: 4.8 Asian Overall: 0.8 G1: 0.5 G2: 0.9 G3: 1.0 American Indian Overall: 0.3 G1: 0 G2: 0 G3: 1.0

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Triller and Hamilton, 2007[38]	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services only	Study conducted to determine whether comprehensive pharmaceutical care services for home care patients with heart failure who were receiving visiting nurse association services could significantly reduce the rate of all-cause hospitalization or death.	(1) Patients with primary or secondary diagnosis of HF documented in the medical record or billing system who were referred from Northeast Health inpatient facilities to Eddy VNA for skilled nursing services; (2) Age ≥21 years; (3) Residence in Albany, Rensselaer or Saratoga county; (4) Patients must have received at least 3 days of care from VNA and ≥1 pharmacist to be included in final study analysis; (5) Non-English speaking patients included only if adequate translation services available from family or friends.	(1) Individuals without telephone service; (2) Individuals, who, due to disability or illness, lacked the mental capacity to provide informed consent	RCT: parallel, not clustered	24	Foundation or non-profit	NR	Overall: NR G1: 81.3 (9.3) G2: 78.1 (11.2)	Overall: NR G1: 73 G2: 72	White Overall: NR G1: 97 G2: 88

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Volume et al., 2001[39]; Kassam et al., 2001[40] PREP	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists. G2: Traditional pharmacy care	Authors describe the goal of pharmaceutical care as the "improvement of patient outcomes and quality of life." They add study objective to be to describe changes in intermediate and primary outcomes after the provision of pharmaceutical care.	Pharmacies: 1) Participation of pharmacists working >8 hours a week dispensing medications; 2) Agreement to participate in practice enhancement program; 3) Agreement to conform with professional standards developed by Alberta Pharmaceutical Association; 4) Alberta Blue Cross Billings represented at least one-third of pharmacy billings; 5) Located ≤200 miles of Edmonton. Patients: 1) >65 years; 2) Prescription medication coverage under Alberta Health and Wellness' Senior Health Plan; 3) Use ≥3 medications concurrently; 4) Residing in Alberta for 12 of 15 study months; 5) Agree to receive prescription medications only from study pharmacy during study period	Patients: 1) Individuals with terminal disease; 2) Could not communicate in English; 3) Could not complete telephone interviews.	RCT: cluster-randomized	12 to 13 months	Multiple (Government, foundation, and pharmaceutical)	NR	Mean (SD) Overall: 74 (NR) G1: 73.9 (6.1) G2: 73.2 (6.1)	Mean (SD) Overall: NR G1: 63.5 G2: 69.6	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Welch et al., 2009[41]	G1: MTM program provided to home-based beneficiaries as part of a Medicare Part D MTM program G2: No-MTM control group (voluntary opt-out)	To reduce mortality, inpatient hospitalizations, ED visits, and Part D-covered medication costs	1) MTM-eligible Kaiser Permanente Colorado (KPCO) beneficiaries; 1) Had ≥2 chronic conditions, one of which was considered high risk; 2) Receiving 5 or more Part D–covered medications; 3) Likely to incur at least $4000 in total costs for Part D–covered medications.	KPCO beneficiaries with end-stage renal disease (ESRD)	Cohort	180 days	Integrated health care system (Kaiser Permanente Colorado)	NR	Mean (SD) Overall: NR G1: 68.8 (10.7) G2: 68.9 (11.3) p=0.949	Overall: NR G1: 56.6 G2: 54.5 p=0.541	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Williams et al., 2004[42]	G1: Medication review and optimization of patient's medication regimen conducted by an interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	To promote regimen changes to simplify regimens in elders taking multiple medications and to see whether these changes improved functioning.	1) Age ≥65 years; 2) Cognitively intact (no evidence of dementia or cognitive dysfunction in the medical record); 3) Minimum of 5 prescription medications, of which 2 had to be potentially problematic for geriatric patients.	NR	RCT: parallel, not clustered	6 weeks	Unspecified	NR	G1: 73.5 (5.9) G2: 73.9 (5.6)	G1: 65.1 G2: 50.6	White G1: 79.4 G2: 76.6 Non-White G1: 20.6 G2: 23.4

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Winston and Lin, 2009[43]	G1: MTM provided in a community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of a Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of a Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Describe experiences with MTM services delivered to beneficiaries of Mirixa's health plan clients	Patients who qualified for MTM services between April 1, 2007 and June 30, 2007. MTM qualification determined by each participating health plan; generally patients who had increased cardiovascular risk due to diabetes and HTN and/or dyslipidemia	(1) Patients whose coverage was discontinued for any reason; (2) Patients who received additional pharmacist-provided services (i.e., formulary review or other MTM) during intervention period.	Cohort	Unclear	Private MTM and pharmacy-delivered service provider	NR	Overall: NR G1: 67.4 (13.1) G2: 67.8 (12.8) G3: 66.5 (13.4)	Overall: NR G1: 70.4 G2: 70.5 G3: 69.5	NR

Table E1. Study and patient-level characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Intervention Goal	Inclusion Criteria	Exclusion Criteria	Study Design	Study Duration	Funding Source(s)	Baseline % Rural	Baseline Age – Mean (SD) or Median (Range)	Baseline % Female	Race/ Ethnicity %
Witry, Doucette, and Gainer, 2011[44]	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided by community pharmacists to patients with private individual-group insurance	To decrease the risk of DRPs	(1) Patients ≥1 chronic condition (i.e., who filled a medication commonly used to treat 1 of 12 chronic conditions, as defined by Medicaid PCM program, at least twice during 3 months prior to screening date); (2) Must have filled ≥4 unique, nontopical medications during 3 months prior to screening date; (3) Patrons of study pharmacies, meaning that ≥50% of patients' prescription claims were paid to those pharmacies	See inclusion criteria	Cohort	21 months	Foundation or non-profit	NR	Mean (SD) Overall: NR G1: 54.1 (0.8) G2: 58.9 (7.51)	Mean (SD) Overall: NR G1: 80 G2: 68.1	NR

Abbreviations: CHF = chronic heart failure; CMR = comprehensive medication review; CMS = Centers for Medicare and Medicaid Services; DHHS = Department of Health and Human Services; DRP = drug-related problem; ED = emergency department; ESRD = end-stage renal disease; GP = general practitioner; HF = heart failure; HMR = home medication review; HTN = hypertension; KPCO = Kaiser Permanente Colorado; mm Hg = milligrams mercury; MTM = medication therapy management; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drugs; OTC = over-the-counter; PCM = pharmaceutical case management; PREP = Pharmaceutical Care Research and Education Project; RCT = randomized controlled trial; SD = standard deviation; US = United States; VNA = visiting nurse agency.

Table E2. Other patient-level and clinical characteristics

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Bernsten et al., 2001[1]; Sturgess et al., 2003[2]	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	RCT: cluster-randomized	Pooled sample Patients living alone (%) Overall: NR G1: 37.2 G2: 37.7 Patients requiring help with daily activities (%) Overall: NR G1: 50.9 G2: 47.4 Northern Ireland Patients living alone (%) Overall: NR G1: 30.9 G2: 26.9 Patients requiring help with daily activities (%) Overall: NR G1: 43.1 G2: 55.7	NR	NR	Pooled sample Overall: NR G1: 7.1 (2.5) G2: 7.0 (2.5) p=NS Northern Ireland Overall: NR G1: 5.9 (1.9) G2: 6.7 (1.9) P<0.05	
Blennerhassett et al., 2007[3]	Implementation of a Home Medication Review (HMR) into a chronic heart failure collaborative care model. HMRs were conducted by accredited pharmacists. G2: No HMR	Cohort	Smoking Status – Never (%) Overall: NR G1: 52 G2: 42 Smoking Status – Ex (%) Overall: NR G1: 28 G2: 20 Smoking Status – Current (%) G1: 3 G2: 5	NR	Atrial Fibrillation Overall: NR G1: 32 G2: 12 Cerebrovascular Accident/Transient Ischemic Attack Overall: NR G1: 18 G2: 5 Diabetes: Overall: NR G1: 27 G2: 15 Chronic Heart Failure Overall: 100 G1: 100 G2: 100	NR	Manage own medications G1: 36% G2: 71% p = 0.016

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Carter et al., 1997[4]; Barnette et al., 1996[5]	G1: Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. G2: Usual care	Cohort	NR	N of comorbid conditions Overall: NR G1: 3.5 (2.4) G2: 3.2 (2.0) p=0.47	No. (%) with controlled blood pressure at baseline	Overall: NR G1: 13 (52) G2: 14 (54)	

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Chisholm et al., 2002[6]	G1: Clinical pharmacy services, including reviewing patients' medication therapy, with an emphasis on controlling blood pressure, and preventing or resolving drug therapy problems. Pharmacists counseled patients about their regimen, including desired clinical responses and possible adverse reactions. G2: Routine clinic services, but without clinical pharmacist interaction. Routine clinical services here entailed meeting a renal transplant clinic team that consisted of 2 nephrologists, a clinical pharmacist, PAs and a nurse.	RCT: parallel, not clustered	NR	NR	Hypertension (%) Overall: NR G1: 92 G2: 90	NR	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Chrischilles et al., 2004[7]	G1: PCM provided by pharmacists G2: Did not receive PCM services	Cohort	NR	NR	NR	Overall: NR G1: 7.5 (0.2) G2: 6.9 (0.1)	NR
Christensen et al., 2007[8]	G1: MTM services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	NRCT	NR	NR	Patients younger than 65: Hypertension G1: 48.1 G2: 47.9 G3: 46.4 >1 Condition G1: 42.8 G2: 34.0 G3: 38.3 Diabetes G1: 37 G2: 31.7 G3: 37.7 Patients older than 65: Hypertension G1: 62.5 G2: 41.5 G3: 48.5 Cardiovascular Disease G1: 55.0 G2: 48.4 G3: 50.2 >1 Condition G1: 46.3 G2: 39.7 G3: 39.9 Diabetes G1: 45.0 G2: 36.8 G3: 33.7	Patients younger than 65: G1: 40.3 (15.3) G2: 37.2 (17.5) G3: 36.9 (17.3) Patients older than 65: G1: 41.7 (16.3) G2: 38.4 (16.3) G3: 41.7 (16.2)	Differences in % with selected conditions and in number of baseline medications were not significant among the three groups.

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Clifford et al., 2002[9]	G1: Pharmaceutical care provided by a clinical pharmacist , which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. G2: Standard outpatient care for diabetes	RCT: parallel, not clustered	NR	NR	Type 1 or 2 Diabetes Overall: 100 G1: 100 G2: 100 Type 1 Diabetes Overall: NR G1: 29.2 G2: 20.0 Type 2 Diabetes Overall: NR G1: 70.8 G2: 80.0 Hypertension: NR Dyslipidemia: NR	NR	

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Fischer et al., 2000[10]	G1: Pharmaceutical care based on the Encara Practice System provided by onsite health maintenance organization staff pharmacists. G2: Standard Community Pharmacy Practice G3: A set of refusers surveyed and included in some analyses among those who were at eligible clinics but initially declined to participate.	NRCT	% Married Overall: NR G1: 68 G2: 71 G3: 72 % Education < HS Overall: NR G1: 9 G2: 18 G3: 20 % Income < 10K Overall: NR G1: 3 G2: 9 G3: 9	% in Fair or Poor Health Overall: NR G1: 28 G2: 26 G3: 35	% Heart/HTN problems Overall: NR G1: 68 G2: 61 G3: 65 % Asthma/Lung Problems Overall: NR G1: 49 G2: 52 G3: 42	Overall: NR G1: 5.2 G2: 4.6 G3: 4.3	Mean N non-prescription meds: Overall: NR G1: 2.2 G2: 1.8 G3: 1.7
Fischer et al., 2002[11]	Pharmaceutical care based on the Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care with no additional interventions.	NRCT	Annual health care charges Overall: NR G1: $9,600 G2: $11,000	Charlson Index G1: 1.2 G2: 1.3	Heart disease (%) Overall: NR G1: 43 G2: 40	Overall: NR G1: 9.1 G2: 9.4	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Fox et al., 2009[12]	G1: Florida Health Care Plans MTM program, consisting of a medication therapy review and evaluation by a clinical pharmacist that was documented and sent to the patient's physician through health plan review G2: Opt-out from MTM program	Cohort	NR	NR	Diabetes: 100	Number of prescriptions per member per month (PMPM) in 2007 Overall: NR G1: 9.4 G2: 8.8	None
Gattis et al., 1999[13]	G1: Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. G2: Usual medical care	RCT: parallel, not clustered	NR	NR	Heart Failure Overall: 100 G1: 100 G2: 100	Overall: NR G1: 6.5 (25%: 5, 75%: 8) G2: 6 (25%: 4.5, 75%: 8)	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Hanlon et al., 1996[14]	G1: Pharmaceutical care provided by a clinical pharmacist G2: Usual care in the General Medicine Clinic	RCT: parallel, not clustered	Married (%) Overall: NR G1: 65.7 G2: 85.4 Mean years of education (SD) Overall: NR G1: 10.2 (3.8) G2: 9.9 (4.2)	N of chronic conditions Overall: NR G1: 9.2 (3.7) G2: 9.0 (3.0)	NR	Overall: NR G1: 7.6 (2.8) G2: 8.2 (2.7) These were limited to medications prescribed by a VA physician.	% of medications for which compliant Overall: NR G1: 73% G2: 74%
Harrison et al., 2012[15]	G1: Pharmaceutical care, provided by clinical pharmacist for purpose of identifying and resolving actual and potential DTPs, medication teaching, adherence optimization, medication reconciliation, and provision of drug information. G2: Retrospective historical control of matched patients who received standard care at a routine medical visit within 8 months prior to study period	Cohort		NR	NR	NR	Authors provide information on cause of need for lung transplant, but not a list of comorbidities.

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Isetts et al., 2008[16]	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM	Cohort	NR	Mean Number of Conditions Overall: NR G1: 6.4 (NR) G2: NR	NR	Overall: NR G1: 14% were age 65 or older G2: NR	These variables were not reported for the HEDIS comparison group other than a statement that says "…were similar to intervention group patients in terms of age, gender, and presence of study medical conditions." (bottom of page 205)
Jameson, VanNoord, and Vanderwoud, 1995[17]	Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	RCT: parallel, not clustered	NR	More than 3 chronic diseases Overall: NR G1: 70% G2: 76%	NR	5 or more long-term medications (%) Overall: NR G1: 89 G2: 90	NR
Jeong et al., 2007[18]	G1: Pharmacist-managed MTMP provided by ambulatory care pharmacists and healthcare support staff G2: Eligible for Part D MTMP but declined enrollment G3: Patients without Part D as their primary drug benefit	Cohort	NR	NR	Hyperlipidemia Overall: NR G1: 65.1 G2: 63.1 G3: 58.6 CAD Overall: NR G1: 28.3 G2: 24.8 G3: 26.1 Diabetes Overall: NR G1: 54.8 G2: 48.1 G3: 46.9	NR	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Krska et al., 2001[19]	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	RCT: parallel, not clustered	NR	Overall: NR G1: 3.9 (1.4) G2: 3.8 (1.4) p=0.968	NR	Repeat medicines on computer records Overall: NR G1: 7.4 (2.7) G2: 7.7 (2.8) p: 0.951	NR
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al., 2001[22]; Ellis et al., 2000[23] IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities. G2: Usual care without pharmaceutical care	RCT: parallel, not clustered	% Married Overall: NR G1: 68.5 G2: 67.8	Mean number of chronic conditions Overall: NR G1: 4.0 (2.0) G2: 3.8 (1.9)	Hypertension Overall: NR G1: 68.5 G2: 66.5 Angina Overall: NR G1: 46.1 G2: 46.7 Hyperlipidemia Overall: NR G1: 39.8 G2: 43.1	Overall: NR G1: 8.4 (4.4) G2: 8.0 (4.0)	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
McDonough et al., 2005[24]	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of does, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	RCT: cluster-randomized	NR	NR	NR	Overall: G1: 5.6 (3.1) G2: 7.0 (3.2)	At baseline, the treatment group was significantly less likely to report alcohol use and more likely to be post-menopausal.
Moczygemba et al., 2011[25]; Moczygemba et al., 2008[26]	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. G2: No-MTM control group	Cohort	NR	Number of chronic dx Mean (SD) Overall: NR G1: 6.5 (2.3) G2: 7.0 (2.1) p: 0.18	Hypertension Overall: NR G1: 95 G2: 95 Dyslipidemia Overall: NR G1: 77 G2: 87 Diabetes Overall: NR G1: 55 G2: 60	Mean (SD) Overall: NR G1: 13.0 (3.2) G2: 13.2 (3.4)	Medication Regimen Complexity Index (MRCI) Mean (range) Overall: NR G1: 21.5 (8-43) G2: 22.8 (9-43) p: 0.32

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Pai et al., 2009[27]; Pai et al., 2009[28]	G1: Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	RCT: cluster-randomized	Mean Time on Hemodialysis in years (SD) Overall: 2.6 (2.0) G1: 2.8 (1.8) G2: 2.4 (2.2)	NR	ESRD etiology - Diabetes mellitus Overall: 43.3 G1: 38.6 G2: 48.9 ESRD etiology - Hypertension Overall: 28.9 G1: 31.6 G2: 25.5 ESRD etiology - Other Overall: 27.9 G1: 29.8 G2: 25.5	Overall: 10 (4) G1: 10 (4) G2: 10 (4)	NR
Park et al., 1996[29]	G1: Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. G2: Usual care	RCT: parallel, not clustered	NR	NR	NR	NR	Mean number of antihypertensives Overall: NR G1: 1.4 G2: 1.3

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Pindolia et al., 2009[30]	G1: Telephone-based MTM services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors). G2: Usual medical care (opt-out)	Cohort	2006 Part D type (%) Donut hole G1: 68 G2: 60 Nondonut hole or coverage gap G1: 6 G2: 8 Low income subsidy G1: 18 G2: 24 Institutionalized G1: 8 G2: 7 Overall p: 0.054 2007 Part D type (%) Donut hole G1: 93 G2: 63 Nondonut hole or coverage gap G1: 1 G2: 9 Low income subsidy G1: 6 G2: 26 Institutionalized G1: 0 G2: 2 Overall p: 0.001	2006 N of qualifying diseases (mean, SD) Overall: NR G1: 5.9 (2.2) G2: 5.6 (2.1) p: 0.047 2007 N of qualifying diseases (mean, SD) Overall: NR G1: 5.8 (2.0) G2: 5.9 (2.0) Overall p: 0.701	NR	2006 Unique prescriptions filled (mean, SD) Overall: NR G1: 16.7 (7.2) G2: 14.8 (6.1) p: 0.001 2007 Unique prescriptions filled (mean, SD) Overall: NR G1: 14.4 (6.2) G2: 14.9 (6.2) p: 0.223	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Planas et al., 2009[31]	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	RCT: parallel, not clustered	Overweight (25-29.9 kg/m^2), %: Overall: NR G1: 15.6 G2: 42.1 p: NR Obese (≥30 kg/m^2), %: Overall: NR G1: 68.8 G2: 47.4 p: NR	NR	Hypertension: 100 Diabetes: 100	NR	NR
Roughead et al., 2009[32]	G1: Home Medication Reviews (HMR), a collaborative model of pharmaceutical care, conducted by accredited pharmacists. G2: No medication review received	Cohort	Socioeconomic index of disadvantage (%) <u>Lowest disadvantage</u> Overall: NR G1: 31 G2: 25 <u>Medium/low disadvantage</u> Overall: NR G1: 25 G2: 25 <u>Medium/high disadvantage</u> Overall: NR G1: 24 G2: 25 <u>Highest disadvantage</u> Overall: NR G1: 20 G2: 25 Overall p: 0.01	N of co-morbidities (median, SD) Overall: NR G1: 8 (2) G2: 7 (2) p: <0.0001	NR	N (range) of prescriptions in last year Overall: NR G1: 95 (69-123) G2: 76 (54-104) p: <0.0001	Changes in medicines during 6-month period in previous year (N, SD) Overall: NR G1: 3 (2-6) G2: 3 (1-5) p: <0.0001

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Sellors et al., 2003[33]	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	RCT: cluster-randomized	Education: highest level attained (%) Elementary School Overall: NR G1: 26.9 G2: 24.1 High school graduate Overall: NR G1: 50.8 G2: 51.0 Some college Overall: NR G1: 22.2 G2: 24.9 % married FPL/ common-law spouse Overall: NR G1: 58.2 G2: 63.1	NR	Hypertension G1: 54.3 G2: 55.7 Osteoarthritis G1: 46.4 G2: 48.3 IHD G1: 36.0 G2: 38.0	NR	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Sidel et al., 1990[34]	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	RCT: parallel, not clustered	Income (%) Overall: NR Under $5000 G1: 23.3 G2: 22.2 $5000-$15000 G1: 61.0 G2: 63.3 >$15000 G1: 15.9 G2: 14.4 Education: % with 9 or more years Overall: NR G1: 62.2 G2: 54.8 % with Self-Assessed Health Fair or Poor Overall: NR G1: 44.0 G2: 42.7 % with Problems with Activities of Daily Living Overall: NR G1: 33.0 G2: 34.6 % with Symptoms of Depression Overall: NR G1: 10.8 G2: 22.6 % with Cognitive Impairment Overall: NR G1: 15.4 G2: 21.4	Number of medical conditions (%) Overall: NR None G1: 3.3 G2: 2.9 1-3 G1: 58.2 G2: 70.2 4 or more G1: 38.5 G2: 29.9	NR	Overall: 65.3% (mean 2.4, range 1-10) G1: NR G2: NR	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Staresinic et al., 2007[35]	G1: MTM services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist G2: Usual care provided to MTM-eligible enrollees who chose not to participate	Cohort	Dual eligible (%) G1: 6 G2: 25	NR	Hypertension/CHF Overall: 96.1 G1: 96.5 G2: 96.0 Hyperlipidemia Overall: 70.7 G1: 75.9 G2: 69.8 Diabetes Overall: 51.2 G1: 51.4 G2: 51.1	NR	NR
Taylor, Byrd, and Krueger, 2003[36]	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	RCT: parallel, not clustered	Median years of education (Range) Overall: NR G1: 12 (4-16) G2: 12 (8-16) No insurance coverage for Rx medications Overall: 17% G1: NR G2: NR Marital status: % married Overall: NR G1: 75.8 G2: 72.2	NR	Hypertension: Overall: 51 Dyslipidemia: Overall: 40 Diabetes Mellitus: Overall: 27	Mean N of medications (SD) Overall: NR G1: 6.3 (2.2) G2: 5.7 (1.7)	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Touchette et al., 2012[37]	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	RCT: parallel, not clustered	NR	Number of comorbidities Overall: 4.9 (1.6) G1: 5.0 (1.6) G2: 5.0 (1.6) G3: 4.9 (1.6)	Hypertension Overall: 90.9 G1: 89.6 G2: 90.8 G3: 92.3 Dyslipidemia Overall: 77.7 G1: 76.3 G2: 80.7 G3: 76.0 Arthritis Overall: 70.2 G1: 68.2 G2: 73.4 G3: 68.8	Mean (SD) Overall: 8.0 (2.4) G1: 8.2 (2.6) G2: 7.7 (2.3) G3: 8.0 (2.3)	NR
Triller and Hamilton, 2007[38]	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services only	RCT: parallel, not clustered	NR	NR	Primary or secondary diagnosis of heart failure Overall: 100	NR	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Volume et al., 2001[39]; Kassam et al., 2001[40] PREP (Pharmaceutical Care Research and Education Project)	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists. G2: Traditional pharmacy care	RCT: cluster-randomized	All Overall %'s NR Education (%) Some high school G1: 46 G2: 50 Completed high school G1: 17 G2: 18 Some trade school/college G1: 19 G2: 17 Completed college G1: 17 G2: 14 Annual income (%, CAD) < $20,000 G1: 40 G2: 40 $20,000 - $39,000 G1: 40 G2: 43 $40,000 - $59,000 G1: 11 G2: 11 ≥$60,000 G1: 8 G2: 5 Living situation (%) Live alone G1: 34 G2: 29 Live with spouse/partner G1: 57 G2: 61 Live with other relative G1: 7 G2: 6 Live with unrelated person G1: 2 G2: 2	Mean number of conditions (SD) G1: 3.3 (1.7) based on study interview and 10 (4.8) based on data collected by treatment pharmacist. G2: NR	NR	Mean (SD) Overall: NR G1: 4.7 (2.8) G2: 3.9 (2.5) p < 0.05	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Welch et al., 2009[41]	G1: MTM program provided to home-based beneficiaries as part of a Medicare Part D MTM program G2: No-MTM control group (voluntary opt-out)	Cohort	NR	NR	NR	NR	Mean Chronic Disease Score (SD) (ranges from 0-35, with larger scores indicating increasing burden of chronic diseases under treatment) Overall: NR G1: 8.8 (3.1) G2: 8.2 (3.5) p: 0.016 NOTE: Difference represents, on average, less than one additional chronic disease per patient Median (IQR) baseline medication cost ($) G1: 3149 (2378 to 4806) G2: 3186 (2363 to 5123) Mean baseline medication cost ($) (no SD reported) G1: 4465 G2: 5197 p: 0.525

