Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Medication Therapy Management Interventions in Outpatient Settings

Draft review available for public comment from December 2, 2013 to January 6, 2014.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Comment #	Commentator & Affiliation	Section	Comment	Response
1	Peer Reviewer #1	Structured Abstract	--The results in the structured abstract do not align with or follow the answers to the key questions. --The conclusion statement is unclear. Please make this statement more explicit. This is also true in the executive summary (p.31, row 41-45)	Revised to align with key questions. Conclusion statement revised to remove reference to future research.
2	Peer Reviewer #1	Executive Summary	(Please note that the majority of these edits also pertain to the full report review sections as well. I have noted the page number and row for the exec summary, but did not note the corresponding page/rows in the primary review.)	No changes required.
3	Peer Reviewer #1	Executive Summary	p.11-12, (Figure A)—I like the figure and analytic framework. It appears that this is based on Donabedian's structure-process-outcome model? If so, some mention of this and a related citation would be appropriate.	Figure A depicting the review's analytic framework in the executive summary and the corresponding figure in the full report are not based on Donabedian's structure-process-outcome model. In the EPC program, analytic frameworks are developed for each review to portray the underlying logic and mechanistic relationships with respect to an intervention, including the relationship between intermediate outcomes (process or disease-oriented outcomes) and more distal outcomes of interest to patients, clinicians, and decision-makers. See the EPC Methods Guide for additional information about the use and development of analytic frameworks. Reference: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. Chapters available at: www.effectivehealthcare.ahrq.gov.
4	Peer Reviewer #1	Executive Summary	p.15, row 17 (Table A)—Under the medication adherence listing, please elaborate on the types of medication adherence outcomes (e.g. self-report, claims-based measures, technology [MEMS], biometric)	Revised to add types of measures to add types of measures of medication adherence

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5	Peer Reviewer #1	Executive Summary	p.15, row 46 (Table A)—The timing statement in relation to "2 episodes" is not clear. I believe the language used in the full report helps to clarify. However, one important point to discuss is the rationale for use of "2 episodes" as opposed to "1 episode". While I understand that MTM, by nature, should be longitudinal, were studies excluded if they provided a CMR, MAP, PMR with referral and documentation during a single visit? In other words, it appears that if a study protocol did not specify a follow-up visit, they were excluded. If this is the case, I believe that a stronger rationale for exclusion of these studies is needed and, at a minimum, a summary of these excluded studies should be in the report. In practice, MTM is commonly delivered during a single session without any additional follow-up due to a variety of circumstances.	We've added additional text in the Executive Summary and the Full Report to more explicitly define the scope of this review. The scope of this review only incudes outpatient MTM interventions that by design include a follow-up component (i.e. at least 2 episodes of care). We did not require interventions to demonstrate that all patients received more than one episode of care, but rather the opportunity to receive follow-up was available by design consistent with the Pharmacy Profession Consensus Definition for MTM and the MTM Core Service Model, both of which include monitoring and follow-up to evaluate the patient's response to therapy, including safety and effectiveness. While MTM services delivered as one-time interventions may be appropriate depending on the goals of the MTM program and care setting, we limited the scope of studies in this review to studies that by design were longitudinal in nature to minimize clinical heterogeneity. We are unable to revisit all abstracts, titles, and full-text articles to ascertain which were excluded for failure to follow up exclusively. Many studies not meeting one exclusion criterion also met others. The list of excluded studies is provided in the appendix.
6	Peer Reviewer #1	Executive Summary	p.16, row 5 (Table A)— Home health should be listed here as well.	The inclusion table is revised to indicate that home health is included as long as residents have control over medication self-administration
7	Peer Reviewer #1	Executive Summary	p.16, row 27 (Lit Search strategy)— It would be helpful to include the search strategy table (table 2) from the full report here in the executive summary.	We are limited by length in what we can include in the executive summary. Readers seeking a fuller understanding of our methods are urged to look at the relevant appendix.
8	Peer Reviewer #1	Executive Summary	p.21, row 3 (beginning with Table C)—For all of the summary tables, can you clarify what (N Analyzed) refers to. It may be easiest to simply state (Number of subjects analyzed).	N clarified as requested

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9	Peer Reviewer #1	Executive Summary	p.21, row 3 (beginning with Table C)—For all of the summary tables, there was an adequate description in the text regarding the strength of evidence labels and how these labels were derived. However, I could not find a similar set of descriptions/definitions for the labels in the "Results" column. For example, how did the authors determine "imprecise" for row 8? Similarly, how were the terms for "inconsistent" and "indirect" determined in other columns?	Clarified in methods section
10	Peer Reviewer #1	Executive Summary	p.21, row 3 (beginning with Table C)—For all of the summary tables, another unclear aspect is related to the results. In row 21, quantitative data is presented for medication appropriateness based on 1 RCT. But, for other categories in the table with 1 (or more RCTs) there is no quantitative data in the results column (only the unclear qualitative labels mentioned above). I believe this is due to some studies being given a "high bias" rating, but this not clear in the tables. Possibly, adding the additional rating for risk of bias to these tables would help.	Revised to indicate why quantitative data are not presented for each outcome.
11	Peer Reviewer #1	Executive Summary	p.25, row 8-19—Please mention of the paucity of high quality (low bias) studies regarding MTM should here.	We have mapped this comment as relating to the discussion section on harms of MTM. Although low risk of bias studies would certainly be useful, the primary constraint for this set of outcomes is not the quality but the quantity of evidence.
12	Peer Reviewer #1	Executive Summary	p.27, Policy section—Further mention of the need to identify those patients who would be most at risk for drug-related problems and most likely to benefit from MTM is warranted. Current policies cast a wide net over those patients who are eligible for MTM using criteria that are not evidence-based. Furthermore, many patient populations who may benefit from MTM are excluded from MTM coverage.	Though findings from our report are insufficient for being able to suggest refinement of patient eligibility criteria, we've added additional text to the Executive Summary and the Full Report to address this suggestion.
13	Peer Reviewer #1	Executive Summary	p.29, row 44-45—Please clarify this sentence. The current state of MTM literature is relatively sparse with regards to low bias studies across a diverse set of outcomes and populations.	Although the quality of research in this and other fields can certainly be improved, our point still holds: despite numerous reasonably run trials, the body of evidence fails to consistently provide evidence of effectiveness across a range of hypothesized benefits. We do not believe that this sentence requires change.

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14	Peer Reviewer #1	Executive Summary	p.31, row 28-35—Please include the need for and use of more precise measures of medication adherence. As this outcome can be improved with MTM, the scientific community needs better measures of adherence. Both self-report and claims-based measures have drawbacks while more novel technology to assess adherence is largely underdeveloped.	We note "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."
15	TEP Reviewer #1	General Comments	I would like to thank the Report authors, task officer(s), and staff for advancing the scientific dialogue related to medication therapy management services (MTMS). The work contained in this draft Report represents an important first step in helping decision-makers and stakeholders understand important scientific distinctions between health care delivery systems that meet the definitions and standards of MTMS articulated in official health reporting nomenclature, as compared to other medication therapy management programs, including the Medicare Part D Medication Therapy Management (MTM) Program.	thank you
16	TEP Reviewer #1	General Comments	Before I commence my comments and critique of this Report, please permit me to first offer my assistance in implementing the suggestions and recommendations for strengthening the Report contained in this review.	thank you
17	TEP Reviewer #1	General Comments	This Report has the potential to greatly assist influential policy-makers and contribute to a growing body of evidence in addressing the persistent and substantial public health burden of drug-related morbidity and mortality in this country. A root causes analyses of why drug therapies are ineffective and unsafe when used in the homes of citizens is complex and multi-factorial. Analysis of solutions for reducing drug-related morbidity and mortality will require mixed methods evaluation approaches to study variations among high performing medication management organizations in relationship to health care organizations that have not yet focused on building accountable medication management systems with patients.	We have added the note about mixed-methods approaches to our discussion section.

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18	TEP Reviewer #1	General Comments	A number of suggestions and recommendations are noted below to strengthen the Report, and to provide decision-makers and stakeholders with a more complete picture of MTMS in concerted national efforts to design a rational medication use system. These suggestions and recommendations are presented in the following order: 1.) Evaluation model employed in the analysis, 2.) Use of a consensus description of MTM rather than the rigorously developed definition of MTMS assigned by the American Medical Association in official health reporting nomenclature, 3.) Reference to standards of practice for MTMS and factors affecting the quality of MTMS without description or citation, and, 4.) Methodological considerations related to inclusion/exclusion criteria.	We respond to each critique in comments 19 through 22.
19	TEP Reviewer #1	General Comments	The first suggestion for improvement relates to the evaluation model employed in this analysis. The evaluation approach employed in this analysis is deeply vested in experimental design that dominates the toolkit of evidence-based medicine. This evaluation approach has been summarized by Pawson and Tilley as an, OXO design: observe a system (O), introduce a perturbation/intervention (X) to some participants but not others, and then observe again (O). [1] Pawson and Tilley assert that when studies use the OXO paradigm to evaluate social programs (including most system improvements in medicine), the result is almost always “a heroic failure, promising so much and yet ending up in ironic anticlimax. The underlying logic seems meticulous, clear-headed and militarily precise, and yet findings seem to emerge in a typically non-cumulative, low-impact, prone-to-equivocation sort of way.” The usual conclusion and assertion from traditional OXO evaluations of quality-improvement efforts in health care is either that nothing works or that the results are inconsistent and more research is needed. [1] The Conclusion section of this Report, as drafted on Page vi of the Structured Abstract, illustrates this assertion. Dr. Don Berwick, former CMS Administrator and champion of the Science of Quality Improvement, has stated that the OXO paradigm most	We are in complete agreement with the reviewer on the difficulties of evaluating complex multi-component interventions using traditional experimental designs. In fact, one of the authors of this review has co-authored a white paper on issues surrounding the synthesis of complex multicomponent interventions (http://effectivehealthcare.ahrq.gov/ehc/products/578/1878/health-care-interventions-review-report-140303.pdf). As the reviewer notes, context is frequently inseparable from mechanism in these types of interventions. A range of evaluation options may be used to address these types of designs: the reviewer specifically calls out mixed methods, statistical process control, time series analysis, simulations, and factorial experiments. Numerous other qualitative approaches not mentioned by the reviewer may also be used to evaluate these interventions. The reviewer’s rejection of experimental research in the context of MTM (“the O-X-O paradigm”) and call for a change in the evaluation approach used by this systematic review raises several important questions, the foremost of which is, **are systematic reviews too blunt an instrument to answer the question about the effectiveness of MTM?** Systematic reviews, by

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			commonly applied in the traditional toolkit of evidence-based medicine is, “a powerful, perhaps unequaled, research design to explore the efficacy of conceptually neat components of clinical practice—tests, drugs, and procedures. For other crucially important learning purposes, however, it serves less well.” [2] The need to reexamine the evaluation paradigm is acknowledged in this Report on Page ES 17, under the heading Implications for Clinical Practice and Policymakers, where the authors state, “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.” The introduction of interprofessional and interdisciplinary systems for establishing a rational medication use system in which patients routinely achieve their goals of therapy with zero tolerance for preventable medication harms is a complex, multicomponent intervention—essentially a process of social change. The first sentence in the Report section titled, Scope and Key Questions (see page ES-1) acknowledges the fact that medication therapy management is, “a complex intervention with numerous and differing components.” MTMS cannot be discreetly detached from integrated delivery systems and studied in the same way as that of a linear, mechanical, tightly coupled causal relationship, such as determining the benefits of beta-blockers for heart failure. With over 30 years of evidence on the impact and outcomes of medication management implemented in dynamic health systems, very few Institutional Review Boards (IRBs) would approve such a study design – This would be similar to randomizing patients to receive medical care (e.g. CPT Evaluation and Management codes 99201-99205, and 99211-99215) to isolate the effects on health outcomes. Pawson and Tilley claim that the reason the OXO model fails in this context is because, “experimentalists have pursued too single-mindedly the question of whether a program works at the expense of knowing why it works.” [1] The OXO model seeks generalizable knowledge depending	their nature, seek a balance of valid and generalizable information across multiple studies. If the effect of a class of interventions cannot be generalized because the fingerprint of each instance of the intervention is utterly unique as a consequence of the interaction of mechanism and context, then the use of systematic reviews is indeed misguided. An immediate consequence, however, of the claim of uniqueness of each instance of the intervention is that they cannot all lay claim to a single label. As long as instances of interventions claim the same label of “medication-therapy management” and are being paid from public coffers for common practices, it is in the public interest to take the self-claimed label at face value and ask the question, “do MTM interventions work as a class?” This question is posed as KQ 2 in our review. We note that this systematic review was commissioned on request by a professional group that believed sufficient commonality existed across MTM interventions to warrant a systematic review. Our preliminary evaluation of the evidence, coupled with an extensive public and peer review of our proposed questions did not raise any concerns about the validity of using the methods of a systematic review. Note that KQ 2 did not require an O-X-O design of observation, “perturbation” or experimentation, and observation. We included all cohort designs, whether observational or experimental. In fact, many of the cohort studies we evaluated were conducted in practice settings and sometimes designed retrospectively. By no means is the pool of admissible evidence limited to pristine trials akin to the beta-blocker example with minimal applicability to real-world practice. We did not consider single-arm studies to be admissible evidence, but we posit that these studies cannot answer the question of effectiveness with the same degree of certainty as studies with control arms: should we have included them in the same pool of evidence as studies with control arms, they would necessarily have occupied a far lower rung in the

