

Evidence-based Practice Center Systematic Review Protocol

Project Title: Medication Therapy Management

I. Background and Objectives for the Systematic Review

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173)¹ established the requirements that Part D plan sponsors must meet with regard to drug utilization management, quality assurance, and medication therapy management (MTM). MTM services include providing education and counseling, improving medication adherence, and detecting adverse drug events and medication misuse.² MTM services are designed to be distinct from medication-dispensing services by their use of a patient-centric and comprehensive approach, rather than an individual product or episodic perspective.³ The legislation that established reimbursement for MTM services provided a general framework that gave Medicare Part D plan sponsors flexibility in designing their MTM programs including the criteria for eligibility; these requirements by the Centers for Medicare & Medicaid Services (CMS) have evolved since their implementation in 2006.

The MTM legislation did not initially define MTM services with specificity. Eleven national pharmacy organizations developed a consensus definition of MTM as “a distinct service or group of services that optimize therapeutic outcomes for individual patients that are independent of, but can occur in conjunction with, the provision of a drug product.”⁴ Despite the widespread consensus concerning the ultimate goal of MTM services, the specific components that make up MTM continue to evolve. For this review, we take a broad perspective on the population and interventions evaluated and will not limit the review to interventions and populations meeting CMS Part D MTM eligibility criteria.

Populations

Medication misuse and poor medication adherence commonly contribute to adverse events and reduced control of chronic medical conditions. 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.³ 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 a plan may require for eligibility into their MTM program. In defining multiple chronic diseases, a plan sponsor may require a maximum of three conditions for targeted enrollment but could set this threshold at two or three conditions. To be eligible for CMS

reimbursement, MTM plan sponsors 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 includes at least five of nine core chronic conditions—Alzheimer’s disease and end-stage renal disease were the added conditions. A plan may require no more than eight Part D drugs, although they may set at 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. MTM program sponsors must enroll eligible Medicare Part D beneficiaries into the MTM program using an opt-out approach only. 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. MTM program sponsors can also offer MTM services to beneficiaries who do not meet the CMS Part D criteria. Furthermore, MTM services or studies of MTM services may be offered and may benefit patient populations using programs and modalities that do not rely on CMS reimbursement. The Veterans Health Administration (VHA) includes MTM as one of several clinical activities provided to VHA health beneficiaries by VHA pharmacy services.⁵ The VHA does not specify patient eligibility criteria for MTM services.

Interventions and Comparators

A number of pharmacy organizations have proposed operational features to describe MTM services and best practices for delivering MTM.^{2,3} 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:

- 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 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.
- Quarterly targeted medication reviews with follow-up interventions when necessary

CMS defines the CMR as “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.”⁶ In addition, CMS describes a CMR as “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.”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.⁷ 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 (CPT®).^{8,9}

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

Because MTM has evolved as a “bundle” of related interventions, we expect to find the following types of studies:

1. Studies that compare individual components of MTM with one another or with usual care
2. Studies that compare the same bundle of MTM services with one another or with usual care but that provide one or more component pieces using a different format, technology, or method of delivery
3. Studies that compare one or more different bundles of MTM services with one another or with usual care

For the first type of studies, we would be able to draw conclusions only about the individual MTM component and not about the effectiveness of the component as part of a larger bundle of MTM services. For the second type of studies, we would be able to draw conclusions only about the effectiveness of different modalities for providing MTM services. Finally, for the third type

of studies, each MTM bundle may have a different mix or number of components (or both). Thus, we would be able to draw conclusions only about the effectiveness of the bundles as a whole, rather than individual MTM components.

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/school, patient satisfaction with care, health-related quality of life).¹⁰

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. MTM is a complex intervention with numerous and differing components. Stakeholders will first be interested in an evaluation of the overall effectiveness of MTM in comparison to usual care. They will also be interested in evidence about the factors under which MTM is effective and optimally delivered, what types of patients are likely to benefit from MTM services and to what degree, and what types of patients may be at risk of harms from the program.