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Williams et al., 2004[42]	G1: Medication review and optimization of patient's medication regimen conducted by an interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	RCT: parallel, not clustered	Education (%) Had not completed high school G1: 33.3 G2: 32.5 High school or some college G1: 25.4 G2: 19.5 Completed college G1: 41.3 G2: 48.1 Marital status (%) Married G1: 47.6 G2: 53.2 Living Alone G1: 38.1 G2: 33.8	NR	NR	G1: 6.6 (1.8) G2: 7.7 (2.3)	Baseline number of non-prescription drugs G1: 5.1 (3.1) G2: 4.6 (2.5)

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Winston and Lin, 2009[43]	G1: MTM provided in a community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of a Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of a Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Cohort	NR	NR	NR	Overall: NR G1: 9.8 (3.2) G2: 9.8 (2.9) G3: 9.7 (2.9)	NR

Table E2. Other patient-level and clinical characteristics (continued)

Author, Year Trial Name[a]	Interventions and Comparator Descriptions	Study Design	Other Baseline Characteristics	Measure of Co-Morbidity	Diagnosed Conditions or Diseases (%)	Baseline Number of Prescribed Medications	Other Patient Clinical Characteristics
Witry, Doucette, and Gainer, 2011[44]	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided by community pharmacists to patients with private individual-group insurance	Cohort	NR	NR	NR	Mean (SD) Overall: NR G1: 7.9 (3.8) G2: 4.7 (2.2) p: <0.001	NR

Abbreviations: BMI = body mass index; CMR = comprehensive medication review; DRP = drug regimen problem; DTP = drug therapy problem; dx = diagnosis; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; HMR = home medication review; ITT = intention-to-treat; LTFU = lost to follow-up; MTM = medication therapy management; MTMP = medication therapy management program; N = sample or group size; NA = not applicable; NR = not reported; NRCT = non-randomized controlled trial; OR = odds ratio; PA = physician assistant; PCM = pharmaceutical case management; PDP = prescription drug plan; RCT = randomized controlled trial; SD = standard deviation; VA = Veterans Affairs

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] 7 European countries: Denmark, Germany, The Netherlands, Northern Ireland, Portugal, Republic of Ireland, and Sweden	*Intervention:* Structured pharmaceutical care provided by community pharmacists. *Level of Integration with Usual Care:* Pharmacists were encouraged to use the patient's GP to obtain information, but specific details regarding pharmacist access to clinical information was NR. Rationalizing and simplifying drug regimens in collaboration with the patient's general practitioner was structured using drug use profiles, however specific details regarding the communication between pharmacist and physicians was NR.	Personal recruitment by pharmacists within pharmacy, or via GP records or pharmacy records	*Setting:* Community pharmacies, but also included some home visits. *Mode of delivery:* NR *Frequency and interval of follow-up:* NR	Health care systems varied by country, but all featured single payer systems. *Reimbursement characteristics:* NR
Chrischilles et al., 2004[7] Iowa, US	*Intervention:* Pharmaceutical case management provided by pharmacists. *Level of Integration with Usual Care:* Pharmacist access to clinical information in medical record NR. Pharmacist written communication with physicians about problems identified. A collaboratively determined action plan can be implemented by the pharmacist without requiring a patient visit to a physician.	Claims data or pharmacy prescription profile records	*Setting:* Community pharmacy. *Mode of delivery:* Face-to-face *Frequency and interval of follow-up:* Initial consultations with follow-up contacts as needed and routine re-assessments every 6 months by design.	Health plan intervention that included a payment reform to allow for reimbursement of multiple participating pharmacies and providers across different systems. *Reimbursement characteristics:* provided as a Medicaid benefit using state and federal matching funds.

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Christensen et al., 2007[8] North Carolina, US	*Intervention:* Medication therapy management services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. *Level of Integration with Usual Care:* Pharmacist access to clinical information in the medical record NR. Pharmacist contacted prescribing physicians to discuss drug therapy problems and implemented any resulting approved action plan.	Eligible patients identified through claims data, then recruited through a letter sent inviting them to participate.	*Setting:* Some patients received services within their medical clinic, some received services within a community pharmacy setting. *Mode of delivery:* Face-to face and telephone *Frequency and interval of follow-up:* study designed as one initial visit and one follow-up, 37.5% of enrolled patients received follow-up contact.	Health plan intervention involving multiple health systems. *Reimbursement characteristics:* Pharmacists compensated through study-related funding (e.g., grant).
Fischer et al., 2000[10] Midwest, US	*Intervention:* Pharmaceutical care based on the Encara Practice System provided by onsite health maintenance organization staff pharmacists. *Level of Integration with Usual Care:* Pharmacist access to clinical information in the medical record NR. Information to and consultation with physicians on behalf of patients mentioned but specific operational details NR.	Claims data or pharmacy prescription profile records to identify eligible participants who were then invited by letter.	*Setting:* Pharmacies located within clinics *Mode of delivery:* Face-to-face *Frequency and interval of follow-up:* NR	Health maintenance organization with clinics and on-site pharmacies. *Reimbursement for services*: NR

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Fischer et al., 2002[11] Minnesota, US	*Intervention:* Pharmaceutical care based on the Encara Practice System provided by pharmacists. *Level of Integration with Usual Care:* Pharmacist access to clinical information in the medical record NR. Communication with the patient's physician about drug therapy problems identified, but specific operational details NR.	Claims data or pharmacy prescription profile records to target eligible participants.	*Setting:* Pharmacies located within clinics and free-standing pharmacies *Mode of delivery:* Face-to-face *Frequency and interval of follow-up:* With each prescription refill (as designed); actual frequency and interval NR.	Health maintenance organization clinics and free-standing pharmacies. *Reimbursement characteristics:* NR
Fox et al., 2009[12] Florida, US	*Intervention:* MTM services provided by staff clinical pharmacist as part of a Medicare Part D MTM program. *Level of Integration with Usual Care:* Pharmacist had access to clinical information in the medical record, including laboratory data. Pharmacist documented findings on a form, which was sent to the patient's physician.	Claims data or pharmacy prescription profile records to target eligible participants.	*Setting:* Health plan pharmacy, unclear whether a single centralized center or outpatient clinic-based pharmacies used. *Mode of delivery:* Primarily telephone, supplemented by mailed written materials. *Frequency and interval of follow-up:* Initial consultation, and up to 3 follow-up contacts if a drug therapy problem identified or based on clinical need.	Mixed-staff model health maintenance organization that combines pharmacist services, primary care, and specialty medical care with a Medicare Advantage Part D Plan. *Reimbursement characteristics*: Medicare Part D drug benefit

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Hanlon et al., 1996[14] North Carolina, US	*Intervention:* Pharmaceutical care provided by a clinical pharmacist *Level of Integration with Usual Care:* Pharmacists had access to clinical information in medical record. Pharmacist recommendations were presented orally and in writing to the patient's primary physician, pharmacist reinforced and amplified the primary physician's instructions.	Computerized and manual chart audits to identify eligible subjects	*Setting:* Outpatient medical clinic *Mode of delivery:* Face-to-face *Frequency and Interval of Follow-up:* NR	Single Veterans Health Administration Medical Center Reimbursement characteristics: NR
Isetts et al., 2008[16] Minnesota, US	*Intervention:* Medication therapy management services provided by staff pharmacists, including the establishment of goals of therapy. *Level of Integration with Usual Care:* Pharmacists had access to clinical information in medical record. Pharmacist urgently consulted with primary care provider for potentially harmful drug therapy problems, but details regarding routine communication were NR.	Claims data or pharmacy prescription profile records used to identify eligible participants who were then invited by letter and provider referral.	*Setting:* Integrated health care delivery system. *Mode of delivery:* Face-to-face *Frequency and Interval of Follow-up:* NR (at least 1 follow-up visit was required for inclusion in the evaluation)	Integrated health system with an established pharmaceutical care program involving pharmacist certification in pharmaceutical care and a specific pharmaceutical care documentation system. *Reimbursement characteristics:* Costs of providing services were funded through research grants, demonstration projects, third-party payer pilot programs, and internal health system funding.

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Jameson, VanNoord, and Vanderwoud, 1995[17] Michigan, US	*Intervention:* Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist. *Level of Integration with Usual Care:* Pharmacist access to clinical information in the medical record was NR. Pharmacist met with treating physician to discuss findings and new regimen was developed collaboratively with the physician.	Medical records of patients seen in an outpatient clinic were randomly screened for risks of adverse medication outcomes.	*Setting:* Outpatient medical clinic *Mode of Delivery:* Face-to-face and telephone *Frequency and interval of Follow-up:* 1 initial visit and 1 follow-up visit 1 month later (by design); actual frequency and interval of follow-up NR.	Single family health clinic that was part of a family medicine residency program. *Reimbursement characteristics:* NR
Jeong et al., 2007[18] California, US	*Intervention:* MTM services provided by ambulatory care pharmacists and health care support staff. *Level of Integration with Usual Care:* Pharmacist access to clinical information in the medical record was NR. Specific details regarding communication with treating physician NR.	NR	*Setting:* Integrated health care delivery system *Mode of delivery:* Primarily telephone *Frequency and interval of Follow-up:* NR	Integrated health care delivery system providing Medicare Part D MTM services to eligible beneficiaries *Reimbursement characteristics:* Medicare Part D drug benefit.
Krska et al., 2001[19] United Kingdom	*Intervention:* Medication reviews led by clinically trained pharmacists. *Level of Integration with Usual Care:* Pharmacist had access to medical notes and practice computer records. Copies of the pharmaceutical care plan developed by the pharmacist were inserted into the patient's medical record and given to the patients' GP, who was asked to indicate level of agreement with recommendations.	Provider referral required but enrollment limited to 70 patients from each participating practice; selection process unclear	*Setting:* Home visits *Mode of Delivery:* Initial consultation was face-to-face; follow-up consultation NR *Frequency and Interval of Follow-up:* Two contacts, 3 months apart as designed; actual frequency and interval NR.	General medicine clinics that were part of a single payer health care system. *Reimbursement characteristics:* NR

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Malone et al., 2000[20]; Ellis et al., 2000[21] (interventions); Malone et al., 2001[22] (detailed QOL outcomes); Ellis et al., 2000[23] (dyslipidemia subgroup intermediate and utilization outcomes) Multiple states, US	*Intervention:* Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities. *Level of Integration with Usual Care:* Pharmacist had access to medical record information. Pharmacist communication with primary care physician or other prescribers NR.	Pharmacy prescription records to identify patients at high risk for drug-related problems.	*Setting:* Outpatient medical clinic *Mode of Delivery:* Face-to-face (76.6% of contacts) and telephone (23.4%) *Frequency and Interval of Follow-Up:* At least 3 visits over 12 months as designed. Actual frequency: mean (SD) number of visits was 3.5 (2.3). 27.7% did not complete the minimum number of visits (3) as designed	Multiple Veterans Health Administration Medical Centers with established ambulatory clinical pharmacy services *Reimbursement characteristics:* Services provided as part of patient's VHA health care benefits
Moczygemba et al., 2011[25] Moczygemba et al., 2008[26] Texas, US	*Intervention*: Medication therapy management services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. *Level of Integration with Usual Care:* Pharmacist had access to medical record information, including laboratory information. Patients are encouraged to share the Personal Medication Record and Medication Action Plan developed in the course of MTM consultation with their health care providers and patients are requested to contact their physicians regarding pharmacist's recommendations. Copies are kept in the patient's MTM file, but no MTM documentation goes back to the patient's medical record.	Eligible patients are identified quarterly and mailed MTM Program information and instructions for opting in to the program.	*Setting:* centralized MTM program *Mode of Delivery:* Telephone *Frequency and Interval of Follow-Up*: one initial consultation by design with follow-up scheduled as needed. Actual frequency and interval of follow-up NR.	Health plan intervention provided by a regional Medicare Part D MTM Provider. *Reimbursement characteristics:* Medicare Part D drug benefit.

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Pindolia et al., 2009[30] Michigan, US	*Intervention:* Medication therapy management services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists. *Level of Integration with Usual Care:* Pharmacists had access to clinical information in the medical record. Communications with physicians were by telephone, face-to-face, or e-mail.	Monthly query of clinical care management systems for eligible patients with subsequent letter mailed and follow-up phone call to enroll patients.	*Setting:* Integrated healthcare delivery system *Mode of Delivery:* telephone *Frequency and Interval of Follow-Up:* NR	Health plan intervention within an Integrated health system with an established pharmaceutical care program. *Reimbursement characteristics:* Medicare Part D drug benefit.
Sellors et al., 2003[33] Ontario, Canada	*Intervention:* Clinical pharmacy consultations provided to patients by community pharmacists. *Level of Integration with Usual Care:* Pharmacist access to clinical information in medical record was NR. Pharmacists provided a consultation letter to physician and subsequently met with physician to review the letter. They met again in 3 months to discuss progress in implementing recommendations.	About 20 randomly chosen eligible senior citizens per practice were recruited by the office staff of the practice, selection process for recruitment not reported.	*Setting:* Outpatient medical clinic *Mode of Delivery:* Face-to-face and telephone *Frequency and Interval of Follow-Up:* Initial contact plus 2 follow-up contacts at 1 and 3 months as designed. Actual frequency and interval of contact NR.	Family medicine practice settings within a single-payer health care system. *Reimbursement characteristics:* NR
Sidel et al., 1990[34] New York, US	*Intervention:* Home visits by pharmacists to identify and correct problems associated with medication use. *Level of Integration with Usual Care:* Pharmacist access to clinical information in medical record was NR. No information about communication with providers was reported.	Study population identified from a combination of the following: Medicare recipients living in the region, Senior Centers, houses of worship, Meals-on-Wheels, hospital admissions records and voter registration rolls.	*Setting:* Community setting *Mode of delivery:* home visits and telephone *Frequency and Interval of Follow-Up:* 2 visits over a 12 month period as designed. Actual frequency and interval of follow-up NR.	Implemented outside the health care system through a multidisciplinary research program on aging. *Reimbursement characteristics:* NR

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Staresinic, 2007[35] Wisconsin, US	*Intervention:* Medication therapy management services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist. *Level of Integration with Usual Care:* Pharmacists request lab data from participants; access to clinical information in medical records was NR. Pharmacists send a tailored letter by fax to each of the patient's health care providers.	Pharmacy claims based algorithm identifies eligible beneficiaries with invitation letters mailed within 2 weeks of identifying eligibility.	*Setting:* centralized MTM program *Mode of Delivery:* telephone *Frequency and Interval of Follow-Up:* One initial contact and one follow-up contact at 3 months as designed. Actual frequency and interval of follow-up NR.	Health plan intervention provided by a regional Medicare Part D MTM Provider *Reimbursement characteristics:* Medicare Part D drug benefit.
Taylor, Byrd, and Krueger, 2003[36] Alabama, US	*Intervention:* Pharmaceutical care provided by pharmacists. *Level of Integration with Usual Care:* Pharmacist access to clinical information in medical record was NR, but visits with pharmacist occurred 20 minutes before seeing the physician in the same clinic. Recommendations to physicians were communicated through discussions or progress notes.	Patients were identified by the participating pharmacists through manual evaluation of clinic medical records and review of computerized medical records in physician offices.	*Setting:* Outpatient medical clinic *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-Up:* Before each scheduled physician visit by design. Actual frequency and follow-up interval NR.	Three community-based family medicine clinics affiliated with an academic medical center. *Reimbursement characteristics:* NR

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Followup	Health Care System and Reimbursement Context
Touchette et al., 2012[37] Multiple States, US	*Intervention:* Patient-safety focused medication therapy management services provided by pharmacists. *Level of Integration with Usual Care:* Two versions of the intervention were evaluated. In the enhanced version, pharmacists were provided with a clinical summary excerpted from the patient's medical record. No such summary was provided to pharmacists in the basic version. Drug therapy problems were communicated to physicians via fax, except urgent issues were communicated by telephone.	Administrative and pharmacy databases and provider referral used for initial eligibility determination followed up with letter or phone call or in clinic for recruitment/enrollment	*Setting:* Outpatient medical clinic *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-up:* 1 initial contact and a follow-up contact at 3 months as designed. Actual: 89.9% completed 1 contact and 75.7% completed 2 contacts in the enhanced MTM arm, 88.6% and 73.8% completed the first and second contacts respectively in the basic MTM arm.	Three academic medical centers in three different states. *Reimbursement characteristics:* NR
Volume et al., 2001[39] and Kassam et al., 2001[40] PREP Alberta, Canada	*Intervention:* Pharmaceutical care using a nine-step process as defined by Hepler and Strand provided by community pharmacists. *Level of Integration with Usual Care:* Pharmacist access to clinical information in the medical record NR. Details regarding communication with physicians regarding drug therapy problems NR.	Pharmacies evaluated 60 consecutive patients during one week for eligibility. Eligible patients were asked in person or by phone about interest in participating.	*Setting:* community pharmacy *Mode of Delivery:* Face-to face *Frequency and Interval of Follow-Up*: Initial contact plus frequent follow-up at unspecified intervals as designed. Actual frequency and interval of follow-up NR.	Community-pharmacy intervention within a non-US single-payer healthcare system. *Reimbursement characteristics*: NR

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Follow-up	Health Care System and Reimbursement Context
Welch et al., 2009[41] Colorado, US	*Intervention:* Medication therapy management services provided by clinical pharmacists as part of a Medicare Part D MTM program. *Level of Integration with Usual Care:* Pharmacists had access to clinical information in the medical record. Pharmacists forwarded copies of consultation notes to providers and also placed a copy in the patient's medical record.	Medicare beneficiaries identified as eligible using a computerized system.	*Setting:* centralized MTM program *Mode of Delivery:* telephone *Frequency and interval of Follow-Up:* Initial consult with follow-up depending on clinical situation as designed. Actual frequency and interval of follow-up NR.	Group-model health maintenance organization using a centralized clinical pharmacy call center. *Reimbursement characteristics:* Medicare Part D drug benefit.
Williams et al., 2004[42] North Carolina, US	*Intervention:* Medication review and optimization provided by a consulting pharmacist. *Level of Integration with Usual Care:* Pharmacist had access to clinical information in the medical record. A MAT comprised of a physician, nurse, and consultant pharmacist met to discuss pharmacy recommendations.	Patients were recruited from practices and through community print and radio advertisements and mass mailings, and presentations to community groups.	*Setting:* Outpatient medical clinic *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-Up:* Initial contact with follow-up contact as needed as designed. Actual frequency and interval of follow-up contact NR.	General medicine clinic of an academic medical center. *Reimbursement characteristics:* NR
Winston and Lin, 2009[43] Multiple States, US	*Intervention:* Medication therapy management services provided by either community pharmacists or call center pharmacists as part of a Medicare Part D MTM Program. *Level of Integration with Usual Care*: Pharmacist access to clinical information in the medical record was NR. Pharmacist contacted prescribers on behalf of the patients by phone or fax for medication adjustments related to cost or safety.	Health plan used pharmacy prescription profile records identify eligible patients. Information on eligible patients was communicated to pharmacies by fax or email.	*Setting:* community pharmacy and centralized pharmacy call center *Method of Delivery:* Face-to-face or telephone *Frequency and Interval of Follow-up:* NR	Health plan intervention provided by a national Medicare Part D MTM provider. *Reimbursement characteristics:* Medicare Part D drug benefit

Table E3. Key Question 1: Components and features of medication therapy management interventions: Broadly focused studies (continued)

Author, Year State (Province) or Country	Intervention and Level of Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and Interval of Follow-up	Health Care System and Reimbursement Context
Witry, Doucette, and Gainer, 2011[44] Iowa, US	*Intervention:* Pharmaceutical case management provided by community pharmacists. *Level of integration with Usual Care:* Pharmacist access to clinical information in the medical record was NR. Pharmacists faxed a one-page summary of findings to physician.	Health plan used pharmacy prescription profile records identify eligible patients. This was sent to each pharmacy. The health plan also sent letters to inform eligible patients about the PCM service benefit, and an article about PCM appeared in the health plan newsletter. Pharmacies also sent letters and telephoned eligible patients.	*Setting:* community pharmacy *Mode of Delivery:* Face-to-face and telephone *Frequency and Interval of Follow-Up:* Initial contact with additional follow-up contacts as needed as designed. Actual frequency and interval of follow-up: 46% received 1 contact, 24% received 2 contacts, 16% received 3 contacts,13% received 4 or more contacts	Health plan intervention executed by pharmacies that had previously participated in a similar intervention sponsored by Medicaid. *Reimbursement characteristics:* Participating pharmacies were reimbursed for services provided by study grant.

Abbreviations: GP = general practitioner; MAT = medication adjustment team; MTM = Medication Therapy Management; NR = not reported; PCM = pharmaceutical case management; PREP = Pharmaceutical Care Research and Education Project; QOL = quality of life; SD = standard deviation; US = United States; VHA = Veterans Health Administration.