Comment #	Commentator & Affiliation	Section	Comment	Response
			on removing most of the details about "how" something works and the contexts in which it works. It reveals little about mechanisms or factors that affect generalizability. Studying a few covariates, using stratified designs, and probing for interactions are inadequate tools for studying complex, unstable, nonlinear social change. This conflict, or dissonance, has been discussed in the health care evaluation field for many years. [1,2,3] It has been pointed out that there is, and ought to be, a strong relationship between what is studied and how it is studied. With social changes involving multicomponent interventions (e.g. comprehensive team-based medication management) which are interpersonal and nonlinear in complex social systems—then other, richer, but equally disciplined, evaluation methods are needed. One alternative evaluation approach, known as the context + mechanism = outcome (CMO) model, highlights the fact that programs only work insofar as they introduce promising ideas, solutions and opportunities in the appropriate social and cultural contexts. [1,2] One example of the CMO model currently in use on a large national scale involves colleagues at AHRQ who are substantially contributing to the use of this evaluation approach in concert with the CMS Center for Medicare and Medicaid Innovation and the CMS Center for Clinical Standards and Quality. In the Partnership for Patients, AHRQ Federal Partners Noel Eldridge and Bill Munier are serving as measurement stewards for rapid cycle evaluation of national efforts to reduce preventable hospital acquired conditions 40% and 30-day readmissions 20% over three years. [4] It is also important to note that the AHRQ Evidence-based Practice Center (EPC) Program (creating the Effective Health Care Program through the same Congressional authorization that brought us the Medicare Part D Program), has been uniquely positioned to involve a broad range of stakeholders to ensure relevancy and transparency by ensuring that research findings, "reflect the various needs of all diverse users, are relevant to their unique challenges, and are applicable in real-world situations. [5]. The purposes and charter of the AHRQ Effective Health Care Program are not prescriptive in requiring use of a traditional, randomized	hierarchy of evidence in their ability to answer the question of effectiveness of MTM interventions. The reviewer's critique raises another question for the systematic review team: **if systematic reviews are indeed a valid approach to reviewing the effectiveness of MTM interventions, how should they deal with heterogeneity inherent in these interventions in addressing the question of effectiveness?** MTM interventions are widely variable in implementation: a coarse-grained evaluation of their effectiveness that stops short at asking "does the class of interventions work?" risks missing important patterns that may be driven by intervention characteristics (including context) and patient characteristics. To address the wide heterogeneity of included interventions, we posed three additional questions: one descriptive laying out the specific components and intervention features (including contextual features) of each included MTM intervention (KQ 1), and two causal, asking how MTM effectiveness varied by intervention components (KQ3) or patient characteristics (KQ 4). We also had the option of conducting meta-regression for KQ 2, using intervention or patient characteristics as predictors of outcomes when we uncovered significant heterogeneity and sufficient numbers of studies for analysis, but such instances did not occur. Again, note that neither KQ 3 nor KQ 4 required an O-X-O design of observation, perturbation, and observation: we accepted both experimental and observational designs, including those from practice settings. We found extremely limited evidence on KQ 3 and KQ 4: our failure to answer these questions with certainty speaks to the paucity of research in the field examining these important questions rather than lack of validity of the questions themselves. It may well be that MTM research on the interplay between mechanism and context in influencing outcomes is in such a state of infancy that these questions require substantial additional effort in primary and secondary research. A traditional systematic review seeking to understand the

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			controlled trial-type (OXO) evaluation paradigm, but rather provides great latitude in using mixed methods evaluation approaches to study complex, multidimensional initiatives that are not conceptually neat components of clinical practice. Another compelling reason for recommending significant adjustments to the evaluation approach used in the Report, relates to evidence of wide variations in outcomes of initiatives that meet the definition and standards of MTMS in official health reporting nomenclature as compared to other MTM programs. Observing and understanding variations in systems ranging from automobile engineering to health care gave rise to the science of quality improvement, focusing on process-based, data-driven approaches to improving the quality of products or services through iterative cycles of action and evaluation. [6] This wide variation in outcomes is apparent among MTM Programs. In the CMS Final Report of Medication Therapy Management in Chronically Ill Populations, using a mixed methods quantitative and qualitative evaluation methodology, there was "substantial variation in outcomes" among Part D Programs. [7] And use of a mixed methods evaluation approach (such as that advocated by Pawson, Tilley, Berwick, Batalden and others) revealed key characteristics of best performing systems able to improve outcomes while keeping total health expenditures from rising. These key medication management system characteristics include: coordination of care, integration and collaboration with trusted community partners, use of efficient communications methods, persistent follow-up, and close attention to patients' unique drug-related needs and barriers to effective medication use. [7] And one additional compelling reason for strongly recommending adjustments to the evaluation methodology used in this Report is alignment with concerted efforts to achieve the three-part measurement aims outlined in the National Quality Strategy. [8] Large multi-dimensional care collaboration systems have evolved through aims-based government contracts to improve care at reduced per capita expenditures. National Quality Strategy measurement parameters related to reductions in hospital acquired conditions and readmissions do not seek to isolate the cause	question the "how" question (how do intervention components or patient characteristics influence outcomes?) may be unable to produce meaningful answers until further primary and secondary research is commissioned. Finally, the third question raised by this critique is, **can systematic reviews meaningfully evaluate the reasons for the success or failure of the intervention in the absence of trials and cohort studies that specifically examine these questions?** We did not pose this question in our systematic review. Note that this question is no longer operating within a traditional causal framework – it seeks patterns or associations that may or may not be causal in origin. The configurational framework (qualitative comparative analysis) offers one such approach in searching for necessary and sufficient conditions for an outcome to occur. The approach is being applied for the first time to systematic reviews by an author on this review (R03 HS22563-01). Another approach, the realist review approach, requires a strong theoretical basis, an iterative approach to analysis and synthesis, a combination of qualitative and quantitative methods. The realist review is more resource-intensive than traditional reviews and requires considerable exercise of judgment. It is not widely used at this time. AHRQ has not so far commissioned a realist review. In conclusion, although we much appreciate the reviewer's offer of help and understand the desire for a complete change in our evaluation paradigm, we believe the questions "do MTM interventions work?" and "how do intervention and patient characteristics influence outcomes?" are appropriate, as are the approaches we took to answering these questions. We did not ask the question "what explains the success or failure of MTM interventions?" The approaches to answering this question using systematic review methodology are experimental and not in wide use. We anticipate a growing need for answers on the question of programmatic success or failure. We would welcome more investment of research funds in the exploration of

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			and effect factor(s) for achieving these bold national aims. Assessment techniques developed in engineering and used in quality improvement—statistical process control, time series analysis, simulations, and factorial experiments—have more power to inform about mechanisms and contexts than do traditional OXO evaluation paradigms. 1.) Pawson R, Tilley N. Realistic Evaluation. London, England: Sage Publications Ltd; 1997. 2.) Berwick DM. The Science of Improvement. JAMA. 2008;299(10):1182-1184. doi:10.1001/jama.299.10.1182. 3.) Davidoff F, Batalden P. Toward stronger evidence on quality improvement: draft publication guidelines: the beginning of a consensus process. Qual Saf Health Care. 2005;14(5):319-325. 4.) U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services. Partnership for Patients. Available at: 5.) U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. Evidence-based Practice Centers Program Overview. Available at: www.ahrq.gov/research/findings/evidence-based-reports/overview/index.html 6.) Robert Wood Johnson Foundation. Improving the Science of Continuous Quality Improvement Program and Evaluation. Published: June 25, 2012, Program Results Report, Grant ID: CQI. Available at: www.rwjf.org/content/dam/farm/reports/program_results_reports/2012/rwjf73230 7.) U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services. Medication Therapy Management in Chronically Ill Populations: Final Report. Contract # HHSM-500-2011-00012I/TOT0001, August, 2013. 8.) U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. 2013 Annual Report to Congress. National Strategy for Quality Improvement in Health Care, July 2013. Available at: www.ahrq.gov/workingforquality/nqs/nqs2013annlrpt.pdf.	alternative systematic review methodologies.
20	TEP Reviewer #1	General Comments	The second aspect of this Report that needs to be examined is the decision to use a consensus-based description of medication therapy management, in lieu of the rigorously	We have revised the introduction and background section to further describe the various definitions and descriptions for MTM services, including CPT

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			developed, peer-reviewed definition of MTMS assigned by the American Medical Association in official health reporting nomenclature. The scientific, peer-reviewed application process for considering assignment of any service in official health reporting nomenclature is articulated by the American Medical Association. The rigorous, peer-review Current Procedural Terminology (CPT®) health reporting nomenclature process engages a 17-member CPT Editorial Panel and over 200 CPT Advisors appointed by diverse medical societies. Each of these individuals review all evidence-based code proposals submitted to CPT for consideration in official health reporting nomenclature using explicit scientific criteria. [9] 9.) American Medical Association. CPT Process ® - How a code becomes a code. At: www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/coding-billing-insurance/cpt/cpt-process-faq/code-becomes-cpt.page. The purpose of CPT is to, "provide a uniform language that accurately describes medical, surgical, and diagnostic services, and thereby serves as an effective means for reliable nationwide communication among physicians and other healthcare providers, patients, and third parties." [9] Reliance on a consensus-based description of medication therapy management, rather than the rigorous, peer-reviewed definition of MTMS, is also inconsistent with evidence-based principles related to grading patient-oriented guidelines within the Strength of Recommendation Taxonomy. [10] 10.) American Academy of Family Physicians, and, U.S. Preventive Services Task Force. The Strength of Recommendation Taxonomy. Available at: www.aafp.org/dam/AAFP/documents/journals/afp/sortdef07.pdf. It will be instructive to briefly discuss the CPT Editorial Panel petition process for MTMS culminating in assignment of official nomenclature, including explicit definitions, descriptions and service level expectations for MTMS. Describing distinctions between CPT MTMS definitions and characteristics in comparison to other medication therapy	definitions. Because most of these definitions and descriptions, including CPT definitions, describe MTM in the context of professional practice, rather than a specific discrete intervention, we could not simply adapt any single definition for MTM into the PICOTS framework for this review. Rather, we drew from the various available MTM definitions to develop bounded PICOTS criteria that could be used to define criteria for study inclusion and exclusion. We did not identify any studies that explicitly described using MTM CPT criteria to identify patients who received MTM interventions, or who used CPT criteria to describe the MTM intervention that was used. Thus, requiring the use of the CPT definition for study inclusion would be overly restrictive and would result in no included studies.

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			management programs is critical for legislators, regulators and stakeholders as they make key policy decisions pertaining to this country's medication use system. Evidence of the effectiveness and safety of medication therapy management contained in the original CPT code proposal was derived from the literature on the practice of pharmaceutical care. It is acknowledged that a profession-wide consensus document of desirable components for medication therapy management was included in the 2004 CPT Code Proposal package for MTMS. However, the American Medical Association strengthened the service level standards and expectations beyond the consensus-wide document by codifying the pre-, intra-, and post-service definitions of MTMS, including a detailed Clinical Example vignette. [11,12,13] The hallmark of these service level standards and expectations is use of a consistent and systematic patient care process characterized by a comprehensive assessment, care plan, and follow-up evaluation.[11] 11.) Isetts BJ, Buffington DE, et. al. CPT code-change proposal: National data on pharmacists' medication therapy management services. J Am Pharm Assoc. 2007; 47:491–495. doi: 10.1331/JAPhA.2007.07013. 12.) American Medical Association. CPT changes 2006: an insider's view. Chicago: American Medical Association; 2005:309–12. 13.) American Medical Association. Current Procedural Terminology (CPT), Professional Edition. Chicago, IL: American Medical Association, 2014.	
21	TEP Reviewer #1	General Comments	Before transitioning to the next section of comments related to standards of practice, there is one fundamental technical aspect contained in this Report that needs to be corrected related to Medication Therapy Management Services provided within the practice of pharmaceutical care. On page ES-10 of this Report, under the heading of, KQ 1: Intervention Components and Implementation Features, pharmaceutical care is described as a synonymous or interchangeable term with medication therapy management. Every health service is supported by a practice management system that is required to consistently provide that service in a manner recognized by society. And Medication Therapy	We have modified the executive summary and introductory sections to reflect the multitude of definitions and standards, which have been promulgated for MTM. A detailed comparison or discussion of these standards is beyond the scope of this review.