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 in long-term care settings such as assisted living or skilled nursing facilities. In addition, telephone-based MTM services may be provided 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.

Rationale for an Evidence Review

Many of the Key Questions (KQs) that the topic nominator posed originally related to the setting, context, specific MTM components, and method of delivery for MTM services. They focus on comparisons of MTM services or programs rather on whether such services achieve

their intended purposes. Our initial literature scan suggested that few experimental studies directly compared one model of MTM with alternative models. Thus, the scope of our review should include both effectiveness and comparative effectiveness (insofar as possible). We will also include experimental studies that compare one MTM model with various types of usual practice not involving any formal MTM efforts. In addition, even with such an expansion, we will probably need to include observational studies for two reasons. First, nonexperimental studies will likely expand the evidence base on effectiveness and perhaps provide more insights into how different components function. Second, given how and the extent to which MTM services have evolved in the past two decades (e.g., before and after the MMA Part D legislation), trials for newer or more complex models may not have been done at all or not completed and reported; however, we may find evidence of more contemporary approaches evaluated in observational studies.

Relevance of Research Question to Clinical Decisionmaking or Policymaking

The KQs 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.

Availability of Scientific Data To Support the Systematic Review and Analysis

Our preliminary literature scan identified few studies or existing systematic reviews in this area. A preliminary review of 1,297 abstracts found 180 that met our initial screening criteria and clearly identified their study designs. Of these, 26 were trials, 31 were controlled clinical trials, and 123 were observational studies. Because of the stage of the science in this area, we anticipate that the benefit from conducting a systematic review of this topic may be to identify and elaborate research gaps in this area, rather than definitively answering all KQs within the analytic framework.

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
- Registered nurse
- Licensed practical nurse
- Nurse practitioner
- Physician assistant

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's of science (B.S.) degree that required a minimum of 5 years of study. Current regulations require that individuals have a Pharm.D. degree, which requires a minimum of 6 years of study and provides more clinical training than the prior 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 influences of provider type, education, and MTM-specific training on MTM effectiveness are not known.

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. Aspects of integration of MTM services with usual care that may predict the success of MTM programs include the ability of the MTM provider to communicate well with patients and multiple prescribers, ease of access to patients' medical records for pharmacists or other MTM providers, and adequate space and staffing levels.

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.

Potential Audiences of the Proposed Review

Potential audiences for our review include payers of MTM services such as CMS; providers of MTM services, particularly pharmacists and pharmacy benefit organizations; health care providers; and patients.

II. The Key Questions

We posted an initial draft of the KQs for public comment from March 6 through April 2, 2013, on the Effective Health Care Program Web site. We received comments from 23 professional organizations and individuals. We revised the KQs in response to these comments by:

1. Adding a new KQ (KQ 1) to describe the components and implementation features of MTM interventions
2. Including additional intermediate outcomes in KQ 2
3. Rewording KQ 3 to include MTM components
4. Specifying MTM components and implementation features for KQ 3 in the PICOTS (populations, interventions, comparators, outcomes, timing, and settings)
5. Specifying additional patient characteristics for KQ 4 in the PICOTS
6. Rephrasing KQ 5 to make the response conditional on identifying whether any harms of MTM exist

The revised KQs are listed below; specific details regarding patient population, intervention components, and outcomes are provided in the section that follows the analytic framework.

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 medication, 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