Table E4. Key Question 1: Components and features of medication therapy management interventions: Narrow focused studies

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Blennerhassett et al., 2007[3] Australia	*Focus:* Chronic heart failure *Intervention*: Implementation of a HMR into a chronic heart failure collaborative care model. HMRs were conducted by accredited pharmacists. *Level of integration with usual care:* General practitioner (GP) provided pharmacist with diagnosis, current medications, relevant test results and medical history. Pharmacist submitted a written and verbal report to the GP for assistance in developing or revising a management plan.	Patients with admission and discharge related to CHF identified as eligible to receive services under a broader Home Medication Review benefit (not necessarily specific to CHF).	*Setting:* Community *Mode of Delivery:* Home visits *Frequency and Interval of Follow-up*: NR	Single payer health care system *Reimbursement characteristics*: Covered service and benefit can be claimed up to once per year.
Carter et al., 1997[4]; Barnette, Murphy, and Carter, 1996[5] Illinois, US	*Focus*: Hypertension *Intervention:* Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. *Level of Integration with Usual Care:* The pharmacist had access to patients' medical records, diagnostic data, and laboratory data, and had face-to-face interaction with the clinic physicians and nurses.	Patients were identified through a computerized profile review, details NR.	*Setting*: Outpatient primary care clinic *Mode of delivery:* Face-to-face *Frequency and Interval of Follow-up:* Monthly contacts for 6 months as designed. Actual frequency and interval of follow-up NR.	Rural medical clinic co-located in same building as a privately owned pharmacy. *Reimbursement characteristics:* NR

Table E4. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Chisholm et al., 2002[6] Georgia, US	*Focus:* Postkidney transplantation *Intervention:* Clinical pharmacy services, including reviewing patients' medication therapy, with an emphasis on controlling blood pressure and preventing or resolving drug therapy problems. Pharmacists counseled patients about their regimen, including desired clinical responses and possible adverse reactions *Level of integration with usual care:* Pharmacist had access to physical examination findings and medical and medication history. Pharmacists were embedded within the clinic and provided recommendations to attending nephrologists.	All African-American patients after a primary kidney transplant receiving care in transplant clinic.	*Setting:* Outpatient transplant clinic *Mode of delivery:* Face-to-face for patients within 8 months of transplant, and telephone for patients more than 8 months post-transplant *Frequency and Interval of Follow-up:* Monthly as designed. Actual frequency and interval NR.	Transplant clinic of an academic medical center. *Reimbursement characteristics*: NR.
Clifford et al., 2002[9] Australia	*Focus:* Diabetes *Intervention:* Pharmaceutical care provided by a clinical pharmacist , which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. *Level of Integration with Usual Care:* Pharmacist had access to patient's case notes. Pharmaceutical care was provided in cooperation with the patient's diabetes physicians and other diabetes health team members.	Medical records were screened for eligible patients. Eligible patients were telephoned about their willingness to participate.	*Setting:* Outpatient hospital diabetes clinic *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-Up*: Initial visit followed by follow-up visits at 6 week intervals for 6 months as designed. Actual frequency and interval of follow-up NR.	Non-US, single payer health care system *Reimbursement characteristics:* NR

Table E4. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Gattis et al., 1999[13] North Carolina, US	*Focus: Chronic heart failure* *Intervention:* Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. *Level of integration with usual care:* Pharmacist had access to patient medical records and verbally recommendations regarding optimization of therapy with attending physician.	Patients seen in a general cardiology clinic meeting inclusion criteria were recruited for enrollment.	*Setting:* Outpatient cardiology clinic *Mode of Delivery:* Initial visit was face-to-face and follow-up visits were by telephone *Frequency and Interval of Follow-Up:* 3 visits, baseline, two weeks, and 24 weeks by design. Actual frequency and interval of follow-up NR.	Single clinic within an academic medical center. *Reimbursement characteristics:* NR
Harrison et al., 2012[15] Ontario, Canada	*Focus:* Post-lung transplant *Intervention:* Pharmaceutical care provided by a clinical pharmacist for identifying and resolving actual and potential drug therapy problems, medication teaching, adherence optimization, medication reconciliation, and provision of drug information. *Level of integration with usual care:* Patients seen separately by pharmacist at a routine clinic visit after transplant. Pharmacist documentation of pharmaceutical care was in the electronic chart. Drug therapy recommendations were made verbally or through electronic communication to clinic physicians.	Combination of provider referral, patient self-referral, and routine evaluation for enrollment at post-transplant outpatient followup.	*Setting:* Outpatient transplant clinic *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-up*: One initial visit with additional follow-up visits as needed by design. Actual frequency and interval of follow-up: 93% received 1 visit.	Transplant clinic of an Academic Medical Center. *Reimbursement characteristics:* NR

Table E4. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
McDonough et al., 2005[24] Iowa, US	*Focus:* Glucocorticoid-induced osteoporosis *Intervention:* Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of does, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education was also provided. *Level of Integration With Usual Care:* Pharmacist access to patient medical records NR. A standardized physician communication form was used by pharmacists to communicate information to prescribing physicians.	Claims data or pharmacy prescription profile records used to identify eligible patients who were then contacted by mail or telephone to participate.	*Setting:* community pharmacy *Mode of Delivery:* NR *Frequency and Interval of Follow-Up*: NR	Network of independent and retail chain pharmacies. Some pharmacies located within a clinic, while others are freestanding. *Reimbursement characteristics:* Pharmacists were reimbursed using a web-based claims system, but entity providing reimbursement was NR.
Pai et al., 2009[27]; Pai et al., 2009[28] New Mexico, US	*Focus:* Hemodialysis *Intervention:* Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education. *Level of Integration with Usual Care:* The pharmacist had access to patient's medical record and laboratory data. The pharmacists provided cognitive services during weekly rounds and during monthly formal reviews of the patients with the multidisciplinary health care team.	Patients on stable hemodialysis regimen for the previous 3 months were approached for participation.	*Setting:* Outpatient hemodialysis clinic *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-Up:* Every 8 weeks for two years by design. Actual frequency and interval of follow-up NR.	University-affiliated outpatient dialysis clinic *Reimbursement characteristics* : NR

Table E4. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Park et al., 1996[29] Wisconsin and Illinois, US	*Focus:* Hypertension *Intervention:* Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. *Level of Integration with Usual Care:* Pharmacists access to patient medical records, or labs or vital signs from clinic was NR. Communication with provider was via fax or mail after each pharmacist visit, unless urgency required telephone communication.	Claims data or pharmacy prescription profile records	*Setting:* Community pharmacy *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-up:* 4 visits scheduled 1 month apart by design. Actual frequency and interval of follow-up NR.	Chain pharmacy with community pharmacy residents. *Reimbursement characteristics:* NR
Planas et al., 2009[31] Oklahoma, US	*Focus:* Patients with both hypertension and diabetes *Intervention:* Medication therapy management services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. *Level of integration with usual care:* Pharmacist access to patient medical records, or labs, or vital signs from clinic was NR. Providers were contacted via fax or telephone when drug therapy problems were identified in order to make recommendations.	Three methods were used: managed care organization identification of patients with uncontrolled diabetes through lab data screening, screening for uncontrolled diabetes at a health fair for employees sponsored by the managed care organization, provider referral of patients with uncontrolled diabetes.	*Setting:* Community pharmacy *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-up:* Monthly visits for 9 months by design. Actual frequency and interval of follow-up NR.	Services provided through a collaboration between a managed care organization and a regional retail chain pharmacy. *Reimbursement characteristics:* NR

Table E4. Key Question 1: Components and features of medication therapy management interventions: narrow focused studies (continued)

Author, Year Country/ Region	Special Focus, Intervention, and Integration with Usual Care	Method of Identifying Patients for Receipt of MTM Services	Setting, Mode of Delivery, Frequency and interval of follow-up (as reported).	Health Care System and Reimbursement Contexts
Roughead et al., 2009[32] Australia	*Focus:* Chronic heart failure *Intervention:* HMR, a collaborative model of pharmaceutical care. HMRs are conducted by accredited pharmacists. *Level of Integration with Usual Care:* NR for this study specifically, but the HMR model is that the GP provides pharmacist with diagnosis, current medications, relevant test results and medical history. Pharmacist conducts the HMR and submits a written and verbal report to the GP for assistance in developing or revising a management plan.	HMRs are conducted upon request of a provider. Claims data or pharmacy prescription profile records	*Setting:* Outpatient clinic and home visits *Mode of Delivery:* Face-to-face *Frequency and Interval of Follow-Up:* NR	Non-US, single payer health care system *Reimbursement characteristics:* services reimbursed through payer's home medicine review benefit.
Triller and Hamilton, 2007[38] New York, US	*Focus:* Heart failure *Intervention:* Comprehensive pharmaceutical care services provided by pharmacist. *Level of integration with usual care:* Pharmacists had access to patient medical records and laboratory results. Pharmaceutical care services were coordinated and provided alongside visiting nurse services. Recommendations to physicians were communicated via fax or telephone, depending on the urgency of the situation.	Enrollment during a transition in care from inpatient to home.	*Setting:* Home visit *Mode of delivery:* Face-to-face *Frequency and interval of Follow-up:* Initial visit plus additional follow-up visits at 7-10 days and 18-21 days, provided patient was still receiving visiting nurse services by design. Actual frequency and interval of follow-up: 53% received all 3 visits, 31% received 2 visits, 12% received 1 visit, and 4% received 4 visits.	Integrated health system and associated Visiting Nurse Association. *Reimbursement characteristics:* NR

Abbreviations: CHF = chronic heart failure; GP = general practitioner; HMR = home medication review; MTM = medication therapy management; NR = not reported; US = United States.

Table E5. Hemoglobin A1c: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Clifford et al. 2002[9] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 48 G2: 25	Mean (SD) HbA1c at six months.	Baseline: G1: 8.4 (1.4) G2: 8.5 (1.6) p: NS 6 months G1: 8.2 (1.5) G2: 8.1 (1.6) Calculated mean difference: -0.2, 95% CI, -0.93 to 0.53 (assuming pre-post correlation of 0.5) p=0.207
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 13 G2: 16 (Study included more subjects, but this outcome was only assessed among patients with diabetes within each study arm)	Percent with HbA1c at goal (defined as less than or equal to 7.5%) at baseline and at 12 months.	Baseline: G1: 23.1 G2: 56.3 p=0.071 Calculated OR: 0.2 95% CI, 0.05 to 1.19 Follow-up G1: 100 G2: 26.7 p=0.001 Calculated OR: 56.5 95% CI, 2.81 to 1,133.91 p=0.008

Table E5. Hemoglobin A1c: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Pindolia et al., 2009[30] Cohort study/High	G1: Opted in to a telephone based MTM Program G2: Usual medical care (opted out of MTM program)	G1: NR G2: NR (Was only assessed among patients with DM in each study arm and N for this outcome was not reported)	Change in percent of patients with HbA1c less than 7 at 6 months	G1: +3 G2: +7 Between-group p: inferred to be NS, exact p NR Within-group p: NR
Jeong et al., 2007[18] Cohort study/High	G1: Participants in Part D Medicare MTM program G2: Control subjects eligible for Part D MTM program but declined enrollment G3: Control subjects without Part D Medicare as their primary drug benefit	G1: 1,211 G2: 1,000 G3: 743 (Study included more subjects but this outcome was assessed among only patients with diabetes within each study arm)	Mean change (SD) in HbA1c at six months	G1: -0.05 (1.0) G2: -0.01 (1.0) Calculated mean difference of G1 vs. G2: 0.04, 95% CI, -0.04 to 0.13; p=0.337 G3: -0.05 (1.0) Calculated mean difference of G1 vs. G3: 0.004, 95% CI, -0.09 to 0.10; p=0.931 Author reported overall p=0.74

Abbreviations: CI = confidence interval; DM = diabetes mellitus; G = group; HbA1C = hemoglobin A1C or glycosylated hemoglobin; MTM = Medication Therapy Management; N = number; NR = not reported; NS = not significant; RCT= randomized controlled trial; SD = standard deviation; vs. = versus

Table E6. LDL cholesterol: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	Baseline G1: 19 G2: 19 (Was only assessed among patients with dyslipidemia in each study arm)	Percent of patients at LDL-C goal based on ATPIII criteria at 12 months.	Baseline: G1: 10.5 G2: 15.8 Calculated OR: 0.6; 95% CI, 0.09 to 4.25; p=0.631
		Follow-up (N inferred from percent in results) G1: 18 G2: 17		Follow-up G1: 77.8 G2: 5.9 Calculated OR: 56.0; 95% CI, 5.58 to 561.75; p: 0.001
Isetts et al., 2008[16] Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percent of patients meeting HEDIS measures related to cholesterol control after cardiovascular event at 12 months.	G1: 52 G2: 30 Calculated OR: 2.5; 95% CI, 1.52 to 4.26; p: 0.001
Pindolia et al., 2009[30] Cohort study/High	G1: Opted in to a telephone based MTM Program G2: Usual medical care (opted out of MTM program)	G1: NR G2: NR (Was only assessed among patients with coronary artery disease in each study arm)	Change in percent of patients with LDL-C less than 100 mg/dl at 6 months.	G1: -5 G2: +7 p: NR and could not be calculated
Fox et al. 2009[12] Cohort study/High	G1: MTM program, provided through a health plan G2: Usual medical care (eligible but opt-out from MTM program)	G1: 255 G2: 56	Percent of patients with diabetes with LDL-C less than 100 mg/dl at 12 to 24 months.	G1: 69 G2: 50 OR: 2.2; 95% CI, 1.24 to 4.01; Calculated p=0.008
		G1: 215 G2: 46	Mean (SD) LDL-C at 12 to 24 months.	G1: 83.4 (31.1) G2: 90.8 (31.0) Calculated mean difference: -7.4, 95% CI, -17.30 to 2.50 p=0.33 as reported by study authors, p=0.143 as calculated

Table E6. LDL cholesterol: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jeong et al., 2007[18] Cohort study/High	G1: Participants in Part D Medicare MTM program G2: Control subjects eligible for Part D MTM program but declined enrollment G3: Control subjects without Part D Medicare as their primary drug benefit	G1: NR G2: NR G3: NR (Was only assessed among patients with hyperlipidemia, diabetes, or coronary artery disease within each study arm)	Mean LDL-C at 6 months	Baseline: G1: 94.2 G2: 95.6 G3: 91.9 Follow-up G1: 87.4 G2: 92.5 G3: 90.2 p: NR and unable to be calculated
			Percent of patients at goal (defined as less than 100 mg/dl) at 6 months	Baseline: G1: 62 G2: 62 G3: 67 p value unable to be reported or calculated Follow-up G1: 73 G2: 67 G3: 69 p value unable to be reported or calculated

[a] p values reported as <0.001 for G1 vs. G2 and G1 vs. G3, but unclear whether these refer to between-group differences at followup in LDL-C, between group differences in LDL-C change, or to between-group differences in change in percent at LDL-C goal. Calculated mean differences and OR were unable to be calculated due to absence of SD and number analyzed.

Abbreviations: ATPIII=Adult Treatment Panel III (Expert Panel on Detection; Evaluation; and Treatment of High Blood Cholesterol); CI = confidence interval; G = group; HEDIS= Healthcare Effectiveness Data and Information Set; LDL-C= low density lipoprotein cholesterol; mg/dl = milligrams per deciliter; MTM = Medication Therapy Management; N = number; NR = not reported; OR = odds ratio; RCT= randomized controlled trial; SD = standard deviation; vs. = versus.

Table E7. Blood pressure: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 24 G2: 29 (Was only assessed among patients with HTN in each study arm)	Percent of patients with SBP and DBP at goal at 12 months.	Baseline: G1: 12.5 G2: 31.0 p=0.109 Follow-up: G1: 91.7 G2: 27.6 p=0.001 Calculated OR: 28.9; 95% CI, 5.49 to 151.99; p<0.001
Chisholm et al. 2002[6] RCT/Medium	G1: Clinical pharmacy services within a kidney transplant clinic. G2: Usual medical care in the kidney transplant clinic.	G1: 13 G2: 10	Mean (SD) SBP (mm Hg) at quarterly points in time for 12 months.	Quarter 1 G1: 142.8 (27.0) G2: 151.2 (22.0) p: 0.544 Quarter 2 G1: 137.8 (15) G2: 168.9 (15.3) p: 0.001 Quarter 3 G1: 135.9 (11.7) G2: 164.6 (20.0) p: 0.001 Quarter 4 G1: 145.3 (16.8) G2: 175.8 (33.9) p: 0.029 Calculated mean difference (Q4-Q1): -22.1; 95% CI, -43.90 to -0.30; p=0.047

Table E7. Blood pressure: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Chisholm et al. 2002[6] (continued)			Mean (SD) DBP (mm Hg) at quarterly points in time for 12 months.	Quarter 1 G1: 81.7 (12.8) G2: 78 (15.5) p: 0.611 Quarter 2 G1: 76.0 (11.8) G2: 84.9 (6.1) p: 0.036 Quarter 3 G1: 71.4 (13) G2: 78.3 (9.5) p: 0.205 Quarter 4 G1: 77.0 (10.2) G2: 91.8 (12.0) p: 0.020 Calculated mean difference (Q4-Q1): -18.5; 95% CI, -29.04 to -7.96; p=0.001

Table E7. Blood pressure: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al. 1996[29] RCT/High	G1: Community-pharmacy based pharmaceutical care program G2: Usual care	G1: 23 G2: 26	Mean (SD) SBP (mm Hg) at four months.	Baseline: G1: 155.5 (21.1) G2: 147.9 (19.6) p:NS (between-group difference) Follow up: G1: 143.2 (11.5) (p<0.05 for within group difference as compared to baseline) G2: 148.6 (20.1) Calculated mean difference: -13.0; 95% CI, -23.74 to -2.26; p=0.018
			Mean (SD) DBP (mm Hg) at four months	Baseline: G1: 87.8 (9.9) G2: 83.3 (8.5) p: NS (between group difference) Follow-up: G1: 83.2 (8.0) (p<0.05 for within group difference as compared to baseline) G2: 83.7 (10.9) Calculated mean difference: -4.9; 95% CI, -10.3 to 0.50; p=0.075
			Percent of patients who were normotensive (SBP<140 and DBP<90)	Baseline: G1: 17.4 G2: 26.9 Calculated p: 0.428 Follow-up: G1: 52.2 (p<0.02 for within group difference compared to baseline) G2: 30.1 OR: 2.5; 95% CI, 0.76 to 7.89; p=0.132

Table E7. Blood pressure: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Planas et al. 2009[31] RCT/High	G1: Community pharmacy-based hypertension MTM program for patients with diabetes G2: Control group (BP recorded, informed of BP goals at three time during study)	G1: 25 G2: 15	Mean (SD) change in SBP (mm Hg) at nine months	G1: -17.3 G2: 2.7 Between-group difference (95% CI): -20.0 (-32.7 to -7.4) p: 0.003
			Percent of patients at BP goal at nine months.	Baseline G1: 16.0 G2: 20.0 Calculated p: 0.714 9 months G1: 48.0 G2: 6.7 p: 0.007
			OR for intervention group participant achieving BP goal relative to control group. (95% CI)	OR : 12.9 (1.5 to 113.8) p: 0.021

Table E7. Blood pressure: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997[4] Barnette, Murphy, and Carter, 1996[5] Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: usual medical care	G1: 25 G2: 26	Mean (SD) SBP (mm Hg) at 6 months	Baseline G1: 151 (21) G2: 145 (19) p: 0.29 Follow-up G1: 140 (14) G2: 143 (20) Calculated Mean Difference: -9.0 95% CI, -19.45 to 1.45; p=0.0914
			Mean (SD) DBP (mm Hg) at 6 months.	Baseline G1: 82 (9) G2: 80 (9) p: NS Follow-up G1: 80 (8) G2: 79 (10) Calculated SMD, -1.0; 95% CI, -5.98 to 3.98; p=0.694
			Percent with blood pressure control	Baseline: G1: 52 G2: 54 Calculated p=0.90 Follow-up: G1: 68 G2: 58 Calculated OR: 1.6; 95% CI, 0.50 to 4.90; p=0.448

Table E7. Blood pressure: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Isetts et al., 2008[16] Cohort study/High	G1: MTM services provided by health plan in existing medical care clinics in collaboration with primary care providers. G2: Usual medical care without MTM	G1: 128 G2: 126	Percent of patients meeting HEDIS measures related to hypertension management at 12 months.	G1: 71 G2: 59 Calculated OR: 1.7; 95% CI, 1.03 to 2.91; p=0.04

Abbreviations: BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; HTN = hypertension; mm Hg = millimeter mercury; MTM = Medication Therapy Management; NR= not reported; OR = odds ratio; Q = quarter; RCT= randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation; SMD = standardized mean difference

Table E8. Drug therapy problems identified: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Krska et al., 2001[19] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Drug therapy problems identified for each study arm at 3 months	G1: 1206 G2: 1380
Harrison et al., 2012[15] Cohort/High	G1: Pharmaceutical care G2: Standard care	G1: 43 G2: 43	Drug therapy problems identified per visit, follow-up 2 weeks after intervention	Baseline G1: 0.5 (0.6) G2: NA Follow-up G1: 1.1 (1.3) G2: 0.7 (0.8) p= 0.19 for pharmaceutical care vs. standard care, not controlling for differences between G1 at baseline and G2
Welch et al., 2009[41] Cohort/High	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 123	At least 1 potential drug therapy problem during MTM process	G1: 89.8% G2: 83.7% Calculated p=0.062

Abbreviations: CI = confidence interval; G = group; MTM = Medication Therapy Management; NA = not applicable; RCT= randomized controlled trial; SMD: standardized mean difference.

Table E9. Drug therapy problems resolved: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Krska et al., 2001[19] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Drug therapy problems wholly or partially resolved at 3 months	G1: 998 G2: 569
Bernsten et al., 2001[1,2] RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 6 months G1: 1024 G2: 953 12 months G1: 863 G2: 764 18 months G1: 704 G2: 636	Number of changes in therapy at baseline, 6, 12, and 18 months	Baseline G1: 1.1 (1.3) G2: 0.9 (1.2) p: <0.05 6 months G1: 1.5 (1.8) G2: 1.1 (1.4) p: <0.05 12 months G1: 1.3 (1.6) G2: 1.2 (1.5) p: NS 18 months G1: 1.4 (1.5) G2: 1.4 (1.4) p: NS
Moczygemba et al., 2011[25] Moczygemba et al., 2008[26] Cohort/Medium	G1: Opt-in telephone MTM program G2: No-MTM control group	G1: 60 G2: 60	Medication and health-related problems identified at baseline and 6 months	Mean (SD) Baseline G1: 4.8 (2.7) G2: 9.2 (2.9) 6 month G1: 2.5 (2.0) G2: 7.9 (3.0) Calculated mean difference: -1.0 (95% CI, -1.97 to -0.03), p=0.4

Abbreviations: CI = confidence interval; G = group; MTM = Medication Therapy Management; NS = not significant; RCT = randomized controlled trial; SD = standard deviation; SMD = standardized mean difference.

Table E10. Medication adherence: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Adherence Outcome Type 1: Proportion of patients adherent based on a threshold of percent of pills taken				
Pindolia et al., 2009[30] Cohort study/High	G1: Telephone based MTM Program G2: Patients eligible for MTM program who declined enrollment	G1: 292 G2: 1081 (study year 1)	Percent of CHF patients who are adherent to at least 75% of ACE/ARB based on 2006 claims data: Measured during 6 months post-MTMP enrollment compared with 6 months pre-enrollment	Pre-test G1: 36 G2: 38.5 OR: 0.9 95% CI (0.7 to 1.2) p: 0.43 Post-test G1: 40 G2: 38 OR: 1.1 95% CI (0.8 to 1.4) p=0.53
			Percent of CHF patients who are Adherent to at least 75% of Beta Blocker based on 2006 claims data: Measured during 6 months post-MTMP enrollment compared with 6 months pre-enrollment	Pre-test G1: 34.5 G2: 33 OR: 1.1 95% CI (0.8 to 1.4) p=0.63 Post-test G1: 34 G2: 30.5 OR: 1.2 95% CI (0.9 to 1.5) p: 0.25
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	G1: 33 G2: 36	Percentage of patients adherent defined as self-reported taking 80% or more of medications 12 months after baseline	G1: 100 G2: 88.9 p: 0.115 Calculated OR: 9.3; 95% CI, 0.5 to 179.3; p=0.140

Table E10. Medication adherence: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Adherence Outcome Type 2: Absolute measure of adherence as percent of prescribed doses taken				
Moczygemba, 2011[25] Moczygemba, 2008[26] Retrospective cohort/ Medium	G1: Opt-in telephone SWHP MTM program G2: No-MTM control group	G1: 60 G2: 60	Percent prescribed doses taken: Overall average MPR across all medication (medication possession ratio) measured at 6 months before MTM participation (i.e., baseline) and 6 months post-MTM (i.e., follow-up) using pharmacy data	Baseline G1: 0.7 (0.2) G2: 0.7 (0.2) p: 0.73 6 months G1: 0.7 (0.2) G2: 0.7 (0.2) p: NR Overall p: 0.79 Calculated Standardized difference in Means: -0.1 95% CI (-0.5 to 0.2) p: 0.50
Planas, et al 2009[31] RCT/High	G1: Collaborative home-based medication review G2: No medication review received	Participants G1: 25 G2: 15	Percent mean adherence (percent of prescribed doses taken) to antihypertensive medication Measured twice (9 months before and 9 months after baseline visit) and continuously using medication acquisition method, in which days' supply of medication compared with dates medication filled using pharmacy refill data.	9 months before baseline, % (95% CI) G1: 80.5 (74.9 to 86.0) G2: 79.5 (71.0 to 88.1) 9 months after baseline, % (95% CI) G1: 87.5 (82.1 to 93.0) G2: 78.8 (69.7 to 87.9) p: 0.0712 Calculated standardized difference in means from Baseline to 9 months: 0.2 95% CI (-0.4 to 0.9) p: 0.46

Table E10. Medication adherence: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al., 1996[29] RCT/High	G1: Comprehensive pharmaceutical care G2: Usual care	Visit 1 G1: 7 G2: 5 Visit 2 G1: 21 G2: 23 Visit 3 G1: 23 G2: 20 Visit 4 G1: 21 G2: 22	Mean percent compliance (percent of prescribed pills taken) from pharmacist report of pill counts 4 month timeframe	Baseline/Visit 1 G1: 87.4 (0.9) G2: 87.8 (13.7) Visit 2 G1: 96.7 (4) G2: 86.0 (20.7) p=0.025 Visit 3 G1: 97.2 (4.4) G2: 86.7 (23.1) p=0.037 Visit 4 G1: 86.8 (28.7) G2: 89.1 (21.8) Calculated standardized difference in means for change from baseline to Visit 4: -0.1 95% CI (-0.7 to 0.5) p=0.77

Table E10. Medication adherence: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Adherence Outcome Type 3: Self-reported Adherence using Morisky Scale				
Bernsten, 2001[1]; Sturgess, 2003[2] RCT/ High (pooled data)	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	Pooled sample (excluding The Netherlands because no baseline adherence data collected) Baseline G1: 867 G2: 748 6 months G1: NR G2: NR 12 months G1: NR G2: NR 18 months G1: 792 G2: 758	Medication adherence: self-reported as assessed by Morisky Scale (Note: Percent of participants who we adherent defined as patients responded that they "never" experienced any aspects of non-compliance on the 4-item 4-point scale)	Pooled sample (percent adherent) Baseline G1: 33.9 G2: 38.6 OR: 0.8 Calculated 95% CI (0.7 to 1.0) p: 0.049 6 months G1: 38.5 G2: 36.6 p: NR 12 months G1: 43.8 G2: 37.3 p: NR 18 months G1: 38.2 G2: 39.4 OR: 1.1 95% CI (0.9 to 1.3) p=0.440101 Percent changing from nonadherent to adherent over 18 months G1: 15.2 G2: 12.2 p: 0.028