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			Management Services have this same attribute similar to physicians diagnosing illness in the practice of medicine, or dentists extracting teeth in the practice of dentistry. Understanding relationships of Medication Therapy Management Services provided within the practice of pharmaceutical care is essential for explaining the service to decision-makers and stakeholders, as well as for measuring quality of the service consistent with standards of practice. A more complete discussion of this relationship can be found in the literature. [11,14] 11.) Isetts BJ, Buffington DE, et. al. CPT code-change proposal: National data on pharmacists' medication therapy management services. J Am Pharm Assoc. 2007; 47:491–495. doi: 10.1331/JAPhA.2007.07013. 14.) Isetts BJ, Brown LM, Schondelmeyer SW, Lenarz LA. Quality assessment of a collaborative approach for decreasing drug-related morbidity and achieving therapeutic goals. Arch Intern Med. 2003; 163:1813-20. Standards of practice establish expectations for the performance of an individual practitioner. For instance, a physician is held to specific standards when conducting a medical exam, as is a dentist when performing a dental examination. One of the reasons why it is so important to include a much more complete evaluation of standards of practice in this Report, is because there are wide variations in service level expectations of MTMS as described in official health reporting nomenclature, as compared to other medication therapy management programs, including the Medicare Part D Medication Therapy Management (MTM) Program. The Medicare Modernization Act of 2003 provided great latitude in designing medication therapy management programs resulting in narrowly drawn eligibility criteria, a limited scope of programs, and care delivered at the lowest level of services. [15] Although colleagues working at CMS in the Medicare Part D MTM Program and at the Pharmacy Quality Alliance have made some progress in developing quality measures, it has been difficult to overcome this lack of legislative direction and standards. A recent Congressional action taken to rectify this oversight can be found in Sec. 3503 of the Affordable Care Act in which service level expectations of MTMS consistent with CPT	

Comment #	Commentator & Affiliation	Section	Comment	Response
			nomenclature and standards of practice are explicitly stated. [16] 16.) United States Congress. Patient Protection and Affordable Care Act. Sec. 3503 – Medication Management Services in treatment of chronic diseases. May 2010. Available at: http://housedocs.house.gov/energycommerce/ppacacon.pdf In the Executive Summary of this Report, on page ES-1, it is accurately noted that standards for medication therapy management services evolved subsequent to initial work in this area. However, a thorough review of the contents in this 397-page draft report does not appear to describe or cite these standards. It is strongly recommended that standards of practice for the delivery of medication therapy management services be included in this analysis. Useful sources for including standards of practice in this Report include the Patient Centered Primary Care Collaborative, and in reference texts on the Practice of Pharmaceutical Care. [17,18,19] 17.) Patient-Centered Primary Care Collaborative. The Patient-Centered Medical Home: Integrating Comprehensive Medication Management to Optimize Patient Outcomes. 2nd ed. Patient-Centered Primary Care Collaborative. Washington, D.C., Available at: www.pcpcc.org/sites/default/files/media/medmanagement.pdf. 18.) Cipolle RJ, Strand LM, Morley PC. Pharmaceutical Care Practice: The Clinician's Guide, 2nd ed. New York: McGraw-Hill; 2004. 19.) Cipolle RJ, Strand LM, Morley PC. Pharmaceutical Care Practice: The Patient Centered Approach to Medication Management, 3rd ed. New York: McGraw-Hill; 2012.	

Comment #	Commentator & Affiliation	Section	Comment	Response
22	TEP Reviewer #1	General Comments	Interrelated with standards of practice is measurement of the quality of care delivered in the context of these standards. When care is delivered in the context of standards, there are methods available for measuring quality of the service. Peer review of quality has been used in medicine and nursing to measure the quality of a service provided by an individual practitioner against pre-determined standards of practice criteria. Colleagues working in conjunction with the Rand Corporation validated a structured implicit review process for evaluating the quality of medical care delivered in ambulatory and hospital settings. Structured implicit review has been used in the Medicare quality management program for evaluating care delivered by physicians. This quality assessment methodology has been utilized to measure the quality of care delivered in relationship to standards of practice for MTMS. [14,20] 14.) Isetts BJ, Brown LM, Schondelmeyer SW, Lenarz LA. Quality assessment of a collaborative approach for decreasing drug-related morbidity and achieving therapeutic goals. Arch Intern Med. 2003; 163:1813-20. 20.) Brown LM. Quality Assessment of an Ambulatory Care Clinic Based Collaborative Care Approach to Achieving Therapeutic Goals. Ph.D. dissertation presented to the University of Minnesota Graduate School, 2004.	We found no studies that measured the fidelity of MTM services or evaluated service delivery using any sort of quality measure. As a result, our review cannot comment on this aspect.
23	TEP Reviewer #1	General Comments	It is noted on page 5 of this Report, under the heading of Contextual Factors, that there are numerous factors affecting the quality of MTMS including the key factor of understanding patient-specific goals of therapy. It is recommended that measurement of quality in delivering MTMS.be reviewed and more thoroughly presented in this Report.	As previously stated, we did not identify any studies that measured quality of MTM services, or specifically address whether the patient or interventionist understood the patient-specific goals of therapy. Thus, we are unable to provide any further discussion. In our opinion, this topic seems more appropriate for development as primary research or a technical brief than a systematic review. If we had required studies to meet inclusion criteria related to measurement of understanding goals of therapy, we would have not had any studies to include.

Comment #	Commentator & Affiliation	Section	Comment	Response
24	TEP Reviewer #1	General Comments	The final section of this review is utilized to comment on aspects of this Report that need to be addressed related to other methodological considerations. Methodological considerations that are the most concerning in this Report are, the criteria used to include and exclude studies, description of the medication therapy management service in studies that are both included and excluded from the evaluation, and assessment of risk of bias.	We have revised the introduction section to further elaborate on our rationale for the review's inclusion and exclusion criteria. In a systematic review, it is necessary to bound PICOTS criteria to ensure that included studies are similar enough to allow for synthesis and comparison. We have gone back and reassessed the risk of bias rating for all included studies, and have fixed some minor inconsistencies and/or errors. Overall, these fixes did not influence any of our substantive findings.
25	TEP Reviewer #1	General Comments	The inclusion criteria listed on page ES-3 pertaining to the Intervention should be consistent with standards of practice for MTMS. The inclusion criteria pertaining to the MTMS intervention should be based on evidence that the service included a comprehensive assessment, care plan, and follow-up evaluation, with a focus on the key factor of patient-specific goals of therapy, as stated on page 5 of this Report, under the heading of Contextual Factors.	Our inclusion criteria required a comprehensive medication review, evidence that the intervention offered followup and care coordination and patient directed education and counseling. Most studies did not describe interventions in enough detail to identify whether patient specific goals of therapy were a factor. Thus, if we had explicitly required this, the pool of studies included would have been markedly smaller. Thus, we considered this factor a contextual element, and captured it during study abstraction where we identified it. However, because of the different degree to which studies reported their intervention description, we were unable to do any substantive synthesis of this factor.
26	TEP Reviewer #1	General Comments	It is strongly recommended that the exclusion criteria applied to studies in this analysis be reexamined. On page ES-4 of Table A it is stated that, "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." Further noting that, "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." This is an unnecessary and invalid criteria for numerous reasons, including but not limited to, inadequacy of this OXO evaluation paradigm in the context of systems improvements in medicine, inconsistencies with the three-part measurement aims of the National Quality Strategy, and as an unrealistic study design expectation from an IRB review and approval perspective.	We respectfully disagree with the reviewer. These types of designs may provide meaningful answers to questions on patterns or associations, but we did not pose these questions. Given the questions that we did pose on effectiveness (that incidentally received a wide and thorough vetting from peers and the public), studies without comparators or with controls arms that cannot be differentiated from comparison arms cannot speak to the question of effectiveness of MTM interventions.

Comment #	Commentator & Affiliation	Section	Comment	Response
27	TEP Reviewer #1	General Comments	The implications of using an OXO evaluation paradigm in this Report are profound. The findings and conclusions of this Report are in stark contrast to other large-scale analyses of efforts to integrate comprehensive medication management in dynamic systems redesign. On page ES-14 under the title of Findings in Relation to What is Known, it is recognized that this draft Report contrasts with findings that Chisholm-Burns and colleagues reached in a systematic review of over 56,000 studies. The conclusions of this draft Report are also in contrast to the recent CMS mixed-methods evaluation conducted by colleagues at Westat and Acumen. [7] 7.) U.S. Department of Health and Human Services, Centers for Medicare & Medicaid Services. Medication Therapy Management in Chronically Ill Populations: Final Report. Contract # HHSM-500-2011-00012I/TOT0001, August, 2013.	The differences between our report and the Chisholm-Burns review stem from many parameters, not just design. We have added text to the writeup to indicate as much. As noted in the draft report, the timing of the release of the CMS report did not permit us to incorporate its findings. The final report incorporates the CMS findings and cannot be considered to be “in contrast” to it.
28	TEP Reviewer #1	General Comments	This Report, as currently written, can be expected to confuse decision-makers and stakeholders more than it will inform. The Conclusions of this Report can be interpreted by decision-makers and stakeholder that concerted national efforts to integrate comprehensive medication management in redesigned health care systems is not working, or at best is ineffective. Lessons learned from over 30 years of hard work building a rational medication use system could be abandoned by this Report. Drug-related morbidity and mortality is multifactorial. There may be as many as 10 citizens who die every hour in this country from preventable medication harms requiring concerted national efforts to build true systems around the way patients use medications. I appeal to the Report authors, AHRQ task officer(s), and AHRQ staff to accept my offer to assist in implementing the recommendations for strengthening the Report contained in this review.	We recognize the importance of this report to decision makers and stakeholders and wholeheartedly agree that improving the rationale use of medications and reducing drug morbidity and mortality is an urgent need. We have revised language throughout the report to convey that insufficient evidence is not the same of evidence of no effect. Given our findings, we suggest that more primary research is needed.
29	Peer Reviewer #2	General Comments	Overall, these authors followed and used sound methods and tools in conducting the review.	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
30	Peer Reviewer #2	General Comments	The biggest issue with this review is the inclusion criterion of interventions having to use a comprehensive medication review. Excluding medication management that addresses single medications or particular diseases definitely limits the contribution of this review. Given that targeted medication reviews are required as part of Medicare Part D MTM programs, their exclusion from this review fails to inform policy makers (E.g. CMS) about the impacts that TMRs can have on patients and their medication use.	We've added additional text in the Executive Summary and the Full Report to more explicitly define the scope of this review. Because of the broad nature of MTM interventions used in practice and in research, it was necessary to identify boundaries for the MTM intervention with respect to study inclusion and exclusion. The scope of this review only incudes outpatient MTM interventions that by design include a comprehensive medication review (CMR). We did not require interventions to include a CMR for all patient care contacts; most often the CMR was provided at the time of the first patient contact. This is consistent with Medicare Part D MTM requirements for an annual comprehensive medication review, with quarterly targeted medication reviews. While targeted medication reviews in the absence of a comprehensive medication review are certainly a reasonable type of MTM service in practice, we limited the scope of studies in this review to studies that by design included a comprehensive medication review to ensure that included studies were reasonably comparable with respect to the intervention.
31	Peer Reviewer #2	General Comments	The overwhelming finding of this review is that there exists insufficient evidence to evaluate the effects of MTM on most outcomes. The authors state this throughout the report, yet in the Conclusion have much more text about some weak findings compared to the absence of findings. As written, the key finding (I.e. insufficient evidence) at times gets lost among minor findings. The Conclusion and Executive Summary should more clearly reflect the primary finding.	The second sentence in our conclusion states "Evidence was insufficient on the effect of MTM on most outcomes." We then go on to describe the evidence for the "limited number of outcomes" for which we found evidence of effectiveness or lack of effect. We believe this frames conveys the level of uncertainty in the field. We have, in response to another reviewer, added text mapping the conclusions back to the key question and this addition may have to further emphasis the uncertainty of our findings.
32	Peer Reviewer #2	Introduction	The Introduction appropriately frames the review with a description of the context for MTM, and statement of the Key Questions used to organize the review. The analytical framework was helpful.	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
33	Peer Reviewer #2	Methods	As stated previously, the inclusion of only studies of interventions that used comprehensive medication reviews seems too narrow. While any review needs to make such decisions, the exclusion of targeted medication reviews (E.g. focused on a single medication of condition) leaves out an important component of Medicare Part D MTM programs -- namely targeted medication reviews.	See response to comment 30. Comprehensive medication reviews are a requirement of Medicare Part D programs. We did not find any Medicare Part D MTM programs that only provided targeted medication reviews so we are not missing otherwise relevant Medicare Part D interventions. We did exclude interventions with only targeted reviews on purpose because they are different from other relevant interventions.
34	Peer Reviewer #2	Methods	The literature search was rigorous and followed accepted approaches. Given the challenge of this review (E.g. different terms for MTM over time), the authors did this well.	Thank you
35	Peer Reviewer #2	Results	Overall, the Results are presented appropriately. Given the large number of outcomes addressed in the studies that were reviewed, it was necessary to have a long Results section.	Thank you
36	Peer Reviewer #2	Results	Organization of the Results by Key Question was helpful.	Thank you
37	Peer Reviewer #2	Discussion/ Conclusion	As stated previously, the Conclusion loses the main finding among description of multiple minor ones. This could be revised to more clearly state that a lack of evidence was the main result.	See response to comment 31.
38	Peer Reviewer #2	Discussion/ Conclusion	Limitations are recognized and described adequately.	Thank you
39	Peer Reviewer #2	Discussion/ Conclusion	Under Implications the authors state that future MTM programs may be less integrated than those represented in the reviewed studies. However, no support is provided for this assumption. It might be the case, but another viable future is that MTM services will be incorporated into accountable care organizations and medical home models -- even for Medicare beneficiaries. Perhaps this could be restated.	We agree with this reviewer's comment. We added text to clarify our intent regarding level of integration of MTM services with routine care, indicating that MTM services could be incorporated into ACO and PCMH models in the future.
40	Peer Reviewer #2	Discussion/ Conclusion	The call for stronger theory to guide studies of MTM services is appropriate, though no guidance is offered for promising approaches.	We believe that primary researchers need to identify appropriate causal mechanisms and hypotheses relevant to their specific investigations.