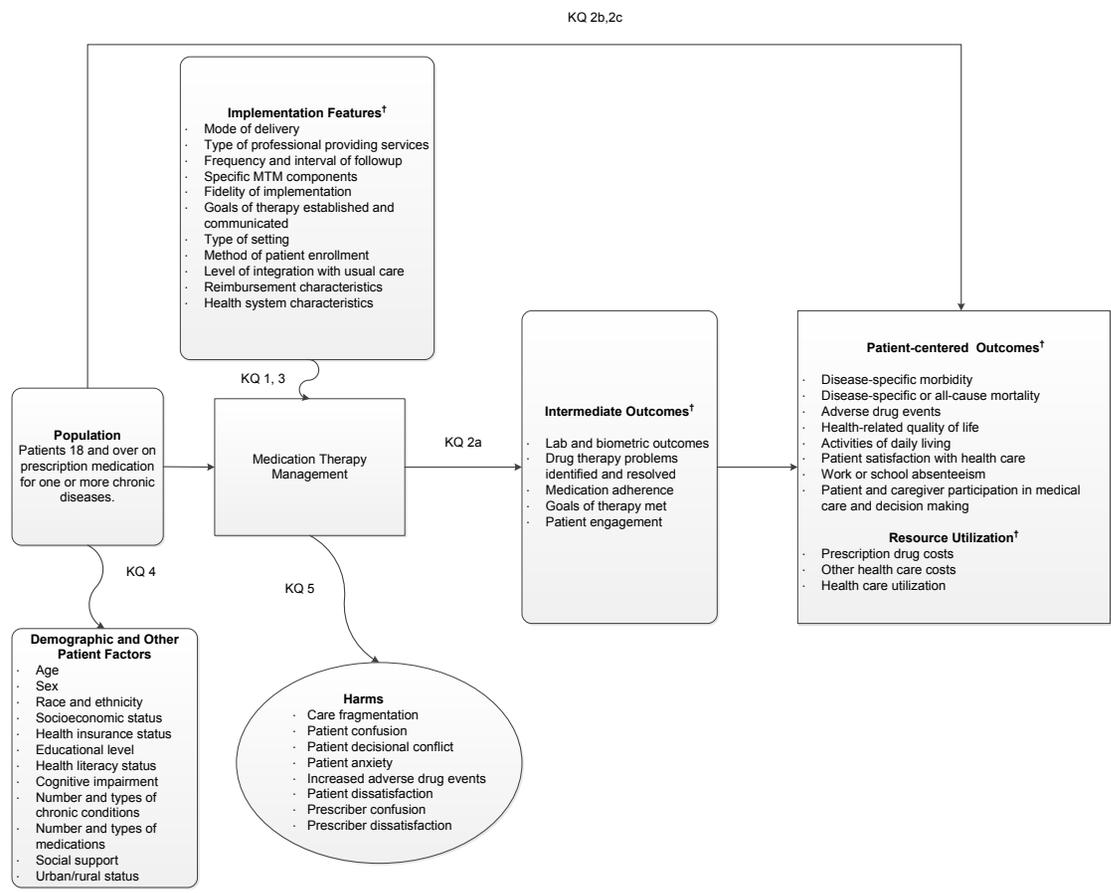
Does the effectiveness of MTM differ by patient characteristics, including but not limited to patient demographics and numbers and types of conditions and medications?

Question 5

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

III. Analytic Framework

Figure 1. Analytic framework for medication therapy management



†The population, intervention, outcomes, timing, and setting are described in detail in the text.
Abbreviations: KQ = key question; MTM = medication therapy management

PICOTS Criteria

The PICOTS criteria for the comparative effectiveness review are as follows:

- **Population(s)**

- 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 appropriate⁶
- *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 will not be included:

- Medication reconciliation interventions
 - Integrated pharmacy services within inpatient settings
 - One-time corrective actions related to medication management
 - Disease management interventions¹¹
 - Case or care management interventions¹¹
- The following types of interventions may include *MTM* services, but *MTM* may represent only one component of the overall intervention:



- Patient-centered home health care—delivery model
- Fully integrated, collaborative care models involving multiple disciplines and specialties

Studies should contain the same level of overall medical care/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. 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
- **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 lab or biometric outcome specific to diseases covered)
 - Drug therapy problems identified as defined by primary studies but typically includes the following: medications being taken but not indicated; medications indicated but not prescribed; patient adherence issues; suprathreshold 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 resolved as defined by primary studies but typically includes 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 care (either patient or provider directed or both), but there is no certain amount of time in between those episodes.
 - For studies that report outcomes at different points in time, we will only consider outcomes measured after the second episode of care.
- **Settings**
 - Patients must have been seen in ambulatory settings (e.g., outpatient clinics or private physician offices, long-term care, or retail pharmacy settings).
 - However, the MTM intervention itself may be delivered by 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 will not be included.
 - Interventions conducted in the United States and other countries and are published in English will be included.