Table E10. Medication adherence: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001 (PREP)[39]; Kassam et al., 2001[40] RCT/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	T1: N=363 G1: 159 G2: 204 T2: N=317 T3: N=292	Self-reported adherence using the 4-item 2-point Morisky Scale where summary score is 0-4 with lower scores being better adherence	Mean Adherence Scale Score Time 1: G1: 0.5 (0.8) G2: 0.6 (0.9) p: NS
		Estimated by group based on overall retention G1: 127 G2: 163	Time 1 (Baseline), Time 2 (mid-point, 6 to 7 months after intervention) and Time 3 (12 to 13 months after intervention)	Calculated standardized difference in means: -0.1 95% CI (-0.3 to 0.1) p=0.208957 Time 2: G1: 0.5 (0.7) G2: 0.6 (0.8) p:NS Time 3: G1: 0.6 (0.8) G2: 0.5 (0.7) p: NS Calculated standardized difference in means: -0.13 95% CI (-0.11 to 0.36) p=0.289285

Table E10. Medication adherence: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Jameson, VanNoord, and Vanderwoud, 1995[17] RCT/High (medium for study overall by high for adherence due to poor measure)	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office.	G1: 27 G2: 29	Self-reported composite "understanding and compliance" 0-12 score at baseline and 6 months (no further information on measure used)	Baseline Means Scale Score (SD not reported) G1: 2.3 G2: 2.3 p: NS
			Change in self-reported composite score over 6 months with negative score representing improvement	6 months G1: 0.6 G2: 2.1 p: NS G1: -1.6 G2: -0.2 p: NS

Table E10. Medication adherence: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Miscellaneous Adherence Outcomes				
Hanlon et al., 1996[14] RCT/Medium (low for study overall but medium for adherence due to lack of information about and precision of adherence measure)	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	G1: 86 G2: 83	Self-report Medication Compliance with 12 month time frame, assessed by determining whether the way patient said they took the medicine (in terms of number of pills and daily frequency) matched how it was prescribed. Compliance was defined as the proportion of medications for which the patients' response agreed with the directions	Baseline: G1: 73% G2: 74% OR: 0.95 95% CI (0.48 to 1.88) p: 0.88 12 Months Follow-up G1: 77.4% G2: 76.1% p: 0.88
Sidel et al., 1990[34] RCT/Medium	G1: received at least 2 pharmacist visits involving medication review, patient specific education and counseling; follow up patient phone calls and contact of physicians as needed G2: only contacted for to complete the survey.	G1: 92 G2: 104	Medication-taking Behavior Subscore in change from baseline to 6 month follow-up (negative scores indicate improvement= decreased risk)	G1: -3.47 G2: -4.38 p< .001 for within group differences p: 0.52 for between group differences
			Change in normative score for Remembering to take Medicine at 6 months	G1: 0.09 G2: -0.19 p: 0.52

Abbreviations: ACE/ARB = Angiotensin-Converting Enzyme/Angiotensin II Receptor Blockers; CHF = Cardiovascular Heart Failure; CI = confidence interval; G = group; GMC = General Medicine Clinic; MPR = medication possession ratio; MTM = Medication Therapy Management; MTMP = Medication Therapy Management Program; NR = not reported; NS = not sufficient; OR = odds ratio; PREP = Pharmaceutical Care Research and Education Project; RCT= randomized controlled trial; SD = standard deviation; SWHP = Scott & White Health Plan; T = time.

Table E11. Medication appropriateness scales: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	G1: 105 G2: 103	Covariate-adjusted Medication Appropriateness Index Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 17.7 (0.6) G2: 17.6 (0.6) 3 months G1: 13.4 (0.6) G2: 16.5 (0.6) 95% CI: NR p:<0.0006 for between group differences, controlling for baseline and other covariates 12 months G1: 12.8 (0.7) G2: 16.7 (0.7) 95% CI: NR p:<0.0006 for between group differences, controlling for baseline and other covariates
		G1: 105 G2: 103	Change in covariate-adjusted Medication Appropriateness Index Assessed at baseline, 3, 12 months by blinded research pharmacist	3 months change in outcome G1: -4.3 G2: -1.1 95% CI: NR 24% improvement in intervention group compared to a 6% improvement in control group p: 0.0006 12 months change in outcome G1: -4.9 G2: -0.9 95% CI: NR 28% improvement in intervention group versus 5% improvement in control group p: 0.0002

Table E11. Medication appropriateness scales: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al., 1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort study/High	G1: Pharmacy-based pharmaceutical care G2: Usual medical care	G1: 25 G2: 26	Appropriateness of BP regimen A blinded review panel of three evaluated cases in random order on a visual analog scale, using medical records. The investigators averaged and converted scores to a numerical value by measuring the distance from the best option. Score arranged from 0-16.2. Higher scores are more positive.	BP Regimen Baseline G1: 8.7 (4.7) G2: 10.3 (4.8) Follow-up G1: 10.9 (4.5) G2: 10.1 (5.2) p for change scores NR
			Appropriateness of daily dosage	Appropriateness of daily dosage Baseline G1: 11.6 (4.5) G2: 12.6 (4.5) Follow-up G1: 13.4 (3.7) G2: 13.2 (4.1) p for change scores NR
			Appropriateness of dosing interval	Appropriateness of dosing interval Baseline G1: 13.8 (4.3) G2: 13.4 (4.6) Follow-up G1: 15.1 (2.3) G2: 13.8 (4.1) p for change scores NR

Abbreviations: BP = blood pressure; CI = confidence interval; G = group; GMC = General Medicine Clinic; NR = not reported; RCT = randomized controlled trial

Table E12. Medication appropriateness for individual medications: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
McDonough et al., 2005[24] cluster-randomized RCT/Medium	G1: Pharmaceutical care provided by pharmacist in a community pharmacy G2: Usual care	Baseline G1: 70 G2: 26 Follow-up G1: 61 G2: 19	Nine Month Follow-up Percentage of patients (at risk for glucocorticoid-induced osteoporosis) on bisphosphonate drug therapy	Baseline G1: 17.1 G2: 0 p: <0.05 for between group difference at baseline 9 Month Follow-up G1: 26.2 (p <0.05 for within group difference as compared to baseline) G2: 10.5 p: NS for between group difference at follow-up; change in outcome between baseline and follow-up was NS between groups
			Percentage of patients (at risk for glucocorticoid-induced osteoporosis) on estrogen drug therapy	Baseline G1: 12.9 G2: 0 p: NS for between group difference at baseline 9 Month Follow-up G1: 16.4 (p <0.05 for within group difference as compared to baseline) G2: 0 p: NS for between group difference at follow-up; change in outcome between baseline and follow-up was NS between groups.
			Percentage of patients (at risk for glucocorticoid-induced osteoporosis) taking calcium supplements	Baseline G1: 38.6 G2: 38.5 p: Between group differences at baseline presumably not significant, since P was reported for other outcomes if significantly different between groups. 9 Month Follow-up G1: 55.7 (p <0.05 for within group difference as compared to baseline) G2: 31.6 p: <0.05 for change in outcome between groups from baseline to follow-up

Table E12. Medication appropriateness for individual medications: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Gattis et al., 1999[13] RCT/Medium	G1: Clinical pharmacist intervention G2: Usual medical care	G1: 90 G2: 91	6 month follow-up Percent receiving an ACEI at follow-up	G1: 87 G2: 79 p: 0.18
			Fraction of target ACEI dose at follow up	G1: 1 (25%: 0.5, 75%: 1) G2: 0.5 (25% 0.188, 75%: 1) 95% CI: NR p: < 0.001
		G1: 12 G2: 19	Of those NOT on an ACEI at follow-up, percentage receiving alternative drug therapy	G1: 75 G2: 26 p: 0.02

Abbreviations: ACEI = Angiotensin-Converting Enzyme Inhibitors; CI = confidence interval; G = group; NR = not reported; RCT = randomized controlled trial

Table E13. Medication Appropriateness Index Item 1 (Is there an indication for the drug?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 10.5 G2: 12.4 3 months G1: 8.1 G2: 10.5 p: NR 12 months G1: 6.0 G2: 9.7 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 33.3 G2: 46.8 12 months G1: 16.1 G2: 48.2

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E14. Medication Appropriateness Index Item 2 (Is the medication effective for the condition?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 4.5 G2: 4.9 3 months G1: 3.6 G2: 4.9 p: NR 12 months G1: 3.4 G2: 4.9 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 29.1 G2: 44.9 12 months G1: 13.6 G2: 44.6

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E15. Medication appropriateness index Item 3 (Is the dosage correct?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 17.4 G2: 17.3 3 months G1: 13.1 G2: 18.2 p: NR 12 months G1: 15.0 G2: 20.4 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 63.3 G2: 62.3 12 months G1: 12.9 G2: 63.8

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E16. Medication Appropriateness Index Item 4 (Are the directions correct?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 32.7 G2: 32.2 3 months G1: 28.1 G2: 32.6 p: NR 12 months G1: 27.5 G2: 29.9 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 70.5 G2: 64.3 12 months G1: 29.7 G2: 56.7

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E17. Medication Appropriateness Index Item 5 (Are the directions practical?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic (GMC)	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 20.7 G2: 20.0 3 months G1: 15.8 G2: 18.9 p: NR 12 months G1: 15.3 G2: 21.2 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 61.0 G2: 57.0 12 months G1: 29.7 G2: 56.7

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E18. Medication Appropriateness Index Item 6 (Are there clinically significant drug-drug interactions?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 0 G2: 0 3 months G1: 0 G2: 0.1 p: NR 12 months G1: 0 G2: 0.1
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 22.9 G2: 17.9 12 months G1: 5.8 G2: 22.8

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E19. Medication Appropriateness Index Item 7 (Are there clinically significant drug-disease interactions?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 1.9 G2: 1.0 3 months G1: 2.0 G2: 0.7 p: NR 12 months G1: 1.9 G2: 1.1 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 18.6 G2: 21.3 12 months G1: 9.0 G2: 19.6

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E20. Medication Appropriateness Index Item 8 (Is there unnecessary duplication with other drugs?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the General Medicine Clinic (GMC)	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescription Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 4.9 G2: 6.4 3 months G1: 3.0 G2: 5.9 p: NR 12 months G1: 4.9 G2: 8.2 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 11.9 G2: 6.8 12 months G1: 4.5 G2: 7.6

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E21. Medication Appropriateness Index Item 9 (Is the duration of therapy acceptable?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	N participants G1: 105 G2: 103 Number of prescriptions: Baseline G1: 798 G2: 846 12 months G1: 734 G2: 847	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 15.4 G2: 17.5 3 months G1: 11.8 G2: 14.9 p: NR 12 months G1: 10.1 G2: 14.9 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	N participants G1: 33 G2: 36 Number of prescriptions: Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 35.2 G2: 48.8 12 months G1: 18.1 G2: 49.1

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; N = number; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E22. Medication Appropriateness Index Item 10 (Is this drug the least expensive alternative compared with others of equal utility?): Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care, plus clinical pharmacist care. G2: Usual care in the GMC	G1: 105 G2: 103	Percent Prescriptions Inappropriate Assessed at baseline, 3, 12 months by blinded research pharmacist	Baseline G1: 29.2 G2: 30.3 3 months G1: 25.6 G2: 27.7 p: NR 12 months G1: 25.3 G2: 28.2 p: NR
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care G2: Standard care	Baseline G1: 210 G2: 207 12 months G1: 155 G2: 224	Percent Prescriptions Inappropriate Assessed at baseline, 12 months by blinded research pharmacist	Baseline G1: 50.0 G2: 62.3 12 months G1: 38.7 G2: 60.3

Abbreviations: CI = confidence interval; diff = difference; G = group; GMC = General Medicine Clinic; NR = not reported; RCT = randomized controlled trial; SE = standard error; Std = standard

Table E23. Medication dosing: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Chisholm, 2002[6] RCT/Medium	G1: Clinical MTM pharmacy services G2: Routine clinic services interaction with renal transplant clinic team, but no clinical pharmacist	G1: 13 G2: 10	(Unspecified timeframe) Mean daily cyclosporin dose (mg/kg)	G1: 6.8 (1.3) G2: 7.1 (1.2) p: 0.703
			Mean daily tacrolimus dose (mg/kg)	G1: 0.2 (0.05) G2: 0.2 (0.04) p: 0.823
			Mean daily prednisone dose (mg)	G1: 12.3 (2.8) G2: 13.2 (3.2) p: 0.705
Jameson, VanNoord, and Vanderwoud, 1995[17] RCT/Medium	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office.	G1: 27 G2: 29	Change in number of doses per day at 6 months follow up.	G1: - 1.6 G2: 2.2 p: 0.007

Abbreviations: CI = confidence interval; G = group; mg/kg = milligram/kilogram; MTM = Medication Therapy Management; NR = not reported; RCT = randomized controlled trial

Table E24. Adverse events: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Clinical pharmacist care within a general medicine clinic. G2: Usual care	G1: 86 G2: 83	Percent with an ADE at 12 months	G1: 30.2 G2: 40.0 p=0.19 Calculated OR: 0.6; 95% CI, 0.37 to 1.15 p=0.014
Touchette et al., 2012[37] RCT/Low	G1: Basic MTM services (with medication information gleaned through patient interview) G2: Enhanced MTM services (pharmacist provided with 2 page clinical summary from patient medical record). G3: Usual pharmacy care	G1: 211 G2: 218 G3: 208	Percent of patients with an ADE between 0 and 3 months and OR	G1: 42.2 G2: 27.9 G3: 33.7 G1 vs. G3: OR: 1.6 (p=0.078) G2 vs. G3: OR: 0.7 (p=0.278)
			Percent of patients with an ADE between 3 and 6 months and OR	G1: 36.1 G2: 31.1 G3: 34.4 G1 vs. G3: OR: 1.1 (p=0.717) G2 vs. G3: OR: 0.9 (p=0.672)
			Mean number (SD) of ADEs per patient between 0 and 3 months	G1: 0.8 (1.1) G2: 0.5 (1.2) G3: 0.6 (1.2) G1 vs. G3: Calculated SMD, 0.2; 95% CI, -0.03 to 0.36 p=0.110 G2 vs. G3: Calculated SMD, -0.01; 95% CI, -0.20 to 0.18 p=0.916
			Mean number (SD) of ADEs per patient between 3 and 6 months	G1: 0.8 (1.4) G2: 0.5 (0.8) G3: 0.5 (0.9) G1 vs. G3: Calculated SMD, 0.2; 95% CI, 0.05 to 0.43 p=0.041 G2 vs. G3: Calculated SMD, -0.1; 95% CI, -0.26 to 0.12 p=0.479

Table E24. Adverse events: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Fischer et al., 2000[10] NRCT/High	G1: Comprehensive drug therapy management program G2: Standard community pharmacy practice	G1: 201 G2: 368	OR for likelihood of reporting side effects or problems due to prescription medication (95% CI)	1.8 (1.20 to 2.80)
Taylor, Byrd, and Krueger, 2003[36] RCT/High	G1: Pharmaceutical care G2: Standard care	G1: 33 G2: 36	Percent of patients with at least one medication misadventure at 12 months	G1: 2.8 [a] (N=4) G2: 3.0 [a] (N=3) Calculated OR based on reported percent: 0.93; 95% CI, 0.056 to 15.603 p: 0.0961 Calculated OR based on reported N: 1.5 (95% CI, 0.31 to 7.34), p= 0.606
Jameson, VanNoord, and Vanderwoud, 1995[17] RCT/High	G1: Consultation with a clinical pharmacist within a primary care office. G2: Standard medical care at the primary care office.	G1: 27 G2: 29	Change in mean medication side effect score at six months.	G1: -3.7 G2: -1.9 p: NS and unable to calculate.

[a] The percent reported by authors cannot be generated based on the reported N and the reported number of events.

Abbreviations: ADE = adverse drug event; CI = confidence interval; DRP = drug-related problems; G = group; MTM = Medication Therapy Management; N = number; NRCT = nonrandomized controlled trial; NS = not significant; NS = not sufficient; OR = odds ratio; RCT = randomized controlled trial; SD = standard deviation; SMD = standardized mean difference; vs. = versus.

Table E25. All-cause mortality: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Triller and Hamilton, 2007[38] RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: 77 G2: 77	RR for all-cause mortality within 180 days	G1: 22% G2: 18% RR: 1.21 (Calculated 95% CI, 0.65 to 2.30) p=0.67
Gattis et al., 1992 [#2564} RCT/Medium	G1: Clinical pharmacist intervention in addition to usual medical care G2: Usual medical care	G1: 90 G2: 91	OR for all-cause mortality within 6 months (95% CI)	G1: 3.3% G2: 5.5% OR: 0.6 (0.12 to 2.49) p=0.48
Welch et al., 2009[41] Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (opt-out)	G1: 459 G2: 336	Adjusted OR for all-cause mortality, within 6 months (adjusted for age, sex, chronic disease score, specific baseline utilization) (95% CI)	G1: 4.1% G2: 7.4% Adjusted OR: 0.5 (0.3 to 0.9) p=0.044

Abbreviations: CI = confidence interval; G = group; MTM = Medication Therapy Management; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk.

Table E26. Self-reported health status: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Physical Functioning Domain (change from baseline)	6-Month Follow-up G1: -4.9 (1.0 SE) G2: -3.4 (0.9 SE) 12-Month Follow-up G1: -5.3 (1.0 SE) G2: -6.1 (1.0 SE) p=0.412
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Physical Functioning Domain	Baseline G1: 62.0 (29.4) G2: 61.9 (24.3) 12-Month Follow-up G1: 68.6 (24.0) G2: 56.1 (27.5) p: NS
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Physical Functioning Domain	Baseline: G1: 48.0 (2.7) G2: 45.3 (2.7) 12-Month Follow-up G1: 44.1 (2.0) G2: 42.2 (2.0) p= 0.99
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 18 months G1: 704 G2: 636	SF-36 Physical Functioning Domain (Change between Baseline and 18-Month Follow-Up)	G1: -1.0 G2: -0.7 p: NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Physical Functioning Domain	Baseline G1: 61.5 G2: 66.5 6-Month Follow-up G1: 70.7 G2: 67.7 p=NR
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Physical Functioning Domain	Baseline G1: 77.0 (26.1) G2: 66.3 (29.1) 4-Month Follow-up G1: 77.8 (30.4) G2: 70.2 (29.2) p=NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Physical Functioning Domain	Baseline G1: 55.6 (95% CI, 55.5 to 56.0) G2: 54.2 (95% CI, 48.0 to 54.4) 5-Month Follow-up G1: 55.0 (95% CI, 54.6 to 55.3) G2: 55.0 (95% CI, 54.8 to 55.2) p: 0.93
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Physical Functioning Domain	G1: NR G2: NR p: NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Role Physical Domain (change from baseline)	6-Month Follow-up G1: -3.5 (1.8 SE) G2: -4.3 (2.1 SE) 12-Month Follow-up G1: -4.3 (2.0 SE) G2: -8.2 (2.00 SE) p=0.245
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Role Physical Domain	Baseline G1: 50.8 (42.2) G2: 47.9 (42.8) 12-Month Follow-up G1: 68.2 (42.1) G2: 52.8 (42.2) 95% CI: NR p=NS
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Role Physical Domain	Baseline: G1: 38.3 (3.2) G2: 36.5 (3.2) 12-Month Follow-up G1: 38.6 (3.2) G2: 32.3 (3.7) p=0.99
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 18 months G1: 704 G2: 636	SF-36 Role Physical Domain (Change between Baseline and 18-Month Follow-Up)	G1: -1.1 G2: -0.3 p=NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997[4], Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Role Physical Domain	Baseline G1: 54.3 G2: 63.5 6-Month Follow-up G1: 74.0 G2: 62.5 p=NR
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Role Physical Domain	Baseline G1: 85.9 (30.0) G2: 77.9 (31.1) 4-Month Follow-up G1: 85.2 (31.5) G2: 73.1 (40.6) p=NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Role Physical Domain	Baseline G1: 53.8 (95% CI, 53.1 to 54.6) G2: 55.0 (54.5 to 55.5) Exit G1: 48.5 (95% CI, 47.8 to 49.3) G2: 52.1 (95% CI, 41.6 to 42.6) p: 0.65
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Role Physical Domain	G1: NR G2: NR p: NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Bodily Pain Domain (change from baseline)	6-Month Follow-up G1: -0.8 (1.0 SE) G2: -3.3 (0.9 SE) 12-Month Follow-up G1: -0.3 (1.0 SE) G2: -4.8 (1.0 SE) p=0.004
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Bodily Pain Domain	Baseline G1: 60.0 (27.0) G2: 65.4 (23.0) 12-Month Follow-up G1: 68.5 (22.3) G2: 63.1 (25.8) p=NS
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Bodily Pain Domain	Baseline G1: 45.0 (2.8) G2: 42.2 (2.8) 12-Month Follow-up G1: 43.6 (2.7) G2: 41.7 (2.7) p=0.99
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 18 months G1: 704 G2: 636	SF-36 Bodily Pain Domain (Change between Baseline and 18-Month Follow-Up)	G1: -0.06 G2: +0.53 p=NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997,[4] Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Bodily Pain Domain	Baseline G1: 58.4 G2: 76.7 6-Month Follow-up G1: 71.1 G2: 74.7 p=NR
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Bodily Pain	Baseline G1: 77.4 (19.0) G2: 73.1 (21.3) 4-Month Follow-up G1: 80.5 (22.9) G2: 73.7 (19.0) p=NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Bodily Pain	Baseline G1: 60.5 (95% CI, 60.2 to 60.8) G2: 60.8 (95% CI, 60.6 to 61.0) 5-Month Follow-up G1: 56.6 (95% CI, 56.4 to 56.8) G2: 59.0 (95% CI, 58.8 to 59.2) p: 0.65
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Bodily Pain	G1: NR G2: NR p: NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 General Health Perception Domain (change from baseline)	6-Month Follow-up G1: -1.6 (0.8 SE) G2: -2.2 (0.7 SE) 12-Month Follow-up G1: -2.4 (0.8 SE) G2: -5.3 (0.8 SE) 95% CI: NR p=0.026
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 General Health Perception Domain	Baseline G1: 50.8 (19.5) G2: 49.9 (19.8) 12-Month Follow-up G1: 57.0 (19.6) G2: 50.1 (15.9) p: NS
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 General Health Perception Domain	Baseline G1: 34.9 (2.1) G2: 34.2 (2.1) 12-Month Follow-up G1: 37.4 (1.6) G2: 35.2 (1.7) p=0.99
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 18 months G1: 704 G2: 636	SF-36 General Health Perception Domain (Change between Baseline and 18-Month Follow-Up)	G1: +0.28 G2: -0.66 p: NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 General Health Perception Domain	Baseline G1: 58.2 G2: 61.2 6-Month Follow-up G1: 58.7 G2: 64.0 p=NR
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 General Health Perception Domain	Baseline G1: 67.8 (18.7) G2: 59.5 (15.1) 4-Month Follow-up G1: 72.3 (13.1) G2: 64.7 (19.0) p: NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 General Health Perception Domain	Baseline G1: 62.2 (95% CI, 61.9 to 62.6) G2: 65.0 (95% CI, 64.8 to 65.2) 5-Month Follow-up G1: 60.5 (95% CI, 60.3 to 60.7) G2: 60.8 (95% CI, 60.6 to 61.0) p: 0.17
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 General Health Perception Domain	G1: NR G2: NR p: NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Social Functioning Domain	Baseline G1: 88.6 (16.8) G2: 81.3 (18.5) 4-Month Follow-up G1: 90.2 (15.5) G2: 81.0 (19.1) p: NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Social Functioning Domain	Baseline G1: 79.2 (95% CI, 79.0 to 79.4) G2: 81.9 (95% CI, 81.8 to 82.0) 5-Month Follow-up G1: 75.4 (95% CI, 75.1 to 75.8) G2: 77.5 (95% CI, 77.3 to 77.7) p: 0.34
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Social Functioning Domain	G1: NR G2: NR p: NS
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Role Emotional Domain (change from baseline)	6-Month Follow-up G1: -2.6 (2.2 SE) G2: -3.4 (1.9 SE) 12-Month Follow-up G1: -0.3 (2.3 SE) G2: -7.4 (2.3 SE) p=0.065