Comment #	Commentator & Affiliation	Section	Comment	Response
41	Peer Reviewer #2	Clarity and Usability	Overall, this report is well-organized, the review followed accepted approaches, and the discussion followed the results. The biggest issue is the inclusion of only studies of comprehensive MTM services. Excluding targeted medication reviews and medication management within disease state management services does limit the contribution of the review.	See prior response to comment 30 regarding exclusion of studies that only provided targeted medication reviews. The issue of excluded disease management interventions is closely related to targeted medication reviews since disease management services provided by pharmacist largely center around a targeted medication review and medication adjustment, though disease management interventions usually include additional components focused on self-monitoring, patient education, laboratory surveillance, and non-pharmacologic treatment. The evidence base for disease management interventions is very large, and systematic reviews of pharmacist-delivered disease management already exist. While we recognize that the pharmacy profession considers disease management interventions as a type of MTM service, for the purpose of this review we needed to bound the intervention definition to ensure reasonably comparable studies.
42	Peer Reviewer #3	General Comments	Overall this is a well-written report and the authors explained the difficulties encountered with the search strategy, study heterogeneity and other issues in a sufficient manner. I agree with their SOE ratings of the limited, available evidence and have some fixable suggestions to offer.	Thank you
43	Peer Reviewer #3	Introduction	No edits to suggest.	Thank you
44	Peer Reviewer #3	Methods	Data Synthesis section: Please state the software used for the meta-analysis. Based on the figures generated, it appears they used Comprehensive Meta-Analysis (CMA). In this section, they state that they performed an MA if they had 3 or more studies. Appendix G contains Figure G12, which is based on 2 studies and should be deleted since it does not meet their methods criteria.	Deleted figure G12. Added a note about the use of CMA.

Comment #	Commentator & Affiliation	Section	Comment	Response
45	Peer Reviewer #3	Methods	Strength of Evidence section: The second paragraph discusses the AHRQ and GRADE criteria which state that studies with different risk of bias ratings should not be pooled, and that reviewers can focus on the studies with the most reliable evidence. It would be helpful to have more clarification in this section for the criteria that the authors used to determine their SOE ratings. For example, were SOE ratings limited to low or medium ROB RCTs, if available, and if not, then the SOE ratings for high ROB RCTs and cohort studies were used (e.g. Table 17 – Drug therapy problems identified)?	We note in methods that we "based our grades on low or medium risk-of-bias RCTs or observational studies unless none were available."
46	Peer Reviewer #3	Results	Page 24 of the report (or page 57 of the ScholarOne PDF): First sentence has a typo – "two main element" should be "two main elements".	Corrected
47	Peer Reviewer #3	Results	The SOE tables list the Number of Subjects (Analyzed) for each outcome. I was unable to confirm or match the Number of Subjects for these studies since the Number of Subjects is not listed in Appendix E. I would recommend adding this to Table E2, perhaps under "Study Design/Number of Subjects" (or also under Tables E5-E41 with the "Study Arms/Number of Subjects in each Arm").	Added table to the Appendix with N
48	Peer Reviewer #3	Results	Table 19 lists the one cohort study as the basis for the SOE rating. The "Study Limitations" has this listed as "High", but Table 18 lists the ROB as "Medium". Table 19 should be corrected.	This rating is correct and is based on the strength of evidence/GRADE system that starts all observational studies, regardless of risk of bias, with a high rating on study limitations.
49	Peer Reviewer #3	Results	The Medication Adherence section lists different measures that were used. In this instance, it may be useful to convert the findings into "effect sizes" and run a meta-analysis based on the effect size estimates from each study.	We reconsidered the issue and continue to believe that we do not have enough numbers of similar studies to pool.
50	Peer Reviewer #3	Results	Table 25 is reported to list the results of 3 studies that used the Medication Appropriateness Index, but it only contains the results of two studies (ref 56 and 67); it appears that reference 68 is missing from Table 25 perhaps because the results are for each individual item on that questionnaire. If so, then it should be stated that those results are available in the Appendix E-?? and not repeated here.	Text revised to indicate which studies are included in each analysis

Comment #	Commentator & Affiliation	Section	Comment	Response
51	Peer Reviewer #3	Results	SF-36 Strength of Evidence Grades – the SOE table for each SF-36 domain score is missing. I acknowledge that the summary estimates are presented in Table 37, but it would be helpful to have a SOE table listing the SOE domains (ROB, consistency, directness, precision), descriptive text of the findings (e.g. no difference) and the SOE rating (low for most, and insufficient for vitality). In Appendix G, it would be helpful to have all the Meta-analysis figures from the full set of studies used in the sensitivity analysis, especially to see the general health perceptions and social functioning forest plots that showed significant results, with no heterogeneity.	We added a SOE table for SF-36 We have not added forest plots for the sensitivity analyses for SF-36 because relevant data are included in Table 39
52	Peer Reviewer #3	Results	Table 40. The use of “Time 1”, “Time 2” and “Time 3” for the Volume study should be changed to specific timepoints (e.g. baseline, 3 months, etc?). This is also present in some of the Evidence tables in Appendix E5-41. Any studies were the timepoint is listed as “Time 1” or “Time One” should be changed to an actual follow-up timepoint (e.g. Table E40 has Touchette listed as “Time One” and “Time Two”, but the same study in Table E38 has this listed as “0 to 3 months” and “3 to 6 months”).	We fixed Volume in Table 40. The same problem in Table 40 occurs for Malone but we could not find the exact data reported in any of the papers cited. We also fixed this in Appendix Tables E26-28, except for Malone due to issue described above.
53	Peer Reviewer #3	Results	Page 70-21 of the report (pages 103-104 of the PDF) reports the meta-analysis of two studies (one NRCT and one cohort, Figure G-12). This should be revised since the MA should be deleted (does not follow the stated Methods).	Deleted
54	Peer Reviewer #3	Results	Table 54 SOE table – when the findings are listed as “variable estimates” it makes it difficult for the reader to summarize the descriptive text that was presented earlier. It would be more helpful to state “all showed no significant differences” instead. This applies to other SOE tables where the Findings are listed as “variable” or “varied”. Please add a description that is more indicative of the findings (See Table 58 which might be better to state “one study showed a significant increase in visits in the intervention arm; the other study showed no significant difference”)	We have tried to provide ranges whenever possible; when ranges are not meaningful, we have added a footnote to the two tables in question.
55	Peer Reviewer #3	Results	Table 56 SOE table – is the number Analyzed “2208” as shown in Figure G13, or is it “2038” as listed in the table?	Corrected
56	Peer Reviewer #3	Results	The use of “CAD” for Canadian Dollars is an acceptable abbreviation, but perhaps “$CAN” would be better to state this currency, and likewise the report could use “$US” instead of “$”.	We elect to refer to the Canadian dollar as CAD (as the commonly used code) and for parallel reference, have replaced reference to $ with USD in the results sections

Comment #	Commentator & Affiliation	Section	Comment	Response
57	Peer Reviewer #3	Results	Page 87 of the report (or Page 120 of the PDF, line 25 or 26?). There is a close parenthesis missing – (denoted "basic" MTM, should be (denoted "basic" MTM).	thank you, corrected
58	Peer Reviewer #3	Results	Two papers related to the Touchette 2012 paper were not listed in the report. One is the methods paper which may contain information pertinent to the evidence tables, risk of bias and applicability tables; and the other contains information about recruitment metrics by site and challenges to MTM implementations that may contain information pertinent to the future research section of the Discussion. Masica AL, Touchette DR, Dolor RJ, Schumock GT, Kliethermes MA, Rodgers PT, Craft JL, Choi YK, Lux LJ, Smith SR. Evaluation of a Medication Therapy Management Program in Medicare Beneficiaries at High Risk of Adverse Drug Events: Study Methods. In Advances in Patient Safety: New Directions and Alternative Approaches. Vol.4. Technology and Medication Safety. AHRQ Publication No 08-0034-4. Rockville MD: Agency for Healthcare Research and Quality; August 2008. PMID: 21249958 Dolor RJ, Masica AL, Touchette DR, Smith SR, Schumock GT. Patient Safety–Focused Medication Therapy Management: Challenges Affecting Future Implementation. Am J Manag Care. 2012;18(7):e238-e244	Thank you. We reviewed the citations and applied the criteria for background studies to these citations. All final decisions are recorded in the Appendix.
59	Peer Reviewer #3	Appendix G	Some of the plots say "Favors" and most of them say "Favours" – please be consistent on whether you are using the US or European version of this word in the plots.	Revised
60	Peer Reviewer #3	Appendix G	Figure G1 uses "Usual Care" and the others use "Control" – please consider changing all items to the term that best describes the comparison group used for these studies.	Revised
61	Peer Reviewer #3	Appendix G	Figures G1 and G2 have the control group on the left hand side, while the rest of the figure have the control group on the right hand side. Is this due to the way that the OR's were calculated (G1-2), while the others use Differences in Means (G3-14)?	Figures G1 and G3 have been dropped
62	Peer Reviewer #3	Appendix G	Figure G3 is missing the Sample sizes in each group.	Figure 3 has been dropped

Comment #	Commentator & Affiliation	Section	Comment	Response
63	Peer Reviewer #3	Appendix G	Figure G13 has the p-value next to the plot, the others have this listed after the upper limit. Also, the footer states "Favours A" and "Favours B", so this should be revised to state "Favors MTM" and "Favors Control". The Statistics header states "Std diff in means" while the others state "Difference in means". Does that mean that a difference statistical test in CMA was used for Figure G13 (Hedges or Cohen's d)?	Revised, we used the standardized difference in means with and without the Hedges small sample correction and it made no difference
64	Peer Reviewer #3	Discussion/ Conclusion	Well-written – see comment above about challenges to MTM implementation that may be useful to add to this section.	Thank you
65	Peer Reviewer #3	Discussion/ Conclusion	To the final sentence of the Conclusion, consider adding "and adequate sample size".	We are unable to determine exactly where to make the proposed edit.
66	Peer Reviewer #3	Clarity and Usability	The report is very clear that the level of evidence for a majority of the key questions and outcomes about MTM are insufficient. Policymakers and practitioners will realize that more work needs to be done to prove the effectiveness of MTM, especially in real-world settings. It would be useful to expand the Future Research Needs by following this up with a FRN prioritization exercise with key stakeholders to determine the next set of studies that need to be done to answer these questions.	We are revising the conclusions to indicate the need for research prioritization
67	Peer Reviewer #4	General Comments	Overall, very well done report in terms of technical approach and manuscript production. Specific suggestions include:	Thank you
68	Peer Reviewer #4	General Comments	1. Improving accessibility to the reader. The full report totals nearly 400 pages. Although the executive summary (and abstract) is concisely written, would consider adding a summary graphic (rather than more tables) with the report's key findings that could be used as a "take-home slide" (i.e., if a presenter was referencing this study in a talk, what slide would they use?)	As the reviewer notes, we have two shorter products within this document, the abstract and the executive summary. We also intend to write a journal article for publication which will also present a succinct summary of findings..
69	Peer Reviewer #4	General Comments	2. Expand the discussion related to the short-term nature of the study outcomes evaluated. This is mentioned briefly, but needs further attention. MTM (much like blood pressure control) might ultimately be something that is more impactful over 4-5 years rather than a few months, and this could account for the observed lack of effect seen here.	Short-term outcomes might have value, but their value varies by condition. We found no studies that evaluated any intermediate health outcomes beyond 24 months, and most only evaluated outcomes between 3 and 12 months.
70	Peer Reviewer #4	General Comments	3. Add a section in the executive summary explaining the nuanced relationship in between "insufficient evidence" and lack of efficacy. This is crucial as the notion that "MTM doesn't work" would be inaccurate without further context...	Added text to methods section, specifically, we now say "An insufficient grade is not a statement about lack of efficacy or effectiveness, rather it is a statement about the lack of evidence on benefit, harm, or lack of effect."