IV. Methods

Table 1 details the study inclusion and exclusion criteria that we will use for our review.

A. Criteria for Inclusion/Exclusion of Studies in the Review

We specified our inclusion and exclusion criteria based on the population, intervention, outcome, timing, and settings identified through the topic refinement exercise. Our exclusion of non–English-language studies is based on limitations of time and resources. We will exclude studies with a high risk of bias and study designs without control groups to ensure that our pool of included studies can inform the causal link between the intervention and outcomes.

Table 1. Inclusion/exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	Patients ages 18 or older with one or more conditions requiring the regular use of prescription medication to manage symptoms or prevent progression of chronic disease	<ul style="list-style-type: none"> • Children under age 18 • Adults with acute conditions
Geography	No limit	No limit
Date of search	No limit; searches will be updated after the draft report goes out for peer review	
Study duration	No limit	
Settings	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Inpatient settings, if delivery of MTM services occurs almost exclusively in the inpatient setting
Interventions	<ul style="list-style-type: none"> • As defined in the PICOTS criteria • Also to be included are larger interventions with an MTM component that are compared to identical interventions without an MTM component (including care management and disease management) 	<ul style="list-style-type: none"> • 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	As defined in the PICOTS criteria	
Outcomes	As defined in the PICOTS criteria	<ul style="list-style-type: none"> • Studies that do not include at least one of the outcomes listed under the inclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Timing of intervention	<ul style="list-style-type: none"> Interventions should have at least two separately identifiable episodes of care (either patient-directed or provider-directed or both), but there is no certain amount of time in between those episodes For studies that report outcomes at different points in time, we will only consider outcomes measured after the second episode of care. 	<ul style="list-style-type: none"> Studies that only measure outcomes after one episode of MTM care
Publication language	English	<ul style="list-style-type: none"> All other languages
Study design	<ul style="list-style-type: none"> Original research Eligible study designs include: <ul style="list-style-type: none"> Randomized controlled trials Nonrandomized controlled trials Prospective controlled cohort studies Retrospective controlled cohort studies Case-control studies Systematic review and meta-analyses 	<ul style="list-style-type: none"> Case series Case reports Nonsystematic reviews Studies rated high risk of bias during quality assessment Studies without a control group
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

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We will systematically search, review, and analyze the scientific evidence for each KQ. We will take the following steps to perform the literature search.

To identify articles relevant to each KQ, we will begin 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 will also search the Cochrane Library and the International Pharmaceutical Abstracts database by using analogous search terms. We selected these databases based on preliminary searches and consultation with content experts. We will conduct quality checks to ensure that the search identifies known studies (i.e., studies identified during topic nomination and refinement). If we do not identify the known studies, we will revise and rerun our searches.

Table 2. Literature search terms

Category	Search Terms
Populations	None; no population terms were used to avoid restricting the search yield

Interventions	<p> (“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” </p>
Outcomes	<p> “optimized treatment outcomes” OR (patient OR patients) AND “medication understanding”) OR (“drug therapy outcome” OR “drug therapy outcomes”) </p>
Study Designs for All KQs	<p>None; no study design terms were used to avoid restricting the search yield</p>
Limits	<p> Humans English language </p>

In addition, we will search the “gray literature” for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information to assess risk of bias. Potential sources of gray literature include ClinicalTrials.gov, the World Health Organization’s International Clinical Trials Registry Platform, Health Services Research Projects in Progress, 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, CMS.gov, and dossiers for MTM providers. The Scientific Resource Center of the Agency for Healthcare Research and Quality (AHRQ) will manage 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 (TEP) and supplemented it according to their recommendations. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that our electronic searches might have missed.