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Role Emotional Domain	Baseline G1: 59.6 (44.7) G2: 69.4 (45.3) 12-Month Follow-up G1: 82.8 (36.4) G2: 65.8 (45.4) p: NS
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Role Emotional Domain	Baseline: G1: 73.0 (4.1) G2: 68.1 (4.1) 12-Month Follow-up G1: 66.4 (1.8) G2: 67.0 (3.9) p=0.99
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 18 months G1: 704 G2: 636	SF-36 Role Emotional Domain (Change between Baseline and 18-Month Follow-Up)	G1: +0.2 G2: -2.9 p: NS
Carter et al.,1997[4], Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Role Emotional Domain	Baseline G1: 50.0 G2: 69.4 6-Month Follow-up G1: 63.9 G2: 65.3 p=NR

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Role Emotional Domain	Baseline G1: 88.4 (25.8) G2: 88.5 (28.2) 4-Month Follow-up G1: 92.8 (24.5) G2: 78.2 (29.7) p: NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Role Emotional Domain	Baseline G1: 71.8 (95% CI, 70.9 to 72.7) G2: 74.9 (95% CI, 74.5 to 75.2) 5-Month Follow-up G1: 66.4 (95% CI, 65.7 to 67.0) G2: 72.7 (95% CI, 72.1 to 73.2) p: 0.80
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Role Emotional Domain	G1: NR G2: NR p: NS
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Mental Health Domain (change from baseline)	6-Month Follow-Up G1: -0.5 (0.8 SE) G2: -1.4 (0.7 SE) 12-Month Follow-up G1: 0.1 (0.8 SE) G2: -2.3 (0.8 SE) p=0.029

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Taylor, Byrd, and Krueger, 2003[36] RCT/Medium	G1: Pharmaceutical care provided by pharmacist in conjunction with an outpatient physician office visit G2: Standard care.	G1: 33 G2: 36	SF-36 Mental Health Domain	Baseline G1: 72.0 (17.4) G2: 69.0 (18.6) 12-Month Follow-up G1: 73.1 (21.2) G2: 72.3 (17.1) p=NS
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	SF-36 Mental Health Domain	Baseline: G1: 61.0 (2.5) G2: 63.5 (2.5) 12-Month Follow-up G1: 61.1 (1.8) G2: 60.4 (1.8) p=0.99
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 18 months G1: 704 G2: 636	SF-36 Mental Health Domain (Change between Baseline and 18-Month Follow-Up)	G1: -0.8 G2: -1.3 p=NS
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Mental Health Domain	Baseline G1: 73.4 G2: 75.5 6-Month Follow-up G1: 71.0 G2: 75.7 p: NR

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Mental Health Domain	Baseline G1: 77.0 (14.6) G2: 73.1 (21.3) 4-Month Follow-Up G1: 80.2 (14.6) G2: 73.7 (19.0) p=NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Mental Health Domain	Baseline G1: 75.2 (95% CI, 75.1 to 75.3) G2: 76.7 (95% CI, 75.8 to 77.6) 5 Month Follow-Up G1: 74.2 (95% CI, 74.0 to 74.3) G2: 74.7 (95% CI: 74.7 to 74.8) p: 0.49
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Mental Health Domain	G1: NR G2: NR p: NS
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 18 months G1: 704 G2: 636	SF-36 Mental Health Domain (Change between Baseline and 18-Month Follow-Up)	G1: -0.8 G2: -1.3 p=NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	SF-36 Mental Health Domain	Baseline G1: 73.4 G2: 75.5 6-Month Follow-Up G1: 71.0 G2: 75.7 p:NR
Park et al, 1996[29] RCT/High	G1: comprehensive pharmaceutical care G2: usual care	G1: 23 G2: 26	SF-36 Mental Health Domain	Baseline G1: 77.0 (14.6) G2: 73.1 (21.3) 4-Month Follow-Up G1: 80.2 (14.6) G2: 73.7 (19.0) p=NS
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Mental Health Domain	Baseline G1: 75.2 (95% CI, 75.1 to 75.3) G2: 76.7 (95% CI, 75.8 to 77.6) 5 Month Follow-Up G1: 74.2 (95% CI, 74.0 to 74.3) G2: 74.7 95% CI, (74.7 to 74.8) p: 0.49
Krska et al, 2001[19] RCT/Medium	G1: Pharmacist-led medication review G2: Usual care involving interviews and identification of PCIs but with no pharmaceutical care plan implemented.	Baseline G1: 168 G2: 164 (Not clear if all were included in analyses)	SF-36 Mental Health Domain	G1: NR G2: NR p: NS

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	SF-36 Change in Health (change from baseline)	6-Month Follow-Up G1: -1.1 (1.3) G2: -4.8 (1.3) 12-Month Follow-Up G1: -2.4 (1.5 SE) G2: -6.3 (1.3 SE) 95% CI: NR p=0.004
Triller and Hamilton, 2007[38] RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: 77 G2: 77	SF -12 assessed at 30, 90, and 180 day follow ups	Values not reported, but results state that values did not significantly differ between the two groups.
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Question 1: Overall Health Rating	Baseline G1: 3.3 (95% CI, 3.3 to 3.3) G2: 3.4 (95% CI, 3.3 to 3.4) 5-Month Follow-Up G1: 3.2 (95% CI, 3.2 to 3.3) G2: 3.2 (95% CI, 3.2 to 3.3) p: 0.35
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Physical Component	Baseline G1: 39.1 (95% CI, 37.2 to 41.0) G2: 38.9 (95% CI, 37.7 to 40.1) 5-Month Follow-Up G1: 37.9 (95% CI, 36.6 to 39.2) G2: 38.4 (95% CI, 37.2 to 39.7) p: 0.30

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001,[39,40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	SF-36 Physical Component	Time 1: G1: 38.4 (12.7) G2: 40.1 (11.9) 6-7 Month Follow-Up G1: 38.0 (11.9) G2: 39.2 (11.6) 12-13 Month Follow-Up G1: 36.9 (11.6) G2: 38.4 (11.4) p= NS (Between group comparisons at follow-up assessments)
Sellors et al., 2003[33] RCT-Cluster randomized/Medium	G1: Pharmacists conducted face-to-face medication reviews with the patients and then gave written recommendations to the physicians to resolve any drug-related problems. G2: Usual Care for Family Physicians and their Patients from matched postal codes.	Baseline G1: 379 G2: 409	SF-36 Mental Component	Baseline G1: 52.2 (95% CI, 50.8 to 53.5) G2: 53.4 (95% CI, 52.6 to 54.3) 5-Month Follow-Up G1: 51.0 (95% CI, 49.7 to 52.4) G2: 52.2 (95% CI, 51.2 to 53.2) p: 0.65

Table E26. Self-reported health status: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001,[39,40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	SF-36 Mental Component	Time 1: G1: 55.1 (8.7) G2: 53.2 (9.3) 6-7 Month Follow-Up G1: 55.9 (9.1) G2: 54.4 (9.3) 12-13 Month Follow-Up G1: 56.1 (8.3) G2: 54.6 (8.7) p= NS (Between group comparisons at follow-up assessments)
Williams et al., 2004[42] RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary team in addition to usual care and "Bound for Health" booklet. G2: Usual care plus provision of "Bound for Health" booklet	G1: 57 G2: 76	SF-36 Overall Score	Baseline: G1: 61.8 (17.8) G2: 63.3 (16.5) 6-Week Follow-Up: G1: 65.5 (18.9) G2: 65.7 (17.0) p=NS

Abbreviations: G = group; N = number; NR = not reported; CI = confidence interval; NS = not sufficient; PCIs = pharmaceutical care issues; RCT= randomized controlled trial; SE = standard error; SF-36 = multi-purpose, short-form health survey with only 36 questions; VA = Veteran's Administration

Table E27. Condition-specific quality-of-life: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Pai et al., 2009[27]; Pai et al., 2009[28] RCT/High	G1: Pharmaceutical care, consisting of one-on-one care, with in-depth drug therapy reviews conducted by a clinical pharmacist G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	Baseline G1: 61 G2: 44 Year 1: G1: 44 G2: 36 Year 2: G1: 24 G2: 32	Renal Quality of Life Profile (Increased score indicates worsening of HRQOL, maximum score=172)	Total Score Baseline G1: 71.9 (40) G2: 74.5 (33.5) Y1 G1: 71.4 (33.6) G2: 87.5 (30.4) Y2 G1: 56.5 (32.6) G2: 68.8 (35.8) p<0.05 for G1 vs. G2 for Y1;
Clifford et al., 2002[9] RCT/Medium	G1: Collaborative pharmaceutical care program G2: Standard outpatient care for diabetes	G1: 48 G2: 25	Diabetes Quality of Life instrument Scale of 1-5, with higher scores indicating greater dissatisfaction, worry, or impact of diabetes	Baseline G1: 2.0 (0.6) G2: 1.9 (0.5) p: NS 6-Month Follow-Up G1: 1.9 (0.5) G2: 1.9 (0.4) p>0.15

Abbreviations: G = group; HRQOL = health related quality of life; N = number; NCRT=Non-randomized controlled trial; NS = not sufficient; RCT= randomized controlled trial; vs. = versus

Table E28. Patient satisfaction: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	General health care satisfaction at 12-Month Follow Up (Higher scores indicate greater dissatisfaction)	G1: 1.5 (0.7) G2: 1.6 (0.8) p=0.70
Hanlon et al., 1996[14] RCT/Low	G1: Usual care at outpatient clinic, plus clinical pharmacist care. G2: Usual care at outpatient clinic	G1: 86 G2: 83	Pharmacy-related health care satisfaction at 12-month Follow-Up (Higher scores indicate greater dissatisfaction)	G1: 5.2 (1.5) G2: 5.4 (1.7) p=0.52
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al, 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care provided by clinical pharmacists within ambulatory VA clinics G2: Usual care (i.e., no pharmaceutical care)	G1: 447 G2: 484	Patient satisfaction with primary health care provider (Higher scores indicate greater satisfaction)	G1: Time 1: 51.9 (7.5) Time 2: 51.7 (7.3) G2: Time 1: 51.9 (7.5) Time 2: NR p=NS
Bernsten et al., 2001[1]; Sturgess et al., 2003[2] RCT, Cluster-Randomized/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 6 months G1: 1024 G2: 953 12 months G1: 863 G2: 764 18 months G1: 704 G2: 636	% rating pharmacy services provided as "excellent"	Baseline G1: 66.2 G2: 68.2 p: NR 6 months G1: 72.8 G2: 63.7 p: <0.05 12 months G1: 73.4 G2: 71.2 p: NR 18 months G1: 73.8 G2: 64.6 p: <0.05

Table E28. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am very satisfied with the pharmacy services I receive," collected at 6 months	G1: 100 G2: 96 p: 0.065
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "Overall, the program provided a valuable service to me," collected at 6 months	G1: 100 G2: 80 p: 0.0018
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "The quality of information provided to me by the pharmacist was excellent," collected at 6 months	G1: 100 G2: 88 p: 0.012
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "My participation in this program helped me to understand high blood pressure better," collected at 6 months	G1: 100 G2: 83 p: 0.011
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "The area was private enough for me to feel comfortable talking about my high blood pressure," collected at 6 months	G1: 96 G2: 96 p: 0.036
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I felt comfortable talking with the pharmacist about my health problems," collected at 6 months	G1: 100 G2: 96 p: 0.052

Table E28. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am confident the pharmacist is able to help me control my high blood pressure," collected at 6 months	G1: 100 G2: 92 p: 0.340
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am confident the information provided by the pharmacist to the physician improved my health care," collected at 6 months	G1: 87 G2: 83 p: 0.325
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "There are things about the high blood pressure program that could be better," collected at 6 months	G1: 9 G2: 0 p: 0.157
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I am very willing to continue to see the pharmacist for help with my high blood pressure control," collected at 6 months	G1: 95 G2: 88 p: 0.459
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I think the pharmacist should provide this type of service for everyone," collected at 6 months	G1: 77 G2: 75 p: 0.890
Carter et al.,1997[4]; Barnette, Murphy, and Carter, 1996[5] Cohort/High	G1: Pharmaceutical care G2: Usual care with patients seen by pharmacists who did not participate in the intensive skills development program	G1: 25 G2: 26	Percent of patients agreeing or strongly agreeing with statement, "I think the pharmacist should be paid for this type of service," collected at 6 months	G1: 91 G2: 82 p: 0.379

Table E28. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	General satisfaction (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.59 (0.77) G2: 1.56 (0.73) Time 2: G1: 1.51 (0.84) G2: 1.57 (0.72) Time 3: G1: 1.53 (0.77) G2: 1.62 (0.88) p= NS for all between-group differences
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Interpersonal skills (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.36 (0.48) G2: 1.37 (0.53 Time 2: G1: 1.37 (0.59) G2: 1.35 (0.57) Time 3: G1: 1.31 (0.50) G2: 1.45 (0.72) p= NS for all between-group differences

Table E28. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Evaluation and goal setting (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 2.58 (1.12) G2: 2.74 (1.09) Time 2: G1: 2.46 (0.98) G2: 2.98 (1.24) Time 3: G1: 2.49 (1.10) G2: 2.90 (1.08) p<0.05 for between-group differences in score changes from Time 1 to Time 2 and Time 1 to Time 3
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Trust (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.62 (0.66) G2: 1.46 (0.57) Time 2: G1: 1.40 (0.54) G2: 1.39 (0.58) Time 3: G1: 1.43 (0.58) G2: 1.51 (0.75) p<0.05 for between-group differences in score changes from Time 1 to Time 2 p<0.05 for group x measure interaction over all three time periods

Table E28. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Helping patients (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 2.25 (1.31) G2: 2.22 (1.14) Time 2: G1: 1.98 (1.17) G2: 2.23 (1.15) Time 3: G1: 2.07 (1.22) G2: 2.37 (1.21) p= NS for all between-group differences
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Explanation (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.34 (0.55) G2: 1.34 (0.63) Time 2: G1: 1.39 (0.67) G2: 1.30 (0.56) Time 3: G1: 1.38 (0.73) G2: 1.35 (0.61) p= NS for all between-group differences

Table E28. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Pharmacy finances (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 3.08 (1.82) G2: 2.85 (1.80) Time 2: G1: 2.89 (1.89) G2: 2.86 (1.75) Time 3: G1: 3.08 (1.80) G2: 3.16 (1.88) p= NS for all between-group differences
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Drug plan finances (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 3.31 (1.70) G2: 3.41 (1.75) Time 2: G1: 3.45 (1.96) G2: 3.39 (1.83) Time 3: G1: 3.65 (1.67) G2: 3.56 (1.83) p= NS for all between-group differences

Table E28. Patient satisfaction: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Volume et al., 2001[39]; Kassam et al., 2001[40] RCT-Cluster Randomized/Medium	G1: Comprehensive pharmaceutical care services G2: Traditional pharmacy care	Time 1: N = 363 G1: 159 G2: 204 Time 2: N = 317 G1: NR G2: NR Time 3: N = 292 G1: NR G2: NR	Communicates with doctor (Higher numbers reflect greater dissatisfaction)	Time 1: G1: 1.50 (0.77) G2: 1.60 (0.89) Time 2: G1: 1.36 (0.63) G2: 1.72 (1.00) Time 3: G1: 1.36 (0.65) G2: 1.74 (0.97) p<0.05 for between-group differences in score changes from Time 1 to Time 3

Abbreviations: G = group; N = study sample size; NRCT=Non-randomized controlled trial; NR = not reported; NS = not significant; RCT= randomized controlled trial

Table E29. Use of generic medications: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Pindolia et al., 2009[30] Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (opt-out)	G1: 292 G2: 1,081	Increase in the overall use of generic drugs	G1: 6% G2: 3% p not calculated because baseline percentages not provided
Winston and Lin, 2009[43] Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed call center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Weighted generic substitution ratio: 30-day equivalent claims divided by total number of claims	Pre-MTM (Jan 1 2007-April 30, 2007) G1: 60.1 (29.8) G2: 58.6 (25.7) G3: 58.7 (27.6) p: NR Post-MTM (Jan 1 2008-April 30, 2008) G1: 65.7 (32.5) G2: 64.6 (30.5) G3: 63.5 (32.2) p: NR Calculated SMD for G1 vs. G3: -0.04 (95% CI, -0.06 to -0.02; p<0.001) Calculated SMD for G2 vs. G3: -0.03 (95% CI, -0.06 to 0.01; p=0.134)

Abbreviations: CI = confidence interval; G = group; MTM = Medication Therapy Management; NR = not reported; SMD: standardized mean difference; vs. = versus.

Table E30. Patient co-payments: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Christensen et al., 2007[8] NRCT/Medium	G1: Patients receiving pharmacist-provided-MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in patient co-payment for prescriptions over 6 months in $ (SD)	G1: 34.3 (263.6) G2: -54.3 (253.9) Calculated SMD for G1 vs. G2, assuming correlation between baseline and followup of 0.5 = -0.3; 95% CI, -0.5 to -0.04 (p=0.025) G3: -46.1 (282.9) Calculated SMD for G1 vs. G3, assuming correlation between baseline and followup of 0.5 = -0.2; 95% CI, -0.6 to -0.1 (p=0.007)
Pindolia et al., 2009[30] Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (opt-out)	G1: 292 G2: 1081	Mean out-of-pocket prescription costs per health plan member in $ (assumed per year, as NR in study) (SD)	2006 G1: 1513 (1171) G2: 1183 (1084) 2007 G1: 1571 (1163) G2: 1164 (1201) Calculated SMD, assuming correlation between baseline and followup of 0.5= -0.1; 95% CI, -0.2 to 0.1 (p=0.328)
Fox et al., 2009[12] Cohort/High	G1: MTM program (acceptors) G2: Opt-out from MTM program	G1: 247 G2: 50	Mean difference in Medicare Part D medication copayment costs per patient per month	G1: 7.4 (76.0) G2: 11.3 (43.8) p: 0.62
			Mean difference in all medication copayments (Medicare Part D and not Part D) costs per patient per month	G1: 5.2 (80.5) G2: 6.9 (37.5) p: 0.82

Abbreviations: CI: confidence interval; G = group; MTM = Medication Therapy Management; NR = not reported; NRCT = nonrandomized controlled trial; RCT= randomized controlled trial; SD = standard deviation; SMD: standardized mean difference; vs. = versus

Table E31. Total expenditures on medications by health plans: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Health Plans	Results
Jameson, VanNoord, and Vanderwoud, 1995[17] RCT/Medium	G1: Pharmacotherapy consultation G2: Usual care	G1: 27 G2: 29	Change in cost (USD) of prescription drugs over 6 months, based on maximum allowable cost for Medicaid reimbursement	G1: -130 G2: 163 Calculated mean difference: -293, 95% CI, -501.5 to -84.5 p< 0.01
Sellors et al., 2003[33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient to the Ontario Drug Benefit Program (assumed CAD) at 5 months	G1: 3.6 G2: 3.8 Calculated mean difference: 0.19, 95% CI, -1.5 to 1.1 p: 0.78
Chrischilles et al., 2004[7] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Mean amount billed per patient for active drugs in USD (based on Medicaid claims) (SD) at baseline and at 9 months	Baseline G1: 488.4 (20.8) G2: 441.9 (14.5) Followup G1: 525.0 (22.1) G2: 477.6 (15.5) Calculated mean difference: -0.95, 95% CI,-58.7 to 56.8, p: 0.974
Christensen et al., 2007[8] NRCT/Medium	G1: Patients receiving pharmacist-provided-MTM services G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	G1: 67 G2: 669 G3: 870	Mean difference in amount insurer paid for prescriptions over 6 months in USD (SD)	G1: -90.1 (793.0) G2: -35.4 (939.5) G3: -97.3 (907.4) Calculated mean difference for G1 vs. G2, assuming correlation between baseline and followup of 0.5= -54.7, 95% CI, -287.6 to 178.2 (p=0.645) Calculated mean difference for G1 vs. G3, assuming correlation between baseline and followup of 0.5 = -7.2; 95% CI, -230.8 to 216.4 (p=0.950)

Table E31. Total expenditures on medications by health plans: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Health Plans	Results
Moczygemba et al., 2011[25] Moczygemba et al., 2008[26] Cohort/Medium	G1: MTM-eligible patients who opting-in to a telephone MTM program (acceptors) G2: MTM- eligible patients who did not opt-in to the MTM program (opt-out)	G1: 60 G2: 60	Mean Part D drug costs in USD (based on prescription claim records, excludes non-Part D drug costs) (SD) at baseline and 6 months	Baseline G1: $2289 ($887) G2: $2131 ($1273) p: NR Follow up G1: $2311 ($1148) G2: $2429 ($1697) Adjusted p: 0.80 Calculated mean difference: -276.0, 95% CI, -751.3 to 199.3, p: 0.26

Abbreviations: CAD= Canadian dollar; CI = confidence interval; G = group; MTM= medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; PCM = pharmaceutical case management; RCT= randomized controlled trial; SD = standard deviation; USD= US dollar

Table E32. Total expenditures on medications by patients and health plans: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs	Results
Malone et al., 2000[20]; Ellis et al., 2000[21] (interventions); Malone et al., 2001[22]; Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual drug costs in USD (calculated from Denver VAMC pharmacy department, individual sites, or the VA Pharmacy Benefits Management group)	G1: +203 G2: +140 Calculated mean difference: 63, 95% CI, -5.1 to 131.1; p: 0.07
Sellors et al., 2003 [33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean daily medication costs per patient at 5 months (assumed CAD)	G1: 5.01 G2: 4.82 Calculated mean difference: 0.2, 95% CI, -0.8 to 1.2; p=0.72
Williams et al., 2004[42] RCT/Medium	G1: Modification of patient's medication regimen by an interdisciplinary medication adjustment team G2: Usual medical care	G1: 57 G2: 76	Average monthly wholesale price (USD) of prescription and non-prescription drugs in USD	G1: -26.92 G2: -0.68 Reported mean difference: -20.2, 95% CI, 5.8 to 34.5 p: 0.006
Krska et al., 2001[19] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: 168 G2: 164	Average monthly costs of prescribed medication per patient in British? pounds (SD) at 3 months (calculated using information from patient on actual use)	Baseline: G1: 39.3 (29.1) G2: 42.8 (33.5) Followup G1: 38.8 (29.6) G2: 42.6 (31.8) Calculated mean difference: -0.2, 95% CI, -6.7 to 6.5) p=0.956

Table E32. Total expenditures on medications by patients and health plans: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs	Results
Pai et al., 2009[27]; Pai et al., 2009[28] RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	Mean drug costs in USD (calculated from average wholesale price) over 2 years	Baseline: G1: 430 (197) G2: 451 (267) Followup: Pharmaceutical care reduced mean drug costs by $6.21 compared with the standard of care group, p=NS, no absolute costs or other details reported
Fox et al., 2009[12] Cohort/High	G1: MTM program (acceptors) G2: Opt-out from MTM program (opt-out)	G1: 247 G2: 50	Mean difference in annual Medicare Part D drug cost in USD (patient copay + insurance plan medication costs + dispensing fee)	G1: -76.7 (350.8) G2: -49.0 (92.8) Calculated mean difference: -27.8, 95% CI, -125.8 to 26.6 p: 0.57
Pindolia et al., 2009[30] Cohort/High	G1: Telephone based MTM program (acceptors) G2: Usual medical care (opt-out)	G1: 292 G2: 1081	Total annual prescription drug cost per health plan member in USD	Pre-enrollment ($) (January-June 2006) G1: 576.3 (394.3) G2: 468.1 (335.9) Post-enrollment ($) (July-December 2006) G1: 480.7 (404.3) G2: 434.7 (421.4) Calculated mean difference: -62.2, 95% CI, -112.5 to -12.0; p=0.015
Staresinic et al., 2007[35] Cohort/High	G1: MTP program (acceptors) G2: Usual care (opt-out)	G1: 282 G2: 1544	Total prescription cost per MTMP beneficiary per month in USD (gross drug cost=ingredient cost paid + dispensing fee + sales tax/member months in part D contract)	Participants spent less on prescription medications on average (described as per member per month drug spending) than non-participants. Figure provided suggests a decrease spend of between 100 and 150 in the intervention group, but exact numbers not reported.