Comment #	Commentator & Affiliation	Section	Comment	Response
71	Peer Reviewer #4	General Comments	4. Explain the potential for MTM interventions to be confounded by other temporal quality improvement interventions that likely would have been going on in the sites represented in the selected articles (e.g., medication adherence in disease management programs, regulatory requirements for medication reconciliation, provider incentive program, etc.). Although not MTM per se, these augmentations to pharmaceutical care to normal delivery practices could have undermined MTM's benefit.	We agree with this reviewer that secular trends in related initiatives may complicate the ability to precisely attribute the effects of MTM interventions. This is one reason we required a comparison group for study inclusion. We have added these additional examples of related initiatives to the discussion section.
72	Peer Reviewer #4	General Comments	5. Try to give the conclusion more punch/stronger direction. It is always a bit intellectually unsatisfying to read a 400-page reviews and learn that the main recommendation is for "more research." Along those lines, it seems that one potential pathway for MTM (like many other population health approaches), is targeting high-risk subgroups likely to benefit from the intervention. Based on the articles reviewed, did any common practices emerge that seemed more successful in ACO/population health models (could these articles be pooled for comparison?) Did any common risk criteria emerge in terms of who needs MTM? Even if statistical power was lacking for subgroup analysis, did MTM have a differential efficacy on general versus disease specific subgroups? Expanding the discussion in these areas would help sharpen the next research priorities.	We agree, but we were ultimately limited by the body of the evidence in terms of what we can answer. Answers to some of these questions are probably best answered by other types of designs than reviews, as noted in our conclusion
73	Peer Reviewer #5	General Comments	Yes, this is clinically meaningful. Yes, target population is defined, and the key questions are very clear, well thought out, and are excellent.	Thank you
74	Peer Reviewer #5	Introduction	Nice framing of the problem (although lines 12-13 (p 11/396) seems to link adverse drug events to inappropriate prescribing (prev sentence). While inappropriate prescribing may lead to adverse drug events, many (?most?) ADE occur in appropriate settings), and good job of giving background to MTM and what these programs are intended to do.	Rewritten in active voice to take the emphasis off the setting of the ADE.
75	Peer Reviewer #5	Methods	The inclusion and exclusion criteria are justifiable- I appreciated the comparison of this review with other reviews, and the rationale for differences in study inclusion/exclusion which accounted for some of the differences in conclusions.	Thank you
76	Peer Reviewer #5	Methods	I am comfortable with the statistical methods.	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
77	Peer Reviewer #5	Methods	The area that I am somewhat uncomfortable with is in the application of the assigning of levels of evidence, and risk of bias assessments.	Addressed in the response to comment 79
78	Peer Reviewer #5	Results	There is a tremendous amount of detail presented, characteristics of studies are described, figures tables and appendices adequate and descriptive. I am not aware of any missing studies.	Thank you
79	Peer Reviewer #5	Results	Where I had issues was in trying to understand some of the assignments of precision, risk of bias, and subsequently deeming those studies as not supporting the benefit of MTM for that outcome. Let me use the "Drug Therapy Problems Identified" outcome as an example (p 67/396). I read the RCT by Krska, to see if I could understand the objections to that study, which ultimately led to the conclusion that "evidence is insufficient to draw any conclusions about the effect of MTM..." on this outcome. I should mention that I had never read that study previously, and do not know the authors. In Table 16 (p67) it lists the Risk of Bias as High. Furthermore, in the text the study is repeatedly referred to as having a High Bias risk. After reading this paper, I did not think this study had a high risk for bias, based on my review of the grading references listed. The study was also listed as imprecise. I went to Appendix F, to try to understand why the bias was high- and in several areas (F2,p 370/396, and F3, p 385/396) it is listed as "Medium risk for bias". Thus, in the section "Risk of Bias Evaluations and Rationale", the study is a medium risk. Furthermore, the justification of medium risk seems to focus on randomization (p 385- "no details on randomization"- and yet I thought there were rather clear and specific in the paper), and another criticism "the study did not specify the expected direction of effect"- however the paper states "the study was powered to detect a 25% reduction...." which seems clear enough to me. Finally, in the narrative of this study (p 68/396) it indicates that the high risk of bias was due to a ..."failure to control for patient level clustering"- and yet this is not mentioned that I find in Appendix F. The comment in the text (p 68) regarding "failing to control for patient level clustering" was curious to me. The randomization scheme was as follows (I have truncated): 6	Thank you for your careful review of the risk of bias rating. On reflection, we agree that the problems with the Krska study (reporting of total events by intervention arm, rather than mean events for individuals) cannot be interpreted as an issue of bias (that is, deviation from the truth), because the study does not offer sufficient information to judge bias. By not giving us information on variance, we are unable to calculate precision and cannot interpret the results. We have rewritten this section and revised the rating for Krska accordingly to medium. We do not agree, however, that the study provides adequate detail on randomization for us to judge that the study is at low risk of bias. As the CONSORT statement indicates, trials need to describe the method used for random allocation sequence generation rather than simply stating that patients were randomly allocated. Krska no longer appears in table 16 to medium. We do not agree, however, that the study provides adequate detail on randomization for us to judge that the study is at low risk of bias. As the CONSORT statement indicates, trials need to describe the method used for random allocation sequence generation rather than simply stating that patients were randomly allocated. We have revised the justification for risk of bias in Appendix E to add detail for studies with different risk of bias ratings for different outcomes. Earlier Appendix F had an overall rating, and detailed evidence tables had outcome specific ratings. Now Appendix F includes all the variation in risk of bias ratings by outcome. We have also revised and added detail on the reasons for risk of bias ratings.

Comment #	Commentator & Affiliation	Section	Comment	Response
			general practices chosen, pts over 65 with 4+ medications consented to participate from each practice, patients stratified (by number of drugs, etc.), then were randomized to intervention or control. I discussed this with a seasoned statistician at our VA Center of Excellence, and she indicated that the bias, if there was any, would tend towards the null, rather than to increase the treatment effect. Regardless, she did not understand why this would render this study essentially useless due to a high bias, since she agrees that this would not introduce such a degree of bias to confound the results. Likewise, this study was rated "imprecise". As this was the only RCT in this section, I am not sure how this can be determined. Thus, I question the conclusion that evidence is insufficient to support benefit of MTM in identifying drug therapy problems. I think there is a low strength of evidence, based on a medium bias RCT with positive outcome.	
80	Peer Reviewer #5	Results	Regarding lowering LDL (p61/396), one RCT with medium risk of bias (which is defined as "a study susceptible to bias, but prob not sufficient to invalidate results") with rather large magnitude of effect. Four cohort studies are referenced (all with high risk of bias), which 3 of 4 studies showed similar results, but with lower magnitude. Thus, the evidence was deemed imprecise (due to variations in treatment effect). The overall conclusion reached is that evidence was insufficient to support benefit of MTM on LDL lowering. So, it appears that the reviewers have used 4 cohort studies with high risk of bias, to call into question the magnitude of effect of a medium risk RCT. I do not understand this logic was made- again, I would think this would be low strength of evidence to support MTM on LDL.	Based on our updated search, additional studies were included for this outcome. In addition, we rigorously reviewed all ROB studies and identified several inconsistencies and errors. These have been fixed and as a result of new studies and fixed to some ROB errors, this outcome now has a low SOE rating.
81	Peer Reviewer #5	Results	In every area where I pulled articles, I found myself confused at some of the assignments of risk of bias, or of precision, or other critiques of some of the studies. I will freely admit that I am not trained to do these systematic reviews- however, I had a hard time agreeing with some of the conclusions. It may well reflect my lack of training in these reviews, but inconsistencies such as I have outlined above would suggest to me that perhaps there is some issues with these assignments of bias.	In some instances, we did not provide adequate detail to explain our ratings and we have added detail. We have also corrected minor inconsistencies – these did not change the overall ratings or the conclusions of our review.

Comment #	Commentator & Affiliation	Section	Comment	Response
82	Peer Reviewer #5	Discussion/ Conclusion	The implications of the findings are stated clearly. Of course, the implications all rest on the conclusion that for the most part there is insufficient evidence to support MTM for most outcomes. I agree that for many of the outcomes the evidence is insufficient- but I am not certain that I have sufficient confidence in this analysis to discount MTM services as lacking sufficient evidence to support them.	As noted in the response to comment 81, we had added detail and addressed minor inconsistencies in rating.
83	Peer Reviewer #5	Discussion/ Conclusion	The recommendation for future research and more rigorous program evaluation is extremely important. I must say that I was surprised at the body of literature for MTM CER (less than impressive), and agree that many of the studies that they reviewed have serious methodological flaws such that one cannot have confidence in the results and conclusions.	Thank you
84	Peer Reviewer #5	Clarity and Usability	Yes. Regarding policy/practice decisions, I think the main conclusion would be that better program evaluation needs to be performed, if these programs are to remain integral to Medicare Part D plans.	Thank you
85	TEP Reviewer #2	General Comments	The report is clinically meaningful in a limited number of ways. This is primarily a result of the paucity and quality of available studies. It is also a result of the inclusion and exclusion criteria imposed. I am pleased that the authors expanded the range of study designs, as well as the number of clinical settings to further enhance the applicability of findings to the real-world settings. I think that this was done in part out of necessity, but also because it does indeed further enhance its generalizability. I am also quite pleased that the report includes intermediate, patient-centered, and resources utilization in its approach to characterizing the data. This too makes the data richer and more meaningful to a variety of stakeholders.	Thank you
86	TEP Reviewer #2	General Comments	Nevertheless, the strength of evidence (i.e., grade of evidence) for those studies that were statistically significant for all included studies is low or insufficient. This means that the results at present are unlikely to convince clinicians, insurers, or other stakeholders to change their clinical practice.	We agree that the evidence is not sufficient to merit a change in practice
87	TEP Reviewer #2	General Comments	The target populations and audience are quite clear. The authors openly admit their “struggle” with deciding which MTM studies to include. However, they provide a very well-thought out set of inclusion and exclusion criteria.	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
88	TEP Reviewer #2	General Comments	I especially like how the authors grounded the key questions in an analytic framework. My only minor suggestion is that to be consistent, that the resource utilization outcomes be placed into its own cell that follows the patient-centered outcomes.	We have revised the analytic framework per the reviewer's suggestion to include separate boxes to more clearly distinguish patient centered outcomes from resource utilization outcomes.
89	TEP Reviewer #2	Introduction	The introduction is well-written, has a logical flow, outlines the key questions in the context of the analytic framework, and outlines the project using the PICOTS perspective which is most beneficial and detailed.	Thank you
90	TEP Reviewer #2	Methods	I believe that the inclusion and exclusion criteria are justifiable, but further clarification can be achieved by the development of a figure or table outlining the similarities and differences between case management, disease management, and prospective/retrospective drug utilization review.It is clearly stated that the author struggled with this and it is understandable why this was the case.	We have added some text in the introduction to describe our approach to developing the inclusion and exclusion criteria in light of care management, disease management definitions, existing MTM definitions, and service level expectations. We did not encounter very much difficulty with respect to excluded drug utilization review studies, as these types of studies rarely, if ever, involve patient education or counseling. Thus, we did not address this in our revisions.
91	TEP Reviewer #2	Methods	The search strategies are explicitly stated and logical. The definitions and diagnostic criteria were also appropriate. Finally, the statistical methods are appropriate and reflect the heterogeneity of the included studies.	Thank you
92	TEP Reviewer #2	Results	The amount of detail presented in the results section is appropriate and in scope with the amount and type of study findings. The bulleted key points on pages 58, 81, and 96 summarize results concisely. The characteristics of the studies are clear and concise, as well as the key messages. One thing that would be welcome is a table of authors whom were contacted and did not respond. That is, were any studies left out or are less precise then desired because of lack of response from the author? Overall, the figures, tables and appendices are adequate and descriptive. I have not found any studies that the authors have overlooked.	Appendix C lists all excluded studies and reasons for exclusion. We do not provide names of authors who did not respond but we generally contacted first authors.