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

We will include pooled estimates of effect or other relevant results from systematic reviews that meet our inclusion/exclusion criteria. We will evaluate the quality of included systematic reviews using the AMSTAR tool.¹² As appropriate, we may update the results of these reviews quantitatively or qualitatively. Should identified systematic reviews use inclusion/exclusion criteria that differ from ours, we will review their reference lists to ensure that we include all relevant studies.

C. Data Abstraction and Data Management

All titles and abstracts identified through the literature searches will be independently reviewed for eligibility against our inclusion/exclusion criteria by two trained members of the

research team. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies that lack adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® (Thomson Reuters, New York, NY) database and the results will be deposited in the Systematic Review Data Repository.

We will retrieve and review the full text of all included titles during the title/abstract review phase. Each full-text article will be independently reviewed by two trained members of the team for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason why each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract relevant information into evidence tables. To test the feasibility of this approach, we will test the approach with a sample of studies. We will design data abstraction forms to gather pertinent information from each article, including the characteristics of the study populations, settings, interventions, comparators, study designs, methods, and results. Specifically, we will abstract information about the interventions as specified in KQ 1, KQ 3, and the analytic framework; outcomes as specified in KQ 2a, 2b, and 2c and the analytic framework; patient characteristics as specified in KQ 4 and the analytic framework, and information about harms as specified in KQ 5 and the analytical framework. Trained reviewers will extract the relevant data from each included article into the evidence tables. All data abstractions will be reviewed for completeness and accuracy by a second member of the team. We will not plan to routinely contact study authors for additional information.

D. Assessment of Methodological Risk of Bias of Individual Studies

To assess the risk of bias of individual studies, we will use predefined criteria based on those developed by AHRQ.¹³ For randomized controlled trials, we will also rely on the risk-of-bias tool developed by the Cochrane Collaboration.¹⁴ We will assess 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. Specific concerns for our review include including questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias (i.e., those about 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 plan to exclude studies deemed at high risk of bias from our main data synthesis and main analyses; we will include them only in sensitivity analyses.

E. Data Synthesis

If we find three or more similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. We will also consider conducting mixed-treatment comparisons in a meta-analysis using Bayesian methods to compare the MTM interventions with each other if we identify a sufficient number of studies with a common comparator (e.g., placebo). For all analyses, we will use random-effects models to estimate pooled or comparative effects. To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.¹⁶ We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. If we conduct quantitative syntheses (i.e., meta-analysis), we will assess statistical heterogeneity in effects between studies by calculating the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates due 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). If we include any meta-analyses with considerable statistical heterogeneity in this report, we will provide an explanation for doing so, considering the magnitude and direction of effects. We will also examine potential sources of heterogeneity using sensitivity analysis or analysis of subgroups. We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate to examine clinical heterogeneity. Planned stratifications or categories for subgroup analyses include the subgroups listed in the analytic framework. When quantitative analyses are not appropriate (e.g., because of heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

F. Grading the Strength of Evidence for Individual Comparisons and Outcomes

We will grade the strength of evidence based on the guidance established for the Evidence-based Practice Center Program.¹⁷ Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (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.

Table 3 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus. We will grade the strength of evidence for the outcomes deemed to be of greatest importance to decisionmakers and those most commonly reported in the literature.

Table 3. Definitions of the grades of overall strength of evidence¹⁵

Grade	Definition
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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.

G. Assessing Applicability

We will assess applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.¹⁸ We will use 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.

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

Not applicable.

VIII. Review of Key Questions

For all Evidence-based Practice Center (EPC) reviews, KQs were reviewed and refined as needed by the EPC with input from Key Informants and the TEP to ensure that the questions are specific and explicit about what information is being reviewed. In addition, the KQs were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the KQs for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not

reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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 are invited to serve as Key Informants, and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as in identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions and design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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 are invited to serve as Technical Experts, and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer Reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the Evidence Report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. 290-2012-00008-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The TOO reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.