Table E32. Total expenditures on medications by patients and health plans: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs	Results
Welch et al., 2009[41] Cohort/High	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Mean change in medication costs per day in USD at 6 months. No SD reported. (from data on study beneficiaries' purchases of ambulatory prescription medications) Mean percent increase in medication costs per day in USD at 6 months (no SD reported)	G1: 0.3 G2: -3.3 Adjusted p: 0.203 NOTE: Age, sex, chronic disease score, and preperiod drug cost included in multivariate regression modeling for adjusted P G1: 49.7 G2: 39.9 p: 0.006 Adjusted OR (95% CI): 1.4 (1.1 to 1.9) NOTE: Model adjusted for age, sex, chronic disease score, and baseline medication cost
Winston and Lin, 2009[43] Cohort/High	G1: Community pharmacy MTM G2: Pharmacist-staffed call center-based MTM G3: Educational mailings	G1: 21,336 G2: 3,436 G3: 49,021	Mean (SD) drug cost per patient per month in USD after 8 months of services (based drug claims processing data, total allowed charges, including ingredient cost paid, dispensing fee, and sales tax, prior to subtracting any patient cost-sharing amounts)	Pre-MTM period (Jan 1 2007-April 30, 2007) G1: 669 (461) G2: 676 (463) G3: 698 (513) Post-MTM period (Jan 1 2008-April 30, 2008) G1: 634 (512) G2: 661 (494) G3: 698 (556) Calculated mean difference for G1 vs. G3: -35.0, 95% CI, -43.4 to -26.6; p<0.001 Calculated mean difference for G2 vs. G3: -15.0, 95% CI, -33.4 to 3.4; p=0.11

Abbreviations: CAD= Canadian dollar; CI = confidence interval; G = group; MTM = Medication Therapy Management; MTMP= Medication Therapy Management Program; NR = not reported; NS = not sufficient; OR = odds ratio; RCT= randomized controlled trial; SD = standard deviation; USD= US dollar; VA = Veterans Administration; VAMC = Veterans Affairs Medical Center; vs. = versus.

Table E33. Medication and other costs: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Prescription Costs to Patients	Results
Sellors et al., 2003 [33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost (SE) of health care resources per patient, including all hospital stays at 5 months (CAD assumed)	G1: 1894.1 (200.7) G2: 1644.7 (220.8) p=0.83 Calculated mean difference: 249.4, 95% CI, -338.4 to 837.2
			Mean cost (SE) of health care resources per patient, including only drug-related hospital stays at 5 months (CAD assumed)	G1: 1281.3 (101.4) G2: 1299.4 (154.7) p=0.45 Calculated mean difference: -18.1, 95% CI, -386.7 to 350.5
Triller and Hamilton, 2007[38] RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: NR G2: NR	Aggregate health system costs Home care agency costs	Values not reported, but results state that costs did not significantly differ between the two groups.
Bernsten et al., 2001[1,2] RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 867 G2: 748 6 months G1: NR G2: NR 12 months G1: NR G2: NR 18 months G1: NR G2: NR	Mean total cost per patient including (1) cost associated with additional time spent by pharmacists; (2) cost associated with contacts with GPs, specialists and nurses; and (3) cost of hospitalizations and drugs	Cost data not pooled and analyzed for costs because of differing health care systems between countries. However, no significant between-group differences in any country (p=NS)
Fischer et al., 2002[11] NRCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Change in total charges (in USD) for inpatient care, outpatient care, and pharmacy	G1: -900 G2: -2000 95% CI: NR p: NS, no details reported Calculated mean difference: 1100.

Abbreviations: CAD = Canadian dollar; CI = confidence interval; G = group; GP = general practitioner; NR = not reported; NS = not significant; RCT= randomized controlled trial; SE = standard error; USD = US Dollar

Table E34. Number of outpatient visits: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone, 2000[20]; Ellis, 2000[21] (interventions); Malone, 2001[22] (detailed QOL outcomes); Ellis, 2000[23] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in number of clinic visits (including visits with the pharmacists in the intervention arm)	G1: +4.8 G2: +2.8 p: 0.003
Sellors et al., 2003[33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Number of clinic visits (SE)	G1: 0.3 (0.15) G2: 0.3 (0.6) p: 0.40
Sidel, 1990[34] RCT/medium	G1: received at least 2 pharmacist visits involving medication review, patient specific education and counseling; follow up patient phone calls and contact of physicians as needed G2: only contacted for to complete the survey.	G1: 92 G2: 104	Change in number of ambulatory visits over 3 months	G1: -1.2 G2: 0.3 p: 0.08
Touchette et al., 2012[37] RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 183 G2: 190 G3: 183	0-3 months G1: 180 G2: 190 G3: 193 3-6 months G1: 183 G2: 190 G3: 183	0-3 months G1: 2.6 (2.2) G2: 2.7 (2.3) G3: 2.6 (2.2) G1 vs. G3: (p=0.646) G2 vs. G3: (p=0.816) 3-6 months G1: 2.2 (2.1) G2: 2.1 (2.1) G3: 2.2 (2.2) G1 vs. G3: (p=0.760) G2 vs. G3: (p=0.458)

Table E34. Number of outpatient visits: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Bernsten et al., 2001[1,2] RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 1290 G2: 1164 6 months G1: 1024 G2: 953 12 months G1: 863 G2: 764 18 months G1: 704 G2: 636	Mean number of contacts with primary care providers, including home visits and office appointments (SD)	Baseline G1: 4.8 (8.4) G2: 4.3 (6.2) p: NS 6 months G1: 4.0 (5.7) G2: 3.6 (4.6) p: NS 12 months G1: 4.0 (7.0) G2: 3.5 (5.5) p: NS 18 months G1: 4.3 (8.0) G2: 3.2 (4.0) p: NS
Krska et al., 2001[19] RCT/High	G1: Pharmacist-led medication review G2: Usual care including identification of pharmaceutical care issues, but no plan	G1: NR G2: NR	Hospital clinic attendance, use of social services or contacts with district nurses and health visitors before and after the pharmacist review	No differences, details NR
Fischer et al., 2002[11] NRCT/High	G1: Pharmaceutical care G2: Usual care	G1: 231 G2: 444	Changes in number of clinic visits over 1 year	Intention-to-treat analysis Adjusted between-group difference not significant, details NR
Carter et al., 1997[4,5] Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Number of distinct dates of service over 6 months	G1: 2.2 (2.4) G2: 1.0 (1.0) p=0.07
Chrischilles et al., 2004[7] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	No. of outpatient facility claims at 12 months	Results NR, p=0.121

Abbreviations: DRP = drug-related problems; G = group; MTM = medication therapy management; NR = not reported; NRCT = nonrandomized controlled trial; NS = not sufficient; QOL = quality of life; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; vs. = versus

Table E35. Costs of outpatient visits: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000[20]; Ellis et al., 2000[21] (interventions); Malone et al., 2001[22] (detailed QOL outcomes); Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual cost of clinic visits in US $	G1: +231 G2: +333 95% CI: NR p: 0.02
Sellors et al., 2003[33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of physician visits in in $ (assumed CAD) (SE) at 5 months	G1: 204.0 (11.1) G2: 198.3 (10.4) 95% CI (calculated for standardized difference in means): -0.11 to 0.12 p (calculated for standardized difference in means): 0.71
			Mean cost of clinic visits in in $ (assumed CAD) (SE) at 5 months	G1: 18.8 (8.1) G2: 20.9 (5.0) 95% CI (calculated for standardized difference in means): -0.16 to 0.12 p (calculated for standardized difference in means): 0.82
			Mean cost of other health care services/visits to health care professionals in in $ (assumed CAD) (SE) at 5 months	G1: 288.30 (40.02) G2: 293.00 (55.25) 95% CI (calculated for standardized difference in means): -0.145 to 0.135 p (calculated for standardized difference in means): 0.97
Chrischilles et al., 2004[7] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Outpatient facility claims at 12 months	Results NR p: 0.107
Carter et al., 1997[4,5] Cohort/High	G1: Pharmaceutical care G2: Usual care	G1: 25 G2: 26	Hypertension-related charges in $ (SD) at 6 months	G1: 122 (124) G2: 52 (65) p=0.03
			Mean visit charges in $ (SD) at 6 months	G1: 823 (1,123) G2: 336 (246) p=0.02

Abbreviations: CAD = Canadian dollars; CI = confidence interval; G = group; NR = not reported; PCM = pharmaceutical case management; QOL = quality of life; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; US = United States

Table E36. Number of laboratory tests: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sellors et al., 2003[33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of laboratory tests and imaging procedures at 5 months	G1: 8.7 (0.6) G2: 8.6 (0.1) 95% CI (calculated for standardized difference in means): -0.12 to 0.16 p (calculated for standardized difference in means): 0.791
Malone et al., 2000[20]; Ellis et al., 2000[21] (interventions); Malone et al., 2001[22] (detailed QOL outcomes); Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual number of laboratory tests	G1: +3.1 G2: +4.7 95% CI: NR p: 0.001

Abbreviations: CI = confidence interval; G = group; NR = not reported; QOL = quality of life; RCT = randomized controlled trial.

Table E37. Costs of laboratory tests: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sellors et al., 2003[33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all lab and imaging procedures at 5 months $ (assumed CAD) (SE)	G1: 249.3 (20.8) G2: 243.1 (17.2) 95% CI (calculated for standardized difference in means): -0.12 to 0.16 p (calculated for standardized difference in means): 0.816
Malone et al., 2000[20]; Ellis et al., 2000[21] (interventions); Malone et al., 2001[22] (detailed QOL outcomes); Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual costs for laboratory tests in US $	G1: +$43 G2: +$76 95% CI, NR p: 0.05

Abbreviations: CAD = Canadian dollar; CI = confidence interval; G = group; NR = not reported; QOL = quality of life; RCT= randomized controlled trial; SE = standard deviation; US = United States

Table E38. ED visits: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012[37] RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	G1: 211 G2: 218 G3: 208	Mean number of ED visits per participant	0 to 3 months G1: 0.3 (0.6) G2: 0.2 (0.6) G3: 0.2 (0.5) G1 vs. G3: (p=0.735) G2 vs. G3: (p=0.963) 3 to 6 months G1: 0.2 (0.5) G2: 0.2 (0.6) G3: 0.4 (0.8) G1 vs. G3: (p=0.077) G2 vs. G3: (p=0.057)
Taylor, Byrd, and Krueger, 2003[36] RCT/High	G1: Pharmaceutical care group G2: Standard care	G1: 33 G2: 36	Change in no, of ED visits from 12 months before baseline through 12 months after	G1: -12 G2: 0 p=0.044
Welch et al., 2009[41] Retrospective cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (opt-out)	G1: 459 G2: 336	Adjusted OR of ED visit from 6 month before MTM through 6 months after (adjusted for age, sex, chronic disease score, specific baseline utilization) (95% CI)	Adjusted OR: 0.9 (0.6 to 1.3)
Sellors et al., 2003[33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean number of ED/urgent care visits and ambulance use (SE) at 5 months	G1: 0.2 (0.03) G2: 0.2 (0.03)

Abbreviations: CI = confidence interval; DRP = drug related problems; ED = emergency department; G = group; MTM = Medication Therapy Management; OR = odds ratio; RCT = randomized controlled trial; SE = standard error; vs. = versus.

Table E39. Costs of emergency department visits: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sellors et al., 2003[33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of ED/urgent care visits and ambulance use at 5 months in $ (assumed CAD) (SE)	G1: 0.2 (0.03) G2: 0.2 (0.03) 95% CI (calculated for standardized difference in means): -0.19 to 0.10 p (calculated for standardized difference in means): 0.53
Chrischilles et al., 2004[7] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Charges of ED claims at 12 months	Results NR p: 0.513

Abbreviations: CAD: Canadian dollar; CI = confidence interval; ED= Emergency department; G = group; NR = not reported; PCM = pharmaceutical case management; RCT = randomized controlled trials; SE = standard error

Table E40. Number of hospitalizations: Summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Malone et al., 2000[20]; Ellis et al., 2000[21] (interventions); Malone et al., 2001[22] (detailed QOL outcomes); Ellis et al., 2000[23] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in number of hospitalizations	G1: +0.1 G2: +0.2 p: 0.29
Sellors et al., 2003 [33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean all-cause hospitalizations (SE)	G1: 0.1 (0.02) G2: 0.1 (0.02) p: 0.77
			Mean drug-related hospitalizations (SE)	G1: 0.04 (0.01) G2: 0.04 (0.01) p: 0.08
Touchette et al., 2012[37] RCT/Medium	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart). G3: Usual care	Time One G1: 180 G2: 190 G3: 193	Percent of participants with at least one hospital visit	Time One G1: 13.9 G2: 7.9 G3: 10.4 G1 vs. G3: 1.6 (p=0.350) G2 vs. G3: 0.6 (p=0.370) G2 vs. G1: 0.4 (p=0.080)
		Time Two G1: 183 G2: 190 G3: 183		Time Two G1: 17.6 G2: 12.1 G3: 9.3 G1 vs. G3: 2.6 (p=0.049) G2 vs. G3: 1.4 (p=0.484) G2 vs. G1: 0.3 (p=0.214)

Table E40. Number of hospitalizations: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Touchette et al., 2012[37] RCT/Medium (continued)			Mean number of hospital visits per participant	Time One G1: 0.2 (0.5) G2: 0.1 (0.4) G3: 0.1 (0.4) G1 vs. G3: (p=0.265) G2 vs. G3: (p=0.619) G2 vs. G1: (p=0.109) Time Two G1: 0.2 (0.5) G2: 0.1 (0.4) G3: 0.1 (0.4) G1 vs. G3: (p=0.056) G2 vs. G3: (p=0.547) G2 vs. G1: (p=0.174)
Triller and Hamilton, 2007[38] RCT/Medium	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services	G1: NR G2: NR	Percent with any hospitalization, all causes	G1: 55 G2: 58 RR: 0.9 95% CI: NR p: 0.63
			Percent with any hospitalization, heart-failure related	G1: 42 G2: 55 RR: 0.8 95% CI: NR p: 0.26

Table E40. Number of hospitalizations: Summary of results (continued)

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Bernsten et al., 2001[1,2] RCT/High	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	Baseline G1: 867 G2: 748 6 months G1: NR G2: NR 12 months G1: NR G2: NR 18 months G1: NR G2: NR	Percent with ≥1 hospitalization in the prior 18 months	Pooled sample Baseline (during 18 months prior to study) Overall: NR G1: 41.7 G2: 41.3 p=NS 18 months Overall: NR G1: 35.6 G2: 40.4 p=NS
Pai et al., 2009[27]; Pai et al., 2009[28] RCT/High	G1: Pharmaceutical care G2: Usual care	G1: NR G2: NR	All-cause hospitalizations	G1: 1.8 (2.4) G2: 3.1 (3.0) p: 0.02
			Cumulative hospitalized time (days)	G1: 9.7 (14.7) G2: 15.5 (16.3) p: 0.06
Roughead et al., 2009[32] Cohort/Medium	G1: Collaborative home-based medication review G2: No medication review received	G1: 273 G2: 5444	Rate of hospitalization for HF at any time during study	Adjusted HR (95% CI): 0.6 (0.4 to 0.8) p: NR NOTE: Model adjusted for age, sex, comorbidity, SES, season, region of residence, and Ns of prescriptions, prescribers, pharmacies, changes in medications, hospitalizations, occupational therapy visits, and speech therapy visits
Welch et al., 2009[41] Cohort study/Medium	G1: MTM program provided to home-based beneficiaries G2: No-MTM control group (voluntary opt-out)	G1: 459 G2: 336	Adjusted OR of hospitalization from 6 month before MTM through 6 months after (adjusted for age, sex, chronic disease score, specific baseline utilization) (95% CI)	Adjusted OR (95% CI): 1.4 (1.1 to 2.0) NOTE: Model adjusted for age, sex, Chronic Disease Score, specific baseline utilization

Abbreviations: CI = confidence interval; DRP = drug related problem; G = group; HR = heart failure; MTM = Medication Therapy Management; NR = not reported; NS = not significant; OR = odds ratio; QOL = quality of life; RCT = randomized controlled trial; SE = standard error; vs. = versus

Table E41. Costs of Hospitalization: summary of results

Study Design/Risk of Bias	Study Arms	N Analyzed	Outcome and Time Period	Results
Sellors et al., 2003 [33] RCT/Medium	G1: Pharmacist consultation program G2: Usual care	G1: 379 G2: 409	Mean cost of all admissions to hospital $ (assumed CAD) (SE)	G1: 753.7 (183.1) G2: 594.9 (135.2) 95% CI (calculated for standardized difference in means), -0.09 to 0.20 p (calculated for standardized difference in means): 0.479
Malone, 2000[20]; Ellis, 2000[21] (interventions); Malone, 2001[22] (detailed QOL outcomes); Ellis, 2000[23] RCT/Medium	G1: Pharmaceutical care G2: Usual care	G1: 523 G2: 531	Mean change in annual hospitalization costs in US $	G1: +542 G2: +763 Variance not reported 95% CI, NR p: 0.21
Chrischilles et al., 2004[7] Cohort/High	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	G1: 524 G2: 1,687	Charges of inpatient claims	Results NR p: 0.937

Abbreviations: CAD = Canadian dollar; CI = confidence interval; G = group; NR = not reported; PCM = pharmaceutical case management; QOL = quality of life; RCT = randomized controlled trial; SE = standard error; US = United States; RCT= randomized controlled trial.

Table E42. Applicability

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Bernsten et al., 2001[1]; Sturgess et al., 2003[2]	G1: Structured community pharmacy-based pharmaceutical care program G2: Normal pharmaceutical Usual community pharmacy services	Yes	Yes	Yes	Yes
Blennerhassett et al., 2007[3]	Implementation of a Home Medication Review (HMR) into a chronic heart failure collaborative care model. HMRs were conducted by accredited pharmacists. G2: No HMR	Yes	No Appears to be very specific to the Heartlink program in NSW; involves developing and maintaining communication pathways between hospital and community pharmacy which would require more time and investment.	Yes	Unclear or NR Appears to be very specific to the population in NSW and the Heartlink program developed there. Unclear about how widely applicable this would be.
Carter et al., 1997[4], Barnette et al., 1996[5]	G1: Pharmaceutical care provided by pharmacists within an interdisciplinary practice model. Patient education (lifestyle, risk factor modifications, and drug therapy) was standardized. G2: Usual care	No Rural population	Yes	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Chisholm et al., 2002[6]	G1: Clinical pharmacy services, including reviewing patients' medication therapy, with an emphasis on controlling blood pressure, and preventing or resolving drug therapy problems. Pharmacists counseled patients about their regimen, including desired clinical responses and possible adverse reactions. G2: Routine clinic services, but without clinical pharmacist interaction. Routine clinical services here entailed meeting a renal transplant clinic team that consisted of 2 nephrologists, a clinical pharmacist, PAs and a nurse.	No Limited to African American kidney transplant patients	Yes	Yes	No Outcomes limited to BP and number of BP medications.
Chrischilles et al., 2004[7]	G1: PCM provided by pharmacists G2: Did not receive PCM services	Yes	Yes	Yes	Yes
Christensen et al., 2007[8]	G1: MTM services designed by a health plan for its beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention (control group 1) G3: Patients from a different county than G1 who did not receive intervention (control group 2)	Yes	Yes	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Clifford et al., 2002[9]	G1: Pharmaceutical care provided by a clinical pharmacist , which included a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of drug therapy problems. G2: Standard outpatient care for diabetes	Yes	Yes	Yes	Yes
Fischer et al., 2000[10]	G1: Pharmaceutical care based on the Encara Practice System provided by onsite health maintenance organization staff pharmacists. G2: Standard Community Pharmacy Practice G3: A set of refusers surveyed and included in some analyses among those who were at eligible clinics but initially declined to participate.	Yes	Yes	Yes	No The outcomes are very intermediate (receipt of information, use of reminders to take medication, and awareness of side effects)
Fischer et al., 2002[11]	Pharmaceutical care based on the Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care with no additional interventions.	Yes	Unclear or NR Pharmacies volunteered to participate in the intervention group. Not clear how representative they are of community pharmacies in general.	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Fox et al., 2009[12]	G1: Florida Health Care Plans MTM program, consisting of a medication therapy review and evaluation by a clinical pharmacist that was documented and sent to the patient's physician through health plan review G2: Opt-out from MTM program	Yes	Yes	Yes	Yes
Gattis et al., 1999[13]	G1: Clinical pharmacy services, including an assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about the purpose of each drug and reinforcing adherence. Detailed written information was also provided to patients. G2: Usual medical care	No Study population limited to patients with moderate to severe heart failure.	Yes	Yes	Yes
Hanlon et al., 1996[14]	G1: Pharmaceutical care provided by a clinical pharmacist G2: Usual care in the General Medicine Clinic	No All male VA patients.	Yes	Yes	Yes
Harrison et al., 2012[15]	G1: Pharmaceutical care provided by a clinical pharmacist for the purpose of identifying and resolving actual and potential drug therapy problems, medication teaching, adherence optimization, medication reconciliation, and provision of drug information. G2: Retrospective historical control of matched patients who received standard care at a routine medical visit within 8 months prior to study period	No Study population limited to recent lung transplant recipients.	Unclear or NR What was done could be applicable, although given the highly specialized nature of the clinical condition, the pharmacists were likely specialized, and as a result, the intervention may not have been applicable.	No Same issue as population applicability because the transplant population is highly selected and requires specialized care.	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Isetts et al., 2008[16]	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM	Yes	Yes	Yes	Yes
Jameson, VanNoord, and Vanderwoud, 1995[17]	Pharmacotherapy consultation and followup provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	Yes	Yes	Yes	Yes
Jeong et al., 2007[18]	G1: Pharmacist-managed MTMP provided by ambulatory care pharmacists and healthcare support staff G2: Eligible for Part D MTMP but declined enrollment G3: Patients without Part D as their primary drug benefit	Yes	No MTM intervention itself may be applicable, but it was delivered within Kaiser Permanente's integrated healthcare system, which does not reflect organization of most healthcare systems in the U.S.	Yes	Yes
Krska et al., 2001[19]	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	No Older adults	Yes	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Malone et al., 2000[20]; Ellis et al., 2000[21]; Malone et al., 2001[22]; Ellis et al., 2000[23] IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities. G2: Usual care without pharmaceutical care	Yes	No VA is a large integrated health system with on-site pharmacy and highly trained clinical pharmacists who are embedded within ambulatory care clinics. This is not typical of most primary care practices.	Yes	No Unclear how applicable VA costing methods and systems are to the rest of the healthcare system.
McDonough et al., 2005[24]	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 drug therapy problems: appropriateness of does, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	Yes	Yes	Yes	Yes
Moczygemba et al., 2011[25] Moczygemba et al., 2008[26]	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or a managed care pharmacy resident based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework. G2: No-MTM control group	Yes	Yes	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Pai et al., 2009[27]; Pai et al., 2009[28]	G1: Pharmaceutical care including drug therapy reviews conducted by a nephrology-trained clinical pharmacist with the patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by a nurse	No Narrow eligibility - Adults with ESRD who were undergoing a stable hemodialysis.	Yes	Yes	Yes
Park et al., 1996[29]	G1: Comprehensive pharmaceutical services including drug therapy monitoring and patient education provided by a community pharmacy resident. G2: Usual care	Yes	Yes	Yes	Yes
Pindolia et al., 2009[30]	G1: Telephone-based MTM services provided as part of a Medicare Part D MTM program by pharmacy care management clinical pharmacists. G2: Usual medical care	Yes	Yes	Yes	Yes
Planas et al., 2009[31]	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	Yes	Yes	Yes	Yes
Roughead et al., 2009[32]	G1: Home Medication Reviews (HMR), a collaborative model of pharmaceutical care, conducted by accredited pharmacists. G2: No medication review received	Yes	Unclear or NR Australia's health care system is different than the U.S. health care system, so it is unclear how generalizable these results are to the U.S.	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Sellors et al., 2003[33]	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	Yes and No Yes for Canada, but may not be for U.S.	Yes	Yes	Yes
Sidel et al., 1990[34]	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	Unclear or NR Narrow eligibility based on excluding low and medium risk patients and those considered to be "difficult".	Yes	Yes	No Short-term, most subjective and not broadly applicable, most surrogate outcomes.
Staresinic et al., 2007[35]	G1: MTM services provided as part of a Medicare Part D MTM program by an MTM Coordinator (non-clinical staff) and a pharmacist G2: Usual care provided to MTM-eligible enrollees who chose not to participate	Yes	Yes	Yes	Unclear or NR
Taylor, Byrd, and Krueger, 2003[36]	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	Yes	Yes	Yes	Yes
Touchette et al., 2012[37]	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2-page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	Yes	Yes	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Triller and Hamilton, 2007[38]	G1: Visiting nurse association home visit services plus comprehensive pharmaceutical care services G2: Visiting nurse association home visit services only	Yes	Yes	Yes	Yes
Volume et al., 2001[39]; Kassam et al., 2001[40] PREP	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists. G2: Traditional pharmacy care	Yes	Yes	Yes	Yes
Welch et al., 2009[41]	G1: MTM program provided to home-based beneficiaries as part of a Medicare Part D MTM program G2: No-MTM control group (voluntary opt-out)	Yes	Yes KPCO's level of integration not widespread, but intervention itself is applicable	Yes	Yes
Williams et al., 2004[42]	G1: Medication review and optimization of patient's medication regimen conducted by an interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	Yes	Yes	Yes	Yes