Comment #	Commentator & Affiliation	Section	Comment	Response
93	TEP Reviewer #2	Discussion/ Conclusion	The implications of the major findings are clearly stated. Likewise, the limitations of the reviewed studies are described adequately. The future research section is clear and easily translated into new research. However, there are a minimal number of concrete recommendations that can be made, given that the evidence-base is limited, as a result of a limited number of studies with a significant amount of heterogeneity in operational definitions, clinical settings, and outcomes assessed.	We thank the reviewer for recognizing the significant challenge with respect to making definitive conclusions or recommendations based on the existing evidence.
94	TEP Reviewer #2	Clarity and Usability	Overall, the report is well-structured and organized, the main points are presented clearly, and the limited number of conclusions presented can be used to inform policy and/or practice decisions.	Thank you
95	TEP Reviewer #3	General Comments	The complexity of Medication Therapy Management and the many ways that these services are offered makes this Systematic Review difficult and I congratulate the researchers on the thorough review.	Thank you
96	TEP Reviewer #3	General Comments	Key questions asked what many stakeholders would like to know, but it seems clear from the Review that these questions cannot be answered at the current time. This should be made clearer in the report. In retrospect, perhaps there are less complicated questions that could have been asked and answered by review of the literature. The main conclusion is that additional well-constructed research is necessary as the evidence compiled here was not sufficient or of low strength.	We agree that additional well-constructed research would be helpful but in our way, the largest concern is not the quality of the research but the underlying heterogeneity of the intervention that is not adequately described across studies
97	TEP Reviewer #3	General Comments	While it is helpful to know what can't be answered, it is just as important not to draw conclusions about the effects of MTM based on limited evidence.	As noted in response to comment #31, we have revised the abstract and conclusion to indicate which key questions lack conclusive evidence. We have also added a sentence to emphasize the difference between insufficient evidence and lack of effect, as noted by another reviewer earlier in this document.
98	TEP Reviewer #3	Introduction	No comment	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
99	TEP Reviewer #3	Methods	The approach taken for the systematic review is reasonable and reflects the quality of other systematic reviews performed by AHRQ. An overall concern of the methodology is whether the criteria eliminated so many studies that the resulting conclusions are not supported.	We understand the reviewer's concerns. The methodology used does require boundaries to be specified regarding patients/population, intervention and comparisons, setting and timing, and outcomes (i.e. the "PICOTS" of the review) for study inclusion and exclusion. This was challenging to do in this review because MTM is used to describe a broad array of services. The implications of overly restrictive criteria is often an evidence base that is too small to draw conclusions from. The implications of criteria that are too broad is significant heterogeneity among included studies that prevents any meaningful synthesis. In this review we attempted to strike a balance between being overly restrictive and being too broad.
100	TEP Reviewer #3	Methods	A possible flaw in the methods design was the decision to not include disease management/case management studies. The systematic review and criteria for inclusion ultimately provided a very limited number of studies. In retrospect, it may have been beneficial to include disease management studies that reflected MTM services, regardless of being termed disease management. While MTM services are a comprehensive management of the patient's medications, it could be that disease management studies focused on the outcomes of one critical medication (e.g. warfarin) or one critical disease (e.g. congestive heart failure) would be informative.	See our response on this issue in comments 40 and 99. We relied primarily on the study intervention description to determine eligibility for inclusion rather based on our MTM intervention criteria, not whether the study was termed "disease management" vs. "MTM". The evidence base for studies of disease management solely focused on one critical medication or disease is very large and heterogeneous and given the number of clinical conditions for which this approach can be used. Further, disease management interventions are typically delivered by a wider range of providers than pharmacists, and would have introduced even more heterogeneity into the types of interventions included within the same review. We identified the use of a comprehensive medication review as part of the MTM intervention as a way to identify interventions that were more likely to have reflected a comprehensive approach to medication management as opposed to interventions designed to optimize therapy for one disease or conditions. This bound on the intervention helps to ensure that included studies are reasonably comparable.

Comment #	Commentator & Affiliation	Section	Comment	Response
101	TEP Reviewer #3	Methods	The timing of this review occurred prior to the release of the Medication Therapy Management in Chronically Ill Populations: Final Report to the Centers for Medicare & Medicaid Services (CMS) by Acumen, LLC and Westat, Inc. This study focused on high-risk, high-cost beneficiary populations with congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and diabetes. The study evaluated the effects of MTM based on a comparison of outcomes between MTM enrollees and non-MTM enrollees. Their findings should be considered in the final report of a Systematic Review of Medication Therapy Management. Specific positive outcomes include: • MTM programs improved medication adherence and quality of prescribing for CHF, COPD and diabetes patients, particularly when comprehensive medication reviews (CMRs) were provided; • MTM programs initially improved the safety of drugs prescribed in new enrollees (first six months) but these positive effects had diminished or reversed by one year after enrollment; • MTM programs decreased hospital utilization and costs in diabetes and CHF patients receiving CMRs but not in COPD patients; • There was substantial variation in outcomes among Part D organizations. The best-performing Part D organizations were able to improve medication adherence and quality of prescribing while keeping health care costs (including drugs) from rising; • MTM programs appeared to improve enrollees' adherence to drug therapies for targeted chronic medical conditions, but have smaller effects on patient adherence to therapies for non-targeted conditions; and • Based on interview responses of high-performing Part D parent organizations, the profile of an effective MTM program could be identified	We have incorporated relevant findings from Marrufo in the report.

Comment #	Commentator & Affiliation	Section	Comment	Response
102	TEP Reviewer #3	Results	The report included several MTM studies that showed positive outcomes. However, when additional studies were evaluated and factors considered the conclusions were that the strength of evidence was insufficient. (pgs 29, 32, 35,) While this is not a criticism of the methodology used, it raises the question of whether the studies and research of MTM are sufficient in size and consistency to provide meaningful conclusions.	Agreed.
103	TEP Reviewer #3	Results	Key Question 1 may have provided the most useful results. That is, the MTM studies were not consistent in manner or in sufficient detail. This result is important for stakeholders to acknowledge and embrace to better identify a framework for future studies that will provide this information, decrease the risk of bias, and address other study gaps such as goals of therapy and patient engagement.	Thank you, we agree.
104	TEP Reviewer #3	Discussion/ Conclusion	The major conclusion of the Systematic Review is the MTM evidence base in the literature is insufficient to address many of the key questions and to draw definitive conclusions. Indeed, after applying the eligibility, and inclusion and exclusion criteria to titles and abstracts of all 2,228 identified citations, the review represented a small number – only 36 – studies and only 22 of these studies had a medium or low risk of bias. This appears to be more than a limitation of the evidence, but rather a main conclusion. This conclusion supports that a major recommendation resulting from the study be the development of a research framework to ensure proper study design and documentation of outcomes of MTM services and programs.	Agreed, our conclusion particularly draws attention to the need for research prioritization.
105	TEP Reviewer #3	Clarity and Usability	Perhaps the Report could further emphasize that due to the nature of MTM services, it is difficult to show a direct link of identifying and resolving drug therapy problems to outcomes or resource utilization. This is included in the Applicability of the Findings section, last paragraph E-16. It isn't clear to me whether this paragraph on page ES-16 leads to the second paragraph on page ES-17. If that is the case, perhaps the link could be made clearer.	We edited the implication section to include a reference back to the previous section.

Comment #	Commentator & Affiliation	Section	Comment	Response
106	TEP Reviewer #3	Clarity and Usability	The Conclusions of the Review support suggestions for practice and policy. However, it could be more clearly stated that given the limitations of the evidence, future studies are needed AND that appropriate funding be allocated to such research efforts. Specifically that funding is needed to support randomized controlled trials. This is particularly important to include in the conclusions of the Abstract and of the Executive Summary as these summaries will be read by many more people without the benefit of the more comprehensive Review. While this might be the intent of the second sentence in the Conclusion sentence of the Abstract, it isn't clear.	We are unable to call for a specific volume of funding, but do note the urgency of new research and have elaborated further on this point in the report.
107	TEP Reviewer #3	Clarity and Usability	Much of this Review is very technical in nature. The authors could add additional clarity around how the risk of bias is assessed and how evidence rated as "low-strength" can still be used to draw conclusions.	We have expanded our discussion of risk of bias ratings. The decision regarding the use of findings of low strength of evidence is one that we elect to defer to guideline panels because they use extra-evidentiary criteria such as preferences and values, and judgment on the balance of benefits and harms.

Comment #	Commentator & Affiliation	Section	Comment	Response
108	TEP Reviewer #4	General Comments	This AHRQ systematic review will exert a significant impact in the health care marketplace and will contribute to numerous studies and reports focused on the role of medication therapy management in the health care system. The researchers are to be commended for positioning the research questions to consider medication therapy management in a broad context. However, while the key questions and inclusion criteria were intended to focus on the broad nature of MTM outside of Medicare Part D MTM programs, the draft manuscript still refers extensively to Medicare Part D MTM program requirements and components and seems that studies included specifically were "Medicare Part D Like" programs in the ambulatory environment and not aligned with the pharmacy profession's consensus definition of MTM which may more accurately reflect the true nature of MTM services in the current health care environment. The exclusion of in-patient MTM services and the rationale for the exclusion of these studies seem inconsistent to services being currently provided to improve the care of patients, reduce medication-related outcomes and improve care and outcomes for patients. Additionally, the comparative analysis of the report and findings of the Chisholm-Burns and the justification of the rationale for the differences may not be completely justified within the context of the current manuscript.	See our response to comments 6 and 30. We have changed the title of the review to more accurately reflect our focus on outpatient-MTM services. In addition we have added additional text in the background to describe the various MTM definitions and criteria and additional text describing the bounds we had to place on intervention criteria in order to be able to have studies that were reasonably comparable.
109	TEP Reviewer #4	Introduction	Structured Abstract (beginning on p. vi) Abstract Results: Results indicate that services must be appropriately targeted, but not sure that enough context is provided for a complete understanding.	We added context to the description of the intervention.
110	TEP Reviewer #4	Introduction	Structured Abstract (beginning on p. vi) Abstract Results: • MTM programs with access to clinical summaries from the electronic records may be confusing, in that the settings, locations and access to electronic health records within the studies was variable. It makes sense that having more relevant clinical information would lead to better/more appropriate clinical decision making.	Revised to indicate that this result was from a single study.

Comment #	Commentator & Affiliation	Section	Comment	Response
111	TEP Reviewer #4	Introduction	Structured Abstract (beginning on p. vi) Abstract Results: • Findings that MTM conferred no benefit in the abstract may lead individuals to inappropriate conclusions about the full nature and context of the report	We have added a sentence to indicate that the primary finding is insufficient evidence, with a limited number of findings of benefit or no benefit.
112	TEP Reviewer #4	Introduction	Structured Abstract (beginning on p. vi) Abstract Limitations: • Recommend to consider incorporating some of the key limitations discussed in the paper into the structured abstract.	We are unable to add sections to the structured abstract, but the conclusion now frames the bounds around the intervention.
113	TEP Reviewer #4	Introduction	Structured Abstract (beginning on p. vi) Abstract Conclusions: • The second sentence (vi line 52) of the conclusion is not clear • Information in the conclusion should be included on the need for additional research and the need for consensus guidelines on a framework describing interventions for MTM	Conclusion is revised, as noted in comment #1
114	TEP Reviewer #4	Introduction	Page 1, line 42 (and Background ES-1) suggest further clarification of this sentence that mixes aspects of the pharmacy profession's consensus MTM definition and MTM core elements service model. The broad MTM consensus definition was developed in 2004 by 11 national pharmacy organizations defining medication therapy management as a distinct service or group of services that optimize therapeutic outcomes for individual patients. This broad definition also delineates a range of professional activities that can be included in an MTM service according to the patient's individual needs. In 2005 and subsequently in 2008 (version 2), a service model for medication therapy management was released that established 5 core elements of an MTM service. • Bluml BM. Definition of medication therapy management: development of profession-wide consensus. J Am Pharm Assoc (2003). 2005 Sep-Oct;45(5):566-72. PMID: 16295641. • Medication therapy management in pharmacy practice: Core elements of an MTM Service Model. J Am Pharm Assoc (2003) 2008;48:341-353. doi:10.1331/JAPhA.2008.08514.	We have revised this section per the reviewer's suggestion.

Comment #	Commentator & Affiliation	Section	Comment	Response
115	TEP Reviewer #4	Introduction	Page 3, bulleted list beginning at line 3. • Patient follow-up and monitoring is an important component of medication therapy management and should be included	We have revised this section to more closely reflect the various MTM definitions, including follow-up and monitoring
116	TEP Reviewer #4	Introduction	Page 3, bulleted list beginning at line 3. • Clarification in bullet 2 should be given between the Medication Action Plan developed and provided to the patient and the professional treatment plan developed in conjunction with the patient's other health care providers	We have revised this section to more closely reflect the various MTM definitions, including the medication action plan.
117	TEP Reviewer #4	Introduction	• Page 3 elimination of disease management, case management and self-management that have MTM components and are consistent with the MTM definition is problematic in that many of these programs include	See response to comments 6 30, 41, and 100 related to the scope and bounds of the review. We recognize that the pharmacy profession includes disease management interventions under its broad MTM definition. If study included a disease management, case management or self-management intervention with an MTM component, we would have included it if a adequate comparator (i.e., disease management without MTM, case management without MTM) was available. We did not identify any such studies.
118	TEP Reviewer #4	Introduction	• Page 7 beginning line 40 minimum 4 elements characterizing MTM services – question requirement of including patient directed medication management action plan which seems very specific to Medicare Part D MTM programs, but may not be part of other MTM programs. If this is excluded potentially could have included other studies that did not include this component	We concur that the requirement to have a patient directed medication action plan as part of intervention criteria may have been overly restrictive. We relooked at studies that we excluded and none were excluded simply for not having a medication action plan.
119	TEP Reviewer #4	Introduction	• Page 8, Table 1, second bullet beginning on line 8 no included interventions: o Medication reconciliation services often involve follow-up and if conducted using a comprehensive medication review as per guidelines in practice should be considered for inclusion.	See response to comments 6 and 30 on the scope of the review. Most studies of medication reconciliation that were identified by our search took place as one time interventions and in inpatient settings, both of which were outside the scope of this review. We recognize that medication reconciliation is an important component of outpatient-based, comprehensive MTM, and if a medication reconciliation intervention met our review's intervention criteria, it was included.

Comment #	Commentator & Affiliation	Section	Comment	Response
120	TEP Reviewer #4	Introduction	• Page 8, Table 1, second bullet beginning on line 8 no included interventions: o Disease management or care management interventions are excluded, however a case can be made that if medication management is included in these interventions and a comprehensive review of the medications is included that these should not be excluded.	See prior response to comments 40 and 99.
121	TEP Reviewer #4	Introduction	Page 10 line 9 – exclusion of MTM services that are provided mostly in the in-patient setting – This exclusion may be problematic. MTM is not strictly limited to the outpatient environment. The MTM services that are provided in the inpatient setting while not fitting into the context of the Medicare Part D definition of MTM are an essential aspect of the complete medication management in patients and are consistent with the services defined in the profession's consensus definition. These services as part of the continuum of care of the patient are essential in improving treatment effectiveness, preventing and/or resolving medication-related problems and improving the quality of care and treatment outcomes achieved by patients.	See prior response to comments 6 and 30.
122	TEP Reviewer #4	Methods	Refer to coments within introduction section regarding inclusion/exclusion. Specific studies that may have added value to the review and were excluded.	Noted and these comments have been addressed inthe responses to comments 115 and 117 through 121.
123	TEP Reviewer #4	Results	Findings in relation to what is already known (page 95 beginning on line 22 and ES-14 -15) question the nature of the comparison the current analysis to Chisholm-Burns. Any aspect of pharmacist provided medication therapy management regardless of whether part of a disease state management program or prospective/retrospective analysis is relevant and pertinent. The current analysis excluding these types of interventions and the institutional based MTM programs.	Agreed, we are evaluating a narrower subset of MTM interventions than the reviewer describes, as noted earlier.

Comment #	Commentator & Affiliation	Section	Comment	Response
124	TEP Reviewer #4	Results	Applicability of findings (page 96 beginning on line 16 and ES-15) Researchers seem to be trying to conform the CMS definition of MTM programs as defining the scope and nature of MTM being provided in clinical practice. While the authors state that the nature of the review was broader than Medicare Part D MTM, as a reviewer I got the sense that Medicare Part D was still the comparator to the types of programs and interventions that were ultimately included in the review.	See prior response to comment 30. The original topic nomination for this review was specifically related to Medicare Part D MTM programs. During the course of topic refinement (a phase in which we scope the topic and seek input from key informants and the public), the scope was expanded beyond Medicare Part D MTM programs, but in order to ensure reasonably comparable studies, the scope was limited to outpatient MTM programs with features that indicate a comprehensive approach (e.g., comprehensive medication review) and some aspect of patient education, care coordination, and follow-up. We have revised the background section to better reflect the rationale for intervention criteria that we used in this review.
125	TEP Reviewer #4	Results	Implications for Clinical Practice and Policymakers (page 97 beginning line 35 and ES17) • Statement that MTM is now shaped in the US by Medicare Part D policy infers again that the program design and review is based on “Medicare Part D Like” MTM programs and leads the reader to this conclusion whether or not this is the intent of the research.	We have revised text in both the introduction and discussion section to better reflect a broader view of outpatient-based MTM. However, we stand by our statement that the structure and content of outpatient MTM programs are now largely shaped by Medicare Part D policy.
126	TEP Reviewer #4	Discussion/ Conclusion	The second sentence (vi line 52) of the conclusion is not clear	Revised as noted in comment#1
127	TEP Reviewer #4	Discussion/ Conclusion	Information in the conclusion should be included on the need for additional research and the need for consensus guidelines on a framework describing interventions for MTM	Revised as noted in comment#1

Comment #	Commentator & Affiliation	Section	Comment	Response
128	TEP Reviewer #4	Clarity and Usability	While comprehensive in nature the findings presented in the report are not readily apparent to the reader. The limited number of studies included and the charachteristics of the programs being “Medicare Part D like” MTM programs may lead the reader to conclusions about MTM that may not be completely appropriate. In addition due to the diverse nature of medication management in the health care environment the strict exclusion criteria that eliminated all in-patient studies of programs that may have significant impact on patient care, but do not meet all of the researchers criteria for the description of an MTM program may be truly problematic. The contradicting evidence previously published by Chisholm-Burns and others and the nature as to the comparison of the research to this review may be confusing to those in the policy making arena.	We have revised the title and the abstract so the bounds around our use of MTM are clear to the reader. Chisholm-Burns and others placed different bounds around the intervention and obtained appropriately different results.

MTM Public Comments

Comment #	Commentator & Affiliation	Section	Comment	Response
129	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	The National Association of Chain Drug Stores (NACDS) appreciates the opportunity to comment on the draft systematic review on Medication Therapy Management (MTM) prepared for the Agency for Healthcare Research and Quality (AHRQ). NACDS represents traditional drug stores, supermarkets, and mass merchants with pharmacies – from regional chains with four stores to national companies. Chains operate more than 41,000 pharmacies and employ more than 3.8 million employees, including 132,000 pharmacists. They fill over 2.7 billion prescriptions annually, which is more than 72 percent of annual prescriptions in the United States. The total economic impact of all retail stores with pharmacies transcends their over $1 trillion in annual sales. Every $1 spent in these stores creates a ripple effect of $1.81 in other industries, for a total economic impact of $1.81 trillion, equal to 12 percent of GDP.1 1 For more information about NACDS, visit www.NACDS.org.	So noted
130	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	BACKGROUND: The impetus for the draft systematic literature review came about as a result of discussions between a diverse coalition of stakeholders, led by the Pharmacy Quality Alliance, and AHRQ regarding the potential for the federal government to fund Medication Therapy Management (MTM) research. Specifically, the parties discussed the potential for conducting prospective research studies under section 3503 of the Patient Protection and Affordable Care Act ("ACA"). This section authorizes the Secretary to establish a program to provide grants or contracts to eligible entities to implement Medication Therapy Management (MTM) services provided by pharmacists, as a collaborative, multidisciplinary, interprofessional approach to the treatment of chronic diseases for targeted individuals. While the federal government failed to provide funding for Section 3503, there are a number of MTM studies currently underway through the Centers for Medicare and Medicaid Innovation, among others, designed to quantify the impact of MTM on patient health and medical spend in Medicare programs and other forums. It is our expectation that these ongoing studies will buttress the findings of the CMS August 2013 report as will be discussed below.	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
131	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	DISCUSSION: In the two years since this systematic review was selected by AHRQ, many new and innovative MTM models have emerged in both the public and commercial channels. Today, MTM services are being increasingly embedded in emerging healthcare models, such as Medical Homes and Accountable Care Organizations (ACOs), with ongoing prospective well-controlled studies to validate the impact of MTM in these innovative care settings. A December 2013 report from America's Health Insurance Plans (AHIP), for example, highlighted sixteen health insurance-based MTM programs that have been incorporated into medical homes, ACOs, and transitions of care programs, and other settings; case studies reported positive results achieved from these programs, and proclaimed: "MTM is an increasingly important part of strategies to achieve these initiatives' goals of boosting health care quality, improving patients' experiences with care, and lowering costs."2 2 AHIP Center for Policy Research. Innovations in Medication Therapy Management. Effective Practices for Diabetes Care and Other Chronic Conditions. December 2013.	So noted
132	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	FEDERAL/STATE PROGRAMS: During the last two years, CMS has also increasingly highlighted the tremendous benefits of MTM services. In so doing, CMS has opined that because of the benefits of MTM as a means to increase the quality of health care, MTM could become a "cornerstone" of the Medicare Prescription Drug Benefit.3 In promoting this notion, CMS, in the 2014 Final Call Letter, encouraged MA and PDP sponsors to make MTM services available to beneficiaries who take a single anti-hypertensive medication as a means to help with the Million Hearts Initiative's stated goal of preventing one million heart attacks and strokes by 2017. CMS also recently proposed for its 2015 Star Ratings program a Comprehensive Medication Review (CMR) measure, a core element of an MTM service model. The rationale for this proposal is that measuring and publicly reporting CMR completion percentage should drive increased utilization of MTM services by targeted Medicare beneficiaries. 3 http://www.gpo.gov/fdsys/pkg/FR-2005-01-28/pdf/FR-2005-01-28.pdf	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
133	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	The above-mentioned CMS actions are well grounded in, and supported by the Agency's August 2013 MTM report entitled, "Medication Therapy Management in Chronically Ill Populations: Final Report" by Perlroth and colleagues.4 This report is among the largest evaluations of Medicare Part D MTM programs to date and should be included within final AHRQ MTM report. Most notably, this evidenced-based report provides that: • MTM programs improved medication adherence and quality of prescribing for CHF, COPD and diabetes patients, particularly when Comprehensive Medication Reviews were provided. • MTM programs decreased hospital utilization and costs in diabetes and CHF patients receiving Comprehensive Medication Reviews; leading to significant cost savings in per-patient hospitalization costs of $526 and $329, respectively. 4 http://innovation.cms.gov/Files/reports/MTM_Final_Report.pdf	So noted
134	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	In addition, states are increasingly turning to MTM as a cost-saving strategy for their Medicaid programs. While several preliminary studies have emerged and reported positive improvements in patient outcomes and cost savings,5,6 we anticipate this body of evidence will grow in the coming years as full evaluations are published. 5 http://www.hhsc.state.tx.us/reports/2012/rider-49-med-therapy-mgmnt.pdf 6 www.healthwellnc.com/PageCopyUploads/Documents/HWTF-CostBenefitAnalyses.pdf	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
135	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	REQUESTS: Given the above information, NACDS respectfully urges the authors to: Consider the scope, strength and credibility of the August 2013 CMS Report relative to the smaller studies it uses as evidence for the final report. Consider separately the effectiveness of MTM services demonstrated in Medicare programs separate from MTM in other populations since the systematic review includes research from international sources as well as in low-risk patient populations. Acknowledge in the final report that that there are ongoing prospective well controlled studies underway to validate the impact of MTM in emerging care models as well as in state Medicaid programs.	For outcomes for which the CMS report provides relevant evidence, we go through the strength of evidence grading process, which does consider the risk of bias of the CMS report in addition to other factors in making a judgment about overall evidence. Of the 44 studies, 10 are definitely Part D, 2 are possibly Part D but we cannot tell. This means the number of Part D for any single outcome is not large enough to conduct a meta-regression. Revised as noted as an aspect to consider in research prioritization.
136	Kathleen Jaeger, National Association of Chain Drug Stores, Public Commenter	General Comments	We support AHRQ's mission to improve the quality of healthcare, reduce costs, and enhance patient safety and access through evidenced-based information on health outcomes; and remain committed to work with AHRQ and others to explore prospective research concepts related to MTM.	So noted
137	Jan D. Hirsch, University of California San Diego, Public Commenter	General Comments	Thank you for the opportunity to comment on the DRAFT systematic review of Medication Therapy Management (MTM) literature conducted by Agency for Healthcare Research and Quality (AHRQ). Overall, based on the studies included, it appears your conclusions and call for further research areas are reasonable.	Thank you
138	Jan D. Hirsch, University of California San Diego, Public Commenter	General Comments	While I understand it was challenging to limit the scope of the review, it is disappointing that only 36 studies were included in the review based on your criteria.	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
139	Jan D. Hirsch, University of California San Diego, Public Commenter	General Comments	As an author of two of the studies not included I would like clarification re: why these studies were not included. While clarification is important for me personally, I also believe it is important for the readers of the AHRQ report. It would be very useful if specific notations were added to the report describing why the many studies were excluded. This information would be beneficial for readers wishing to learn more from studies that did not meet the specific criteria for the AHRQ review and for researchers wishing to improve upon the prior investigations. I would think AHRQ has this information in its evidence tables used during the review process – therefore the additional work would be in inserting and formatting into the report. Making the evidence tables available to the public would also be very useful.	The Appendix on excluded studies give specific reasons for exclusion for each study.
140	Jan D. Hirsch, University of California San Diego, Public Commenter	General Comments	The two studies I would like clarification from AHRQ are below. 1. The first is listed as “awaiting authors response” Hirsch JD, Gonzales M, Rosenquist A, et al. Antiretroviral therapy adherence, medication use, and health care costs during 3 years of a community pharmacy medication therapy management program for Medi-Cal beneficiaries with HIV/AIDS. J Manag Care Pharm. 2011 Apr;17(3):213-23. PMID: 21434698. I am very concerned about this study being listed in this section. I have no record of ever being contacted by AHRQ about this study. When I saw this in the report I searched my emails and see no requests from AHRQ for information. Who would have contacted me? Perhaps I am not searching for the appropriate sender. Regardless, please let me know what information you require. I do not want my study listed under this category since it implies I chose not to, or neglected to respond – which is not the case. It is also concerning to me that if I did not know I was supposed to be responding, are there other authors who AHRQ thought they contacted that were also not aware of the need to provide more information?	We are unable to determine why the reviewer did not receive our emails. We followed up and included these studies on receiving additional information.