Table E42. Applicability (continued)

Author, Year Trial name[a]	Interventions and Comparator Descriptions	Study Population broadly applicable? (e.g., not selected using narrow eligibility criteria, similarity in demographics between study population and community patients)	Intervention broadly applicable? (e.g., design of interventions reflected in current practice)	Comparator(s) broadly applicable? (e.g., alternative therapy or usual care reflective of current practice)	Outcomes broadly applicable? (e.g., not limited to short-term, surrogate, or composite outcomes)
Winston and Lin, 2009[43]	G1: MTM provided in a community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of a Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of a Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Yes	Yes	Yes	Yes
Witry, Doucette, and Gainer, 2011[44]	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided by community pharmacists to patients with private individual-group insurance	Yes	Yes	Yes	Yes

Abbreviations: BMI = body mass index; CMR = comprehensive medication review; DRP = drug regimen problem; DTP = drug therapy problem; G = group; HEDIS = Healthcare Effectiveness Data and Information Set; HMR = home medication review; ITT = intention-to-treat; KPCO = Kaiser Permanente Colorado; MTM = medication therapy management; MTMP = medication therapy management program; N = sample or group size; NA = not applicable; NR = not reported; NRCT = non-randomized controlled trial; OR = odds ratio; PA = physician assistant; PCM = pharmaceutical case management; PDP = prescription drug plan; PREP = Pharmaceutical Care Research and Education Project; RCT = randomized controlled trial; VA = Veterans Affairs

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Appendix F. Risk of Bias Evaluations and Rationale

Table F1. Risk of bias domains and ratings

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi-zation method adequate? (RCTs only)	Allocation conceal-ment ad-equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome asse-ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group charac-teristics?
Bernsten et al., 20011; Sturgess, 20032	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	RCT: cluster-rando-mized	Unclear or NR	Unclear or NR	No	Yes	Yes	Unclear or NR	Yes	Yes	Yes
Blennerhassett et al., 20073	G1: Implementation of HMR, a collaborative model of pharmaceutical care, into a chronic heart failure collaborative care model, conducted by accredited pharmacists G2: No HMR	Cohort	NA	NA	Yes	No	NA	No	NA	Yes	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Carter et al., 1997[4]; Barnette et al., 1996[5]	G1: Pharmaceutical care provided by pharmacists within interdisciplinary practice model. Standardized patient education (lifestyle, risk factor modifications, and drug therapy). G2: Usual care	Cohort	NA	NA	Yes	No	Yes	Unclear or NR	NA	No	NA
Chisholm et al., 2002[6]	G1: Clinical pharmacy services, including reviewing patients' medication therapy, with emphasis on controlling BP, and preventing or resolving DTPs. Pharmacists counseled patients about their regimen,	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Chisholm et al., 2002[6] (continued)	including desired clinical responses and possible adverse reactions. G2: Routine clinic services, but without clinical pharmacist interaction. Routine clinical services here entailed meeting renal transplant clinic team consisting of 2 nephrologists, clinical pharmacist, PAs and nurse.										
Chrischilles et al., 2004[7]	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	Cohort	NA	NA	Yes	No	Unclear or NR	Unclear or NR	NA	No	No

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Christensen et al., 2007[8]	G1: MTM services designed by a health plan for beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention. G3: Patients from a different county than G1 who did not receive intervention.	NRCT	NA	NA	Yes	Unclear or NR	Unclear or NR	No	Yes	Yes	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Clifford et al., 2002[9]	G1: Pharmaceutical care provided by a clinical pharmacist, including a comprehensive review relating to pharmacotherapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of DTPs. G2: Standard outpatient care for diabetes	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	Unclear or NR	No	No	Unclear or NR	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Fischer et al., 2000[10]	G1: Pharmaceutical care based on Encara Practice System provided by onsite health maintenance organization staff pharmacists (acceptors). G2: Standard Community Pharmacy Practice. G3: A set of those at eligible clinics who initially declined to participate (opt-out).	NRCT	NA	NA	No	Yes	No	Unclear or NR	Unclear or NR	Unclear or NR	Yes
Fischer et al., 2002[11]	G1: Pharmaceutical care based on Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care.	NRCT	NA	NA	Yes	Yes	Unclear or NR	No	Unclear or NR	Unclear or NR	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Fox et al., 2009[12]	G1: Florida Health Care Plans MTM program, consisting of medication therapy review and evaluation by a clinical pharmacist that was documented and sent to patient's physician through health plan review (acceptors) G2: Opt-out from MTM program	Cohort	NA	NA	Yes	Yes	NA	Unclear or NR	NA	No	No

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Gattis et al., 1999[13]	G1: Clinical pharmacy services, including assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about purpose of each drug and reinforcing adherence. Detailed written information also provided to patients. G2: Usual medical care	RCT: parallel, not clustered	Yes	Yes	No	Yes	No	No	No	No	No
Hanlon et al., 1996[14]	G1: Pharmaceutical care provided by clinical pharmacist. G2: Usual care in the General Medicine Clinic	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	Yes	Unclear or NR	Unclear or NR	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Harrison et al., 2012[15]	G1: Pharmaceutical care provided by a clinical pharmacist for the purpose of identifying and resolving actual and potential DTPs, medication teaching, adherence optimization, medication reconciliation, and provision of drug information. G2: Retrospective historical control of matched patients who received standard care at a routine medical visit within 8 months prior to study period	Cohort	NA	NA	Yes	Yes	Unclear or NR	No	Unclear or NR	No	No

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Isetts et al., 2008[16]	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM.	Cohort	NA	NA	Yes	Unclear or NR	No	No	Unclear or NR	Unclear or NR	Unclear or NR
Jameson et al., 1995[17]	G1: Pharmacotherapy consultation and follow-up provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	No	Unclear or NR	No	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Jeong et al., 2007[18]	G1: Pharmacist-managed MTMP provided by ambulatory care pharmacists and healthcare support staff (acceptors) G2: Eligible for Part D MTMP but declined enrollment (refusers) G3: Patients without Part D as their primary drug benefit	Cohort	NA	NA	Yes	Unclear or NR	Unclear or NR	No	NA	Yes	Unclear or NR
Krska et al., 2001[19]	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	No	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Malone et al., 2000[20]; Ellis, 2000[21]; Malone, 2001[22]; Ellis, 2000[23] IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities G2: Usual care without pharmaceutical care	RCT: parallel, not clustered	Yes	Unclear or NR	No	Yes	Unclear or NR	No	No	No	Unclear or NR
McDonough et al., 2005[24]	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 DTPs: appropriateness of dose, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	RCT: cluster-randomized	Unclear or NR	Unclear or NR	No	No	Unclear or NR	No	Unclear or NR	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Moczygemba et al., 2011[25]; Moczygemba et al., 2008[26]	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or managed care pharmacy resident based on American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework (acceptors) G2: No-MTM control group (opt-out)	Cohort	NA	NA	Yes	Yes	Unclear or NR	Unclear or NR	Unclear or NR	Yes	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Pai et al., 2009[27]; Pai et al., 2009[28]	G1: Pharmaceutical care including drug therapy reviews conducted by nephrology-trained clinical pharmacist with patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by nurse	RCT: cluster-randomized	No	Yes	No	Yes	Unclear or NR	Unclear or NR	Unclear or NR	Yes	No
Park et al., 1996[29]	G1: Comprehensive pharmaceutical services, including drug therapy monitoring and patient education provided by community pharmacy resident. G2: Usual care	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	No	No	Unclear or NR	No	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Pindolia et al., 2009[30]	G1: Telephone-based MTM services provided as part of Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors) G2: Usual medical care (opt-out)	Cohort	NA	NA	Yes	No	NA	Unclear or NR	NA	Unclear or NR	Unclear or NR
Planas et al., 2009[31]	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	RCT: parallel, not clustered	Yes	Yes	No	No	Unclear or NR	Unclear or NR	Unclear or NR	Yes	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Roughead et al., 2009[32]	G1: HMRs conducted by accredited pharmacists G2: No medication review received	Cohort	NA	NA	No	Yes	Unclear or NR	Unclear or NR	NA	Unclear or NR	Unclear or NR
Sellors et al., 2003[33]	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	RCT: cluster-randomized	Yes	Yes	No	Yes	Yes	No	Unclear or NR	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Sidel et al., 1990[34]	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	Yes	Yes	No	NA	Yes	Unclear or NR
Staresinic et al., 2007[35]	G1: MTM services provided as part of a Medicare Part D MTM program by MTM Coordinator (non-clinical staff) and pharmacist (acceptors) G2: Usual care provided to MTM-eligible enrollees who chose not to participate (opt-out)	Cohort	NA	NA	No	No	NA	Unclear or NR	NA	Yes	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Taylor, Byrd, and Krueger, 2003[36]	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recommendations given to patients or physicians	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	No	Unclear or NR	Unclear or NR	Unclear or NR	No	Unclear or NR
Touchette et al., 2012[37]	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	RCT: parallel, not clustered	Yes	Yes	No	Yes	Yes	Unclear or NR	No	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Triller et al., 2007[38]	G1: VNA home visit services plus comprehensive pharmaceutical care services G2: VNA home visit services only	RCT: parallel, not clustered	Yes	No	No	No	Unclear or NR	NA	Yes	No	Unclear or NR
Volume et al., 2001, PREP[39]; Kassam et al., 2001[40]	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists G2: Traditional pharmacy care	RCT	Unclear or NR	Yes	Unclear or NR	Yes	No	Unclear or NR	No	Yes	Unclear or NR
Welch et al., 2009[41]	G1: MTM program provided to home-based beneficiaries as part of Medicare Part D MTM program (acceptors) G2: No-MTM control group (voluntary opt-out)	Cohort	NA	NA	Yes	No	NA	Unclear or NR	NA	No	No

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Williams et al., 2004[42]	G1: Modification of patient's medication regimen conducted by interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	RCT: parallel, not clustered	Unclear or NR	Unclear or NR	No	Yes	Unclear or NR	No	No	No	Unclear or NR

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomization method adequate? (RCTs only)	Allocation concealment adequate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome assessors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group characteristics?
Winston and Lin, 2009[43]	G1: MTM provided in community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Cohort	NA	NA	Yes	Yes	NA	Unclear or NR	Unclear or NR	NA	NA

Table F1. Risk of bias domains and ratings (continued)

Author, Year Trial Name	Intervention and Comparator Descriptions	Study Design	Randomi-zation method adequate? (RCTs only)	Allocation conceal-ment ad-equate? (RCTs only)	Recruitment strategy for study different across groups?	Groups similar at baseline, or differences adjusted for in analysis?	Outcome asse-ssors blinded? (RCTs or NRCTs only)	Impact from concurrent intervention or unintended exposure ruled out by researchers?	Did variation from study protocol compromise conclusions? (RCTs or NRCTs only)	High overall (i.e., ≥20%) or differential (i.e., ≥15%) attrition	Did attrition result in differences in group charac-teristics?
Witry, Doucette, and Gainer, 2011[44]	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided to patients with private individual-group insurance	Cohort	NA	NA	No	No	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR	Unclear or NR

Abbreviations: DTP = drug therapy problem; G = group; HMR = home medication review; IMPROVE = specific name of the MTM trial that was done in the Veterans Affairs health system; MTM = medication therapy management; MTMP = medication therapy management program; NA = not applicable; NR = not reported; NRCT = non-randomized controlled trial; PCM = pharmaceutical case management; PREP = Pharmaceutical Care Research and Education Project; RCT = randomized controlled trial; VNA = visiting nurse association.

Table F2. Risk of bias domains and ratings

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Bernsten et al., 2001[1]; Sturgess, 2003[2]	G1: Structured community pharmacy-based pharmaceutical care program G2: Usual community pharmacy services	RCT: cluster-rando-mized	No	Yes	Yes	Yes	Yes	Yes	Partial (some variables were taken in to account)	High
Blennerhassett et al., 2007[3]	G1: Implementation of HMR, a collaborative model of pharmaceutical care, into a chronic heart failure collaborative care model, conducted by accredited pharmacists G2: No HMR	Cohort	NA	Unclear or NR	NA	NA	NA	Yes	No (Not accounted for or not identified)	High

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Carter et al., 1997[4]; Barnette et al., 1996[5]	G1: Pharmaceutical care provided by pharmacists within interdisciplinary practice model. Standardized patient education (lifestyle, risk factor modifications, and drug therapy). G2: Usual care	Cohort	No	Yes	No	Yes	Yes	Unclear or NR	No (Not accounted for or not identified)	High
Chisholm et al., 2002[6]	G1: Clinical pharmacy services, including reviewing patients' medication therapy, with emphasis on controlling BP, and preventing or resolving DTPs. Pharmacists counseled patients about their regimen, including desired clinical	RCT: parallel, not clus-tered	No	Yes	Yes	NA	Unclear or NR	Yes	Yes	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Chisholm et al., 2002[6] (continued)	responses and possible adverse reactions. G2: Routine clinic services, but without clinical pharmacist interaction. Routine clinical services here entailed meeting renal transplant clinic team consisting of 2 nephrologists, clinical pharmacist, PAs and nurse.									
Chrischilles et al., 2004[7]	G1: PCM-eligible patients who received PCM services G2: PCM-eligible patients who did not receive PCM services	Cohort	No	Yes	Yes	NA	Yes	Yes	No (Not accounted for or not identified)	High

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Christensen et al., 2007[8]	G1: MTM services designed by a health plan for beneficiaries and provided by either community pharmacists or medical clinic-based pharmacists. G2: Patients from same counties as G1 who did not receive intervention. G3: Patients from a different county than G1 who did not receive intervention.	NRCT	Un-clear or NR	Unclear or NR	Yes	Yes	Yes	Yes	Partial (some variables were taken in to account)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Clifford et al., 2002[9]	G1: Pharmaceutical care provided by a clinical pharmacist , including a comprehensive review relating to pharmaco-therapy and diabetes, use of proprietary and non-proprietary medications, such as complementary medicines, and identification of DTPs. G2: Standard outpatient care for diabetes	RCT: parallel, not clus-tered	Yes	Yes	Yes	Yes	Yes	Yes	Partial (some variables were taken in to account)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Fischer et al., 2000[10]	G1: Pharmaceutical care based on Encara Practice System provided by onsite health maintenance organization staff pharmacists (acceptors). G2: Standard Community Pharmacy Practice. G3: A set of those at eligible clinics who initially declined to participate (opt-out).	NRCT	Un-clear or NR	Yes	No	No	NA	Unclear or NR	Yes	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Fischer et al., 2002[11]	G1: Pharmaceutical care based on Encara Practice System provided by pharmacists. Communication of pharmacist with the patient's physician about drug therapy problems identified by the pharmacist. G2: Usual care.	NRCT	No	Yes	NA	NA	Yes	Yes	Yes	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Fox et al., 2009[12]	G1: Florida Health Care Plans MTM program, consisting of medication therapy review and evaluation by a clinical pharmacist that was documented and sent to patient's physician through health plan review (acceptors) G2: Opt-out from MTM program	Cohort	NA	Yes	Unclear or NR	NA	Yes	Yes	No (Not accounted for or not identified)	High

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Gattis et al., 1999[13]	G1: Clinical pharmacy services, including assessment of prescribed regimen, compliance, and adverse effects, and symptoms and response to therapy. Providing patient education about purpose of each drug and reinforcing adherence. Detailed written information also provided to patients. G2: Usual medical care	RCT: parallel, not clus-tered	Yes	Yes	Yes	No	NA	Yes	Yes	Medium
Hanlon et al., 1996[14]	G1: Pharmaceutical care provided by clinical pharmacist. G2: Usual care in the General Medicine Clinic	RCT: parallel, not clus-tered	Yes	Yes	Yes	Yes	Yes	Yes	Yes/No/Partial	Low

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Harrison et al., 2012[15]	G1: Pharmaceutical care provided by a clinical pharmacist for the purpose of identifying and resolving actual and potential DTPs, medication teaching, adherence optimization, medication reconciliation, and provision of drug information. G2: Retrospective historical control of matched patients who received standard care at a routine medical visit within 8 months prior to study period	Cohort	Un-clear or NR	Unclear or NR	Unclear or NR	NA	NA	Yes	Partial (some variables were taken in to account)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Isetts et al., 2008[16]	G1: MTM services provided by staff pharmacists, including the establishment of goals of therapy, in collaboration with primary care providers. G2: Usual medical care without MTM.	Cohort	Un-clear or NR	Unclear or NR	Yes	NA	NA	Unclear or NR	No (Not accounted for or not identified)	High
Jameson et al., 1995[17]	G1: Pharmaco-therapy consultation and follow-up provided by clinical ambulatory care pharmacist. G2: Standard office-based primary care.	RCT: parallel, not clus-tered	No	Yes	Yes	NA	Yes	Yes	No (Not accounted for or not identified)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Jeong et al., 2007[18]	G1: Pharmacist-managed MTMP provided by ambulatory care pharmacists and healthcare support staff (acceptors) G2: Eligible for Part D MTMP but declined enrollment (refusers) G3: Patients without Part D as their primary drug benefit	Cohort	NA	Yes	Yes	NA	NA	Unclear or NR	No (Not accounted for or not identified)	High
Krska et al., 2001[19]	G1: Medication reviews led by clinically-trained pharmacists. G2: Usual care involving interviews and identification of pharmaceutical care issues but with no pharmaceutical care plan implemented.	RCT: parallel, not clus-tered	No	Yes	Yes	Yes	Unclear or NR	Yes	No (Not accounted for or not identified)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Malone et al., 2000[20]; Ellis, 2000[21]; Malone, 2001[22]; Ellis, 2000[23] IMPROVE	G1: Pharmaceutical care provided by clinical pharmacists practicing according to scope of practice within their respective health care facilities G2: Usual care without pharmaceutical care	RCT: parallel, not clus-tered	Yes	Yes	Yes	Yes	Yes	Unclear or NR	Yes	Medium
McDonough et al., 2005[24]	G1: Pharmaceutical care provided by community pharmacists. Drug therapy monitoring focused on 5 DTPs: appropriateness of dose, proper regimen, potential interactions, nonadherence, and adverse effects. Patient education also provided. G2: Usual care	RCT: cluster-rando-mized	Yes	Yes	Yes	NA	NA	Unclear or NR	No (Not accounted for or not identified)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Moczygemba et al., 2011[25]; Moczygemba et al., 2008[26]	G1: Opt-in telephone-based MTM program, in which MTM services provided by clinical pharmacists or managed care pharmacy resident based on American Pharmacists Association and National Association of Chain Drug Stores Foundation MTM framework (acceptors) G2: No-MTM control group (opt-out)	Cohort	Un-clear or NR	NA	Yes	NA	Yes	Yes	Partial (some variables were taken in to account)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Pai et al., 2009[27]; Pai et al., 2009[28]	G1: Pharmaceutical care including drug therapy reviews conducted by nephrology-trained clinical pharmacist with patient. Also included patient and health care provider education. G2: Standard of care, consisting of brief therapy reviews conducted by nurse	RCT: cluster-rando-mized	No	Yes	Yes	NA	Yes	Yes	Yes	High
Park et al., 1996[29]	G1: Comprehensive pharmaceutical services, including drug therapy monitoring and patient education provided by community pharmacy resident. G2: Usual care	RCT: parallel, not clus-tered	Yes	Yes	Yes	Yes	NA	Unclear or NR	No (Not accounted for or not identified)	High

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Pindolia et al., 2009[30]	G1: Telephone-based MTM services provided as part of Medicare Part D MTM program by pharmacy care management clinical pharmacists (acceptors) G2: Usual medical care (opt-out)	Cohort	Yes	Yes	Unclear or NR	Unclear or NR	Yes	Yes	No (Not accounted for or not identified)	High
Planas et al., 2009[31]	G1: MTM services provided by community pharmacists. Also included patient education on diet and lifestyle modifications to lower blood pressure. G2: No MTM received, but only informed of blood pressure goals for patients with diabetes	RCT: parallel, not clus-tered	Yes	Yes	Unclear or NR	NA	NA	Yes	No (Not accounted for or not identified)	High

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Roughead et al., 2009[32]	G1: HMRs conducted by accredited pharmacists G2: No medication review received	Cohort	Un-clear or NR	Yes	NA	NA	Yes	Yes	Yes	Medium
Sellors et al., 2003[33]	G1: Clinical pharmacist consultations provided to family physicians and their patients by community pharmacists. G2: Usual care for family physicians and their patients from matched postal codes.	RCT: cluster-randomized	Un-clear or NR	Yes	NA	Yes	Yes	Yes	Yes	Medium
Sidel et al., 1990[34]	G1: Home visits by pharmacists and, when needed, consultations with physicians to identify and correct problems associated with medication use. G2: Standard care without any visits or information provided to G1.	RCT: parallel, not clus-tered	No	No	Yes	Yes	Yes	Yes	No (Not accounted for or not identified)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Staresinic et al., 2007[35]	G1: MTM services provided as part of a Medicare Part D MTM program by MTM Coordinator (non-clinical staff) and pharmacist (acceptors) G2: Usual care provided to MTM-eligible enrollees who chose not to participate (opt-out)	Cohort	Yes	Yes	Yes	NA	Yes	Unclear or NR	No (Not accounted for or not identified)	High
Taylor, Byrd, and Krueger, 2003[36]	G1: Pharmaceutical care provided by pharmacists G2: Standard care without advice or recom-mendations given to patients or physicians	RCT: parallel, not clus-tered	Un-clear or NR	Yes	Yes	Yes	Yes	Yes	N/A	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Touchette et al., 2012[37]	G1: MTM basic (comprehensive medication review and DRP assessment) G2: MTM enhanced (MTM plus 2 page clinical summary abstracted from patient's medical chart) G3: Usual care, consisting of medication counseling per clinic's normal routine but no formal MTM from a study pharmacist	RCT: parallel, not clus-tered	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Triller et al., 2007[38]	G1: VNA home visit services plus comprehensive pharmaceutical care services G2: VNA home visit services only	RCT: parallel, not clus-tered	Yes	Yes	NA	Yes	Yes	Yes	No (Not accounted for or not identified)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Volume et al., 2001, PREP[39]; Kassam et al., 2001[40]	G1: Comprehensive pharmaceutical care services using a nine-step process as defined by Hepler and Strand provided by community pharmacists G2: Traditional pharmacy care	RCT: cluster-rando-mized	Un-clear or NR	Yes	Yes	Yes	NA	Yes	No (Not accounted for or not identified)	Medium
Welch et al., 2009[41]	G1: MTM program provided to home-based beneficiaries as part of Medicare Part D MTM program (acceptors) G2: No-MTM control group (voluntary opt-out)	Cohort	Un-clear or NR	Yes	Unclear or NR	Yes	Yes	Yes	Partial (some variables were taken in to account)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Williams et al., 2004[42]	G1: Modification of patient's medication regimen conducted by interdisciplinary medication adjustment team in addition to usual medical care and "Bound for Health" booklet. G2: Usual medical care plus provision of "Bound for Health" booklet	RCT: parallel, not clus-tered	Un-clear or NR	Yes	Yes	Yes	No	Yes	No (Not accounted for or not identified)	Medium

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Winston and Lin, 2009[43]	G1: MTM provided in community pharmacy (i.e., care in face-to-face meetings or by telephone) as part of Medicare Part D MTM program G2: MTM provided by pharmacist-staffed call centers as part of Medicare Part D MTM program G3: Educational mailings (i.e., mailed letter containing patient-specific medication related information, personal medication record, and tips to save money on prescriptions)	Cohort	No	Yes	NA	NA	Yes	Unclear or NR	No (Not accounted for or not identified)	High

Table F2. Risk of bias domains and ratings (continued)

Author, Year Trial Name[a]	Interventions/ Comparator Descriptions	Study Design	ITT?	Eligibility criteria measured consistently using valid and reliable measures?	Intermediate Outcomes: assessed consistently using valid and reliable measures?	Patient-Centered Outcomes: assessed consistently using valid and reliable measures?	Utilization Outcomes: assessed consistently using valid and reliable measures?	Potential outcome pre-specified and reported?	Were important confounding and modifying variables taken into account in design and/or analysis?	Risk of Bias
Witry, Doucette, and Gainer, 2011[44]	G1: PCM provided by community pharmacists to Iowa Medicaid enrollees G2: PCM provided to patients with private individual-group insurance	Cohort	Un-clear or NR	Yes	Unclear or NR	NA	NA	Yes	No (Not accounted for or not identified)	High

Abbreviations: BP = blood pressure; DTP = drug therapy problem; G = group; HMR = home medication review; IMPROVE = specific name of the MTM trial that was done in the Veterans Affairs health system; ITT = intention-to-treat; MTM = medication therapy management; MTMP = medication therapy management program; NA = not applicable; NR = not reported; NRCT = non-randomized controlled trial; PA = physician assistant; PCM = pharmaceutical case management; PREP = Pharmaceutical Care Research and Education Project; RCT = randomized controlled trial; VNA = visiting nurse association.

Table F3. Rationale for high and medium risk of bias ratings

Author, Year Trial Name[a]	Risk of Bias Rationale for Rating
Bernsten et al., 2001[1]; Sturgess, 2003[2]	High Potential for performance and selective outcome reporting bias: • Issues concerning site and country-specific variation in pooled analyses • Some selective reporting of country-specific outcomes when statistically significant Potential for attrition bias: • High overall attrition and no strategies used to take into account baseline differences between patients LTFU and study completers Potential for selection bias: • Some important potential confounders not measured at baseline, like baseline disease severity and co-morbidity
Blennerhassett et al., 2007[3]	High Potential for selection bias: • Different methods of recruiting into each arm (self-selection) • Differences between HMR and non-HMR groups which are not accounted for clearly, and exclusion criteria not specified Potential for attrition bias: • Differential and high attrition rates Potential for measurement bias: • Unvalidated outcome measure for eligible outcome (Table 3: “information received confused them”) Missing information: • Intervention with patients not clearly defined or explained
Carter et al., 1997[4]; Barnette et al., 1996[5]	High Potential for selection bias: • No accounting for differences in recruitment strategies or for baseline differences
Chisholm et al., 2002[6]	Medium Potential for attrition bias: • Did not use ITT analysis. Potential for measurement bias: • Unclear that all outcome assessments blinded Missing information: • Lack of information about how utilization outcomes were measured.
Chrischilles et al., 2004[7]	High Potential for selection bias: • High risk of confounding from the pharmacist potentially selecting patients for the intervention who were on high risk medications • Differences in the prevalence of high risk medications at baseline not controlled for the analysis.

Table F3. Rationale for high and medium risk of bias ratings (continued)

Author, Year Trial Name[a]	Risk of Bias Rationale for Rating
Christensen et al., 2007[8]	Medium Potential for selection bias: • Group assignment not randomized • Intervention group patients had more prescriptions at baseline, suggesting difference in severity of disease between intervention group and both control groups Potential for measurement bias: • No outcomes presented in the study actually provided comparison among study groups. DTPs identified and resolved and patient satisfaction only provided as pre/post for the study group, and economic outcomes presented as pre/post for each of the three groups, but they were not compared to each other.
Clifford et al., 2002[9]	Medium Potential for selection bias: • Not clear how groups compare in terms of comorbidity or number of medications at baseline. Still, measures taken to reduce bias in other domains, like having the same pharmacist provide the intervention to all patients.
Fischer et al., 2000[10]	Medium Potential for selection bias: • Unclear reporting of N's in outcome analyses makes fully determining selection bias difficult Potential for measurement bias: • Outcome measures, although piloted and assessed for face validity prior to study, were unvalidated and relied on self-report. • While authors claim research questions a priori included assessment of "awareness of side effects", they apparently found it paradoxical that intervention arm reported more side effects and so post hoc decided to interpret this as "increased awareness" making it very difficult to draw a valid conclusion.
Fischer et al., 2002[11]	Medium Potential for selection bias: • Lack of randomization
Fox et al., 2009[12]	High Potential for selection bias: • No baseline clinical data provided about patients, in particular number of diagnosed conditions, number of medications prescribed, and healthcare utilization

Table F3. Rationale for high and medium risk of bias ratings (continued)

Author, Year Trial Name[a]	Risk of Bias Rationale for Rating
Gattis et al., 1999[13]	Medium Potential for measurement bias: • Lack of blinded outcome assessment • Additional potential source of bias because intervention pharmacist was responsible for assessing control group's outcomes • Reliability of self-report for capturing events that occurred outside of Duke questionable Missing information • Unclear to what extent included patients had care outside of Duke
Harrison et al., 2012[15]	Medium Potential for selection bias: • Differences in recruitment Potential for measurement bias: • Lack of information regarding how outcomes measured and degree of blinding of assessors
Isetts et al., 2008[16]	High Potential for selection bias: • Differences in recruitment methods, but no evidence that any methods used to adjust for these differences • Unclear how clinics with MTM differed from clinics without MTM in terms of patient populations served and other services available that might also influence outcomes • Unclear how HEDIS comparison group was identified Potential for measurement bias: • Did not take into account different confounding and modifying variables into a multivariate analysis • Unclear whether HEDIS comparisons controlled for differences between groups Missing information • Data on baseline covariates between intervention and HEDIS control group not presented
Jameson et al., 1995[17]	Medium Potential for detection and attrition bias: • Outcome assessment not blinded and no ITT analysis conducted
Jeong et al., 2007[18]	High Potential for selection bias: • Cohort study in which patients self-selected group assignment and appropriate statistical controls for selection bias not in place • Baseline characteristics did not capture important variables that could potentially bias results, such as burden of co-morbidity, number of prescriptions, and multiple demographic variables

Table F3. Rationale for high and medium risk of bias ratings (continued)

Author, Year Trial Name[a]	Risk of Bias Rationale for Rating
Krska et al., 2001[19]	Medium Potential for selection and measurement bias: • No details on randomization or allocation concealment • No details about blinding. • Statistically significant differences at baseline in hospitalizations not controlled for in analysis.
Malone et al., 2000[20]; Ellis, 2000[21]; Malone, 2001[22]; Ellis, 2000[23] IMPROVE	Medium Potential for selection bias: • Lack of information about allocation concealment • Impact of attrition on randomization unclear Potential for detection bias: • Blinding of outcome assessors unclear. Potential for performance bias: • Numerous concurrent changes within the VA clinical setting may have impacted either the intervention patients, control patients, or both
McDonough et al., 2005[24]	Medium Potential for selection and detection bias: • Differences in outcome at baseline not adjusted for in analysis • Uncertain whether outcome assessors blinded • Outcome measurement based on self-report only
Moczygemba et al., 2011[25]; Moczygemba et al., 2008[26]	Medium Potential for selection bias: • 16.7% of patients allocated to the intervention group withdrew, and attrition not fully accounted for in design
Pai et al., 2009[27]; Pai et al., 2009[28]	High Potential for selection bias: • Inadequate sequence generation • >50% attrition

Table F3. Rationale for high and medium risk of bias ratings (continued)

Author, Year Trial Name[a]	Risk of Bias Rationale for Rating
Park et al., 1996[29]	High Potential for selection bias and contamination: • Lack of cluster randomization increasing likelihood of contamination of the usual care arm at each site • Method of randomization and whether allocation concealment used NR • Differences in important factors at baseline despite randomization, with no statistical adjustment Potential for performance bias: • Potential for secular effects or uncontrolled confounding from other interventions or exposures because the intervention was conducted at separate time points at the two separate sites, using two different interventionists Potential for detection bias: • Lack of outcome assessor blinding
Pindolia et al., 2009[30]	High Potential for selection bias: • Neither baseline differences in health utilization characteristics nor important confounders (e.g., polypharmacy, number of conditions) accounted for in statistical analysis Potential for detection bias: • Not clear that outcome assessors were blinded
Planas et al., 2009[31]	High Potential for selection bias: • No steps taken to control for baseline differences in demographic characteristics and BMI that were measured, and other important potential confounders not measured at all. Important risk of confounding despite use of ITT analysis and RCT design. Potential for detection bias: • Not clear that outcome assessors were blinded
Roughead et al., 2009[32]	Medium Missing information: • Lack of clarity on various risk of bias criteria
Sellors et al., 2003[33]	Medium Potential for selection bias and contamination: • Unclear if ITT analysis used or if investigators controlled for potential co-interventions

Table F3. Rationale for high and medium risk of bias ratings (continued)

Author, Year Trial Name[a]	Risk of Bias Rationale for Rating
Sidel et al., 1990[34]	Medium Potential for selection and detection bias: • High attrition • Outcomes all self-reported and not validated • Unclear if or how researchers blinded when obtaining questionnaires • No confounders taken into account in analysis
Staresinic et al., 2007[35]	High Potential for selection bias: • Group assignment based on self-selection, since intervention group formed from those who returned a survey
Taylor, Byrd, and Krueger, 2003[36]	Medium Potential for detection bias: • Lack of blinded outcome assessment Missing information: • No other major issues with study methods, but little detail reported for key aspects related to study execution (i.e., method of randomization, allocation concealment, outcome assessment)
Triller et al., 2007[38]	Medium Potential for selection and detection bias: • Baseline differences in medication use imply differing disease severity among groups • Unclear allocation concealment • No adjustment of results for baseline differences in age or disease severity or medication usage Note (not a source of bias): study powered based on assumption of a 40% relative reduction in composite outcome
Volume et al., 2001 [39]; Kassam et al., 2001[40] PREP (Pharmaceutical Care Research and Education Project)	Medium Potential for performance bias: • Intervention provided at different pharmacy sites by different interventionists with no mention of measures used to ensure fidelity of intervention Potential for selection bias: • Lack of adjustment for differences at baseline • Borderline high attrition and possibility of selection bias due to pharmacist control over patient recruitment

Table F3. Rationale for high and medium risk of bias ratings (continued)

Author, Year Trial Name[a]	Risk of Bias Rationale for Rating
Welch et al., 2009[41]	Medium Potential for detection bias: • Adjusted ORs most reliable outcomes to use because other non-OR outcomes not adjusted for baseline differences with exception of medication cost/day • Validity and reliability of sources for outcome data unclear.
Williams et al., 2004[42]	Medium Potential for selection bias: • Although randomized design used, method of randomization and allocation concealment not reported • Unclear whether outcome assessors blinded Potential for measurement bias: • Questionable methods used for calculating costs of drugs, particularly if intervention only 6 weeks long
Winston and Lin, 2009[43]	High Potential for selection bias: • Study does not control underlying confounders leading to patients' selection of pharmacies • Pharmacies' inability to provide MTM leading to other modalities and outcomes
Witry, Doucette, and Gainer, 2011[44]	High Potential for selection bias: • Use of historical control group with much larger N, not addressed in design • No attempts to adjust for potential and actual differences in confounders and baseline characteristics, including baseline comorbidities, age, and sex • No reporting of attrition at all Missing information: • Lack of reporting about major aspects of study design

Abbreviations: HEDIS = Healthcare Effectiveness Data and Information Set; HMR = home medication review; IMPROVE = specific name of the MTM trial that was done in the Veterans Affairs health system; ITT = intention-to-treat; MTM = medication therapy management; N = sample or group size; NR = not reported; OR = odds ratio; RCT = randomized controlled trial; VA = Veterans Affairs.

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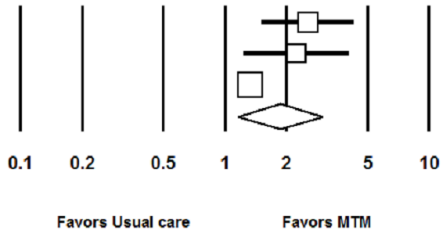
Appendix G. Meta-analyses

Figure G1: Effect of MTM on LDL Cholesterol

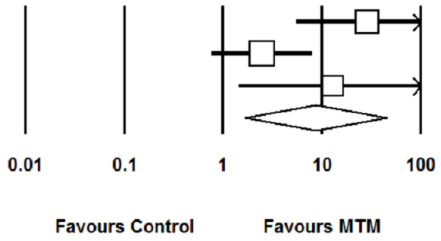
Study name	Outcome	Time point	Odds ratio	Lower limit	Upper limit	p-Value	MTM	Usual Care
Isetts 2008	At goal LDL at followup	12 months	2.544	1.520	4.256	0.000	128	126
Fox 2009	At goal LDL at followup	12 to 24 months	2.228	1.238	4.008	0.008	255	56
Jeong 2007	At goal LDL at followup	9 months	1.331	1.209	1.464	0.000	3927	4154
			1.848	1.146	2.980	0.012	4310	4336



Cohort studies

Figure G2: Effect of MTM on achieving hypertension goals

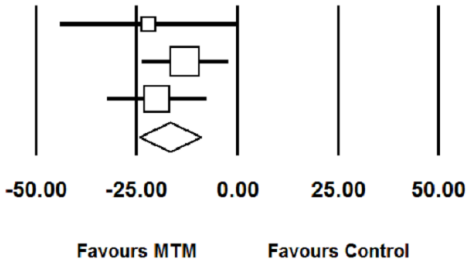
Study name	Outcome	Time point	Odds ratio	Lower limit	Upper limit	p-Value	MTM	No MTM
Taylor 2003	At goal BP at followup	12 months	28.875	5.486	151.993	0.000	24	29
Park 1996	At goal BP at followup	4 months	2.455	0.764	7.888	0.132	23	26
Planas 2009	At goal BP at followup	9 months	12.923	1.468	113.773	0.021	25	15
			8.683	1.665	45.276	0.010	72	70



Medium and high risk of bias RCTs

Figure G3: Effect of MTM on systolic blood pressure

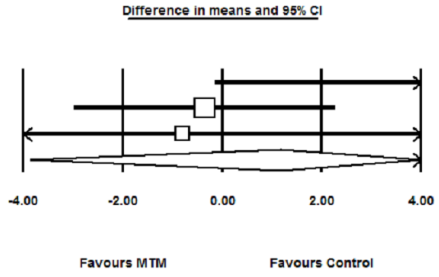
Study name	Time point	Difference in means	Lower limit	Upper limit	p-Value
Chisholm 2002	12 months	-22.100	-43.896	-0.304	0.047
Parks 1996	4 months	-13.000	-23.739	-2.261	0.018
Planas 2009	9 months	-20.000	-32.247	-7.753	0.001
		-16.774	-24.346	-9.202	0.000



Medium and high risk-of-bias RCTs

Figure G4: Effect of MTM on SF-36 Physical Functioning Domain

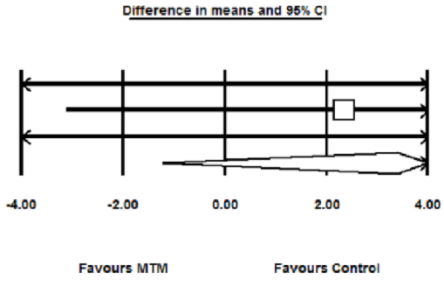
Study name	Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size MTM	Sample size No MTM
Taylor 2003	SF-36 Physical Functioning Domain	baseline to 12 month follow-up	12.400	-0.145	24.945	0.053	33	36
Malone 2000	SF-36 Physical Functioning Domain	Combined	-0.350	-2.978	2.278	0.794	447	484
Hanlon 1996	SF-36 Physical Functioning Domain	baseline to 12 month follow-up	-0.800	-7.529	5.929	0.816	86	83
			1.171	-3.871	6.214	0.649	566	603



Low or medium risk of bias

Figure G5: Effect of MTM on SF-36 Role Physical Domain

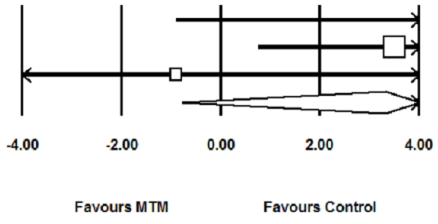
Study name	Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size MTM	Sample size No MTM
Taylor 2003	SF-36 Role Physical Domain	baseline to 12 month follow-up	12.500	-7.497	32.497	0.221	33	36
Malone 2000	SF-36 Role Physical Domain	Combined	2.350	-3.113	7.813	0.399	447	484
Hanlon 1996	SF-36 Role Physical Domain	baseline to 12 month follow-up	4.500	-5.056	14.056	0.356	86	83
			3.392	-1.223	8.007	0.150	566	603



Low or medium risk of bias

Figure G6: Effect of MTM on SF-36 Bodily Pain Domain

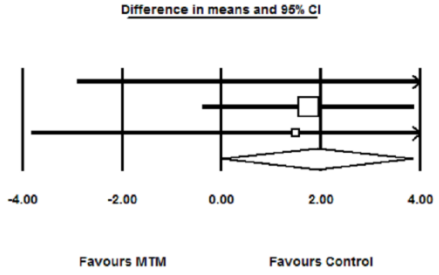
Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	MTM	No MTM
Taylor 2003 SF-36 Bodily Pain Domain	baseline to 12 month follow-up	10.800	-0.887	22.487	0.070	33	36
Malone 2000 SF-36 Bodily Pain Domain	Combined	3.500	0.757	6.243	0.012	447	484
Hanlon 1996 SF-36 Bodily Pain Domain	baseline to 12 month follow-up	-0.900	-8.529	6.729	0.817	86	83
		3.320	-0.792	7.433	0.114	566	603



Low or medium risk of bias

Figure G7: Effect of MTM on SF-36 General Health Perception Domain

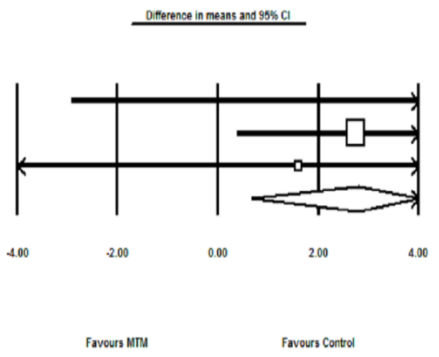
Study name	Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	MTM	No MTM
Taylor 2003	SF-36 General Health Perception Domain	baseline to 12 month follow-up	6.000	-2.899	14.899	0.186	33	36
Malone 2000	SF-36 General Health Perception Domain	Combined	1.750	-0.371	3.871	0.106	447	484
Hanlon 1996	SF-36 General Health Perception Domain	baseline to 12 month follow-up	1.500	-3.810	6.810	0.580	86	83
			1.916	-0.007	3.839	0.051	566	603



Low or medium risk of bias

Figure G8: Effect of MTM on SF-36 Vitality Domain

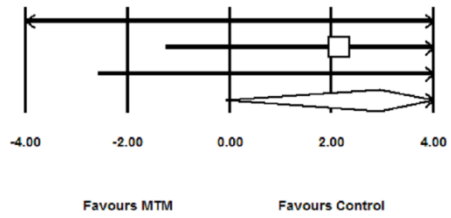
Study name	Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	MTM	No MTM
Taylor 2003	SF-36 Vitality Domain	baseline to 12 month follow-up	7.600	-2.909	18.109	0.156	33	36
Malone 2000	SF-36 Vitality Domain (aka Energy, Fatigue Domain)	Combined	2.750	0.390	5.110	0.022	447	484
Hanlon 1996	SF-36 Vitality Domain	baseline to 12 month follow-up	1.600	-4.242	7.442	0.591	86	83
			2.797	0.666	4.928	0.010	566	603



Low or medium risk of bias

Figure G9: Effect of MTM on SF-36 Social Functioning Domain

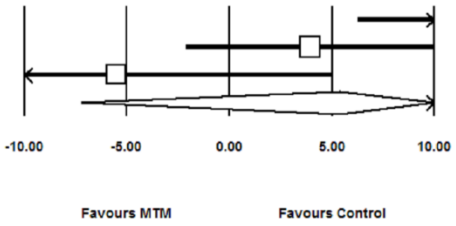
Study name	Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size MTM	Sample size No MTM
Taylor 2003	SF-36 Social Functioning Domain	baseline to 12 month follow-up	7.500	-4.839	19.839	0.234	33	36
Malone 2000	SF-36 Social Functioning Domain	Combined	2.150	-1.237	5.537	0.213	447	484
Hanlon 1996	SF-36 Social Functioning Domain	baseline to 12 month follow-up	5.300	-2.577	13.177	0.187	86	83
			2.932	-0.085	5.949	0.057	566	603



Low or medium risk of bias

Figure G10: Effect of MTM on SF-36 Role Emotional Domain

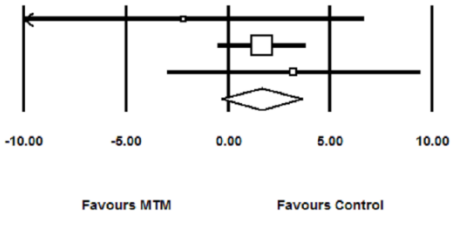
Study name	Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size MTM	Sample size No MTM
Taylor 2003	SF-36 Role Emotional Domain	baseline to 12 month follow-up	26.800	6.296	47.304	0.010	33	36
Malone 2000	SF-36 Role Emotional Domain	Combined	3.950	-2.079	9.979	0.199	447	484
Hanlon 1996	SF-36 Role Emotional Domain	baseline to 12 month follow-up	-5.500	-15.981	4.981	0.304	86	83
			5.386	-7.244	18.016	0.403	566	603



Low or medium risk of bias

Figure G11: Effect of MTM on SF-36 Mental Health Domain

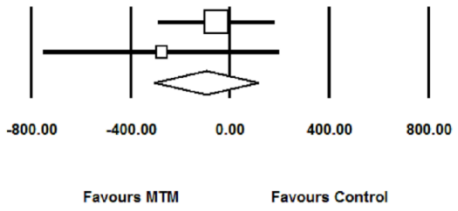
Study name	Outcome	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size MTM	Sample size No MTM
Taylor 2003	SF-36 Mental Health Domain	baseline to 12 month follow-up	-2.200	-11.042	6.642	0.626	33	36
Malone 2000	SF-36 Mental Health Domain	Combined	1.650	-0.498	3.798	0.132	447	484
Hanlon 1996	SF-36 Mental Health Domain	baseline to 12 month follow-up	3.200	-2.994	9.394	0.311	86	83
			1.615	-0.362	3.593	0.109	566	603



Low or medium risk of bias

Figure G12: Effect of MTM on health plan expenditures

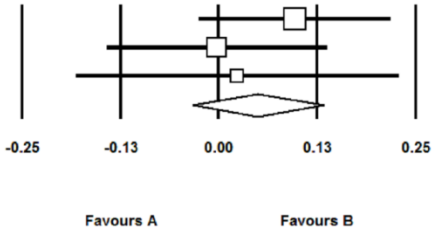
Study name	Comparison	Time point	Difference in means	Lower limit	Upper limit	p-Value	MTM	No MTM
Christensen 2007	same county	over 6 months	-54.700	-287.587	178.187	0.645	67	669
Moczygemba	usual care	over 6 months	-276.000	-751.246	199.246	0.255	60	60
			-97.551	-306.679	111.576	0.361	127	729



Medium risk-of-bias non-randomized studies

Figure G13: Effect of MTM on outpatient visits

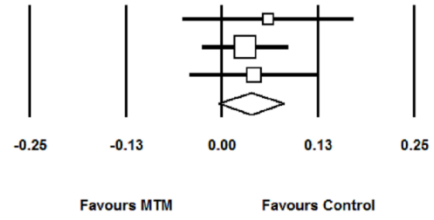
	Outcome	Comparison		Std diff in means	Lower limit	Upper limit	MTM	no MTM	p-Value
Malone 2000	Clinic visits	MTM	12 months	0.097	-0.024	0.218	523	531	0.116
Sellors 2003	Clinic visits	MTM	5 months	-0.002	-0.142	0.138	379	409	0.975
Touchette	Physician visits	MTM basic	3-6 months	0.023	-0.181	0.228	183	183	0.823
				0.049	-0.034	0.133	1085	1123	0.247



Medium risk-of-bias RCTs

Figure G14: Effect of MTM on mean number of hospitalizations

Study name	Comparison	Outcome	Difference in means	Lower limit	Upper limit	p-Value	MTM	No MTM
Malone 2000	MTM	Change in hospitalizations	0.060	-0.051	0.171	0.290	523	531
Sellors 2003	MTM	Overall no. of hosp	0.030	-0.025	0.085	0.289	379	409
Touchette 2012	Combined	Overall no. of hosp	0.042	-0.042	0.126	0.327	187	183
			0.038	-0.005	0.080	0.085	1089	1123



Medium risk-of-bias RCTs