Comment #	Commentator & Affiliation	Section	Comment	Response
141	Jan D. Hirsch, University of California San Diego, Public Commenter	General Comments	2. The second is listed as having an ineligible comparator: Hirsch JD, Rosenquist A, Best BM, et al. Evaluation of the first year of a pilot program in community pharmacy: HIV/AIDS medication therapy management for Medi-Cal beneficiaries. J Manag Care. Why was the comparator ineligible? The comparator group of patients was Usual Care provided by non-HIV/AIDS specialty pharmacies that were not participating in the MTM program. Please let me know what information you require from me as soon as possible. I am anxious to at least rectify the misclassification of my study that is listed under “awaiting author response”.	We have included both studies by this author in the Final report.
142	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments to the Agency for Healthcare Research and Quality (AHRQ) on the Draft Systematic Review: Medication Therapy Management (draft report) as published on December 3, 2013.i ASHP is the national professional organization whose 42,000 members include pharmacists, pharmacy technicians, and pharmacy students who provide patient care services in acute and ambulatory care settings, including hospitals, health systems, and clinics. For 70 years, the Society has been on the forefront of efforts to improve medication use and enhance patient safety. i. http://www.effectivehealthcare.ahrq.gov/ehc/products/516/1826/medication-therapy-managementdraft-131203.pdf	So noted
143	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	Overall, ASHP supports the methodology of dividing measured outcomes into intermediate (e.g., drug-related problems, adherence issues) and patient-centered (e.g., morbidity, mortality, quality of life). However, it is essential the final report note that the overwhelming majority of studies evaluated were not designed to measure longer term outcomes. Study timeframes averaged three to six months, with some interventions only extending for a handful of visits. Therefore, it is not surprising the major finding is that there is insufficient evidence to determine whether or not MTM has an impact on outcomes. As currently stated, the primary study conclusion could be interpreted as medication therapy management confers no benefit.	The findings of the CMS report appear to indicate that MTM has more of an effect in the short-term than in the long-term. Based on the CMS report, it is possible to argue that short-term outcomes are the ones most likely to demonstrate effect. As a separate issue, we agree and have attempted to clarify in several places that insufficient evidence does not equal evidence of no effect.

Comment #	Commentator & Affiliation	Section	Comment	Response
144	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	However, as described in the report a primary finding is that available evidence is limited or inconclusive in its ability to determine benefit as determined by the authors' schemata. As noted by the authors on page ES-15, "This body of evidence has significant clinical and methodological heterogeneity, which limits the ability to make any universal statements about effectiveness." This statement is in stark contrast to the statements on effectiveness included in the "Structured Abstract," which will be the most read and cited aspect of the report. ASHP strongly encourages the authors to reconcile this discrepancy.	As noted in response to comments 31 and 97, the second sentence in the results section in the abstract stated the insufficiency of evidence for most results for KQ 2. We have further expanded this introduction to the results in the abstract.
145	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	Further, in the conclusion on page vi, the authors state that "…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." The intent of this statement is unclear. Are the report authors recommending that future studies be structured to address limitations in the current evidence base? For example, there is a clear need to further design studies to evaluate the long-term impact of these programs. ASHP requests that the authors revise the conclusion to improve the clarity of the recommendation that is being provided.	Revised, as noted in comment#1

Comment #	Commentator & Affiliation	Section	Comment	Response
146	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	ASHP is concerned that the exclusion of programs initiated in the inpatient setting fails to recognize some of the significant improvements that have resulted from interventions at care transitions. There is significant evidence that medication-related issues frequently arise from changes in the setting of care or a loss of disease state control that necessitates hospitalization. Therefore, medication therapy management programs are increasingly being directed at this high-impact scenario. Exclusion of these programs by the study authors overlooks programs that have resulted in improved patient outcomes and reduced overall costs. The emergence of these programs supports the need for continued study of the effectiveness of medication therapy management programs. For additional information, please see ASHP-APhA Medication Management in Care Transitions Best Practices.ii Additional reports demonstrating the effectiveness of these programs are found in the published and gray literature. ii. http://media.pharmacist.com/practice/ASHP_APhA_MedicationManagementinCareTransitionsBestPracticesReport2_2013.pdf	See prior response to comments 6, 30, and 119.
147	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	On page vi, the intent of the following sentence is unclear and likely to be misinterpreted: “Similarly, we found sufficient evidence to conclude that MTM conferred no benefit for a limited number of outcomes.” As written this implies that the results of comparator groups demonstrated no improvement, yet a review of the program evaluated indicates that improvement was demonstrated by groups receiving MTM.	We wrote what we meant, that for a limited number of outcomes, MTM confers no benefit. Indeed, for those outcomes, studies did not record any significant improvement in the MTM arm over and above the control arm.
148	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	On page vi, fourth paragraph under “Results,” ASHP requests clarification of the term “brief clinical summaries,” which is used to describe the information available to pharmacists to support the medication therapy programs that are the subject of this evaluation. On page ES-13, the authors note that only one study provided pharmacist access to patient records. This fact should be highlighted given that all medical interventions, regardless of health care provider, are best implemented when the health care provider has access to complete and accurate patient information.	We have revised the abstract to indicate that this intervention describes a single study. Further details are available in the executive summary. We want to clarify that only a single study evaluated pharmacist access to patient records. Many studies likely included some level of access to patient records but all did not describe the level of access in detail, but did not evaluate the effect of that specific element of the intervention.

Comment #	Commentator & Affiliation	Section	Comment	Response
149	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	On page ES-5, under "Timing," the authors note that outcomes measured at the first intervention were not considered if two or more interventions (i.e., episodes of care) were provided. While this approach is consistent with achievement of long-term outcomes, it overlooks the value of intermediate outcomes such as prevention or treatment of adverse drug events and non-adherence that are identified and corrected at the first intervention. These interventions represent significant improvements in patient care and cost avoidance.	See response comment 6.
150	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	As noted previously, ASHP is concerned that the study excluded interventions initiated in the inpatient setting, as described under "Settings" on page ES-5. The Society respectfully requests that the authors provide a rationale for excluding medication management programs in the inpatient setting. Table A on pages ES-3 to ES-6 does not clearly state which criteria are inclusion criteria and which are criteria for exclusion. The table seems more of a list of what was considered when assessing each of the studies for inclusion, but does not provide specific and detailed requirements.	See prior response to comments 6, 30, and 119. We have revised Table A to better reflect the inclusion and exclusion criteria.
151	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	On page ES-7, under "Data Synthesis," the authors describe using a process of meta-analysis to evaluate the results of three or more "similar" studies. However, among key findings for KQ 1 and elsewhere in the report the authors acknowledge significant variability in the structure of medication therapy management programs. ASHP requests additional information regarding the criteria for determining similarity of programs. For example, ASHP recommends that the disease state addressed should be a primary characteristic for determining similarity. The finding (low strength of evidence) that the rate of hospitalizations among heart failure patients decreased compared to usual care illustrates the importance of this stratified approach.	All studies include at least the core components of interventions required for inclusion. Beyond that, all studies have significant differences in intervention implementation. Notably, our meta-analyses did not find statistical heterogeneity despite the heterogeneity of interventions. Lastly, we rely on both a qualitative and a quantitative assessment of the evidence – because we are aware of the underlying heterogeneity of interventions, we do not rely solely on meta-analyses results

Comment #	Commentator & Affiliation	Section	Comment	Response
152	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	Further, anecdotal reports and limited evidence indicate that focusing on specific high-risk patients or disease states may demonstrate the most benefit. To further elicit these factors, the ASHP Research and Education Foundation recently awarded a grant to Almut G. Winterstein, Ph.D., Professor, Department of Pharmaceutical Outcomes and Policy in the University of Florida (UF) College of Pharmacy to develop a medication complexity index. The tool, which will be available in 2015, will prospectively identify patients at greatest need for pharmacist provided drug therapy management. ASHP highly encourages AHRQ to schedule a re-evaluation of the impact of medication therapy management following completion and implementation of this project.	So noted
153	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	Pages ES-14 to ES-15 compare this analysis to earlier work completed by Chisholm-Burns and colleagues. The authors appropriately acknowledge the key differences in these studies, including the inclusion of studies in which pharmacists provided direct patient care services that expand beyond medication therapy management. While the authors of the Draft Report limit the studies evaluated to those focusing on MTM, the Chisholm-Burns evaluation includes studies that focus on other types of direct patient care beyond MTM. The inclusion of these studies more accurately conveys the current state of pharmacy practice.	We are not attempting a review of pharmacy practice on the whole. We have retitled our report to clarify the bounds on our work.

Comment #	Commentator & Affiliation	Section	Comment	Response
154	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	Further, the authors note that results from a yet-to-be included study by the Centers for Medicare and Medicaid Services found improved adherence and appropriateness of therapy. Key findings from this study include: 1. MTM programs improved medication adherence and quality of prescribing for CHF, COPD, and diabetes patients particularly when comprehensive medication reviews were provided; 2. MTM programs initially improved the safety of drugs prescribed in new enrollees for the first 6 months while the effects diminished by 1 year; and 3. MTM programs decreased hospital utilization and costs in diabetes and CHF patients receiving CMR but not in COPD patients. ASHP believes that the "Structured Summary" and "Executive Summary" will require significant revisions when these results are included in the final draft. iii. Medication Therapy Management in Chronically Ill Populations: Final Report (http://innovation.cms.gov/Files/reports/MTM_Final_Report.pdf)	Our revised report includes relevant findings from the CMS report.
155	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	ASHP believes the following statement on page ES-15 is an oversimplification of the intent of medication therapy management programs, specifically their impact on resource utilization: "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." Similar statements are found on page ES-21 under "Research Gaps." ASHP asserts that it is not possible, and is in fact inappropriate to predetermine the desired impact based on the number of prescribed medications. Medication therapy management is intended to be a patient-centered process geared at optimizing the drug therapy regimen for the individual patient, rather than a predetermined target that may or may not meet patient-specific needs.	We are in complete agreement with the reviewer and have clarified the specific sentence as follows. "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 because the desired impact will be based on the goal of therapy for each individual."

Comment #	Commentator & Affiliation	Section	Comment	Response
156	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	ASHP supports the finding under "Implications for Clinical Practice and Policymakers" that encourages that medication therapy management be positioned as contributor to overall improvement in processes of care. As we experience increases in team-based and integrated care, it will become increasingly important to identify and quantify the contributions of each member of a patient-care team in improving patient outcomes.	Thank you
157	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	Under "Research Gaps" on page ES-20, ASHP agrees that the effectiveness of medication therapy management provided by pharmacists would be best measured when compared to other interventions (e.g., MTM provided by other providers) as compared to usual care. However, the ability to design studies to evaluate comparative effectiveness is limited by the absence of other caregivers with similar training and expertise to provide these interventions. This is especially true as the complexity of medication therapy increases.	So noted. The agent of MTM delivery is one of many important variables in the typical multicomponent MTM intervention that is deserving of further careful evaluation.
158	Christopher J. Topoleski, American Society of Health-System Pharmacists, Public Commenter	General Comments	The Society appreciates the opportunity to comment on the Draft Report. Please contact me if you have any questions or wish to discuss our comments further.	Thank you
159	OutcomesMTM, Public Commenter	General Comments	OutcomesMTM appreciates the opportunity to comment on the draft report on Medication Therapy Management (MTM) prepared for the Agency for Healthcare Research and Quality (AHRQ). OutcomesMTM is an MTM program administrator on behalf of over 150 Medicare Part D contracts in addition to health plans in the private sector.	Thank you
160	OutcomesMTM, Public Commenter	General Comments	A conclusion was made that evidence was insufficient on the effect of MTM on most outcomes. We feel it is important to state that this does not mean that MTM is ineffective, but rather there is an insufficient evidence base to evaluate whether MTM is effective. Thus, more studies are needed.	Revised for clarity as suggested to focus on insufficiency of evidence.

Comment #	Commentator & Affiliation	Section	Comment	Response
161	OutcomesMTM, Public Commenter	General Comments	Nearly 40% of the studies included (n = 14) had methods problems (concerns about randomization failures, confounding, overall attrition) and were rated high risk of bias. Again, we feel it is important to reiterate that not only are more studies needed to be able to evaluate the effectiveness of MTM but, in particular, high quality studies are imperative.	So noted
162	OutcomesMTM, Public Commenter	General Comments	It was noted that, whether termed “pharmaceutical care” or “MTM,” studies did not describe intervention components and features in a consistent manner or in sufficient detail. It is difficult to come to a conclusion about the intervention’s effect without a standard definition of the intervention, particularly when the review included multiple interventions, all classified as “MTM”. A standard, widely-adopted definition of MTM across healthcare does not exist today. Therefore, we agree with the study authors that a systematic system for classifying the different types of direct patient care services pharmacists can provide is needed. Furthermore, specific definition of the services that are classified as MTM is critical to future research on this topic.	Thank you
163	OutcomesMTM, Public Commenter	General Comments	For each outcome, the number of studies evaluating intervention impact on an intermediate outcome was extremely low (ranging from 0 for goals of therapy and patient engagement to 10 studies evaluating medication adherence, with the number of studies available for analysis on the majority of intermediate outcomes at 1-2). (Table C) A similar observation is made for the number of studies available for analysis for each of the patient-centered outcomes (Table D) as well as the resource utilization outcomes. Combined with the difference in intervention from study to study and the low number of studies available to evaluate the study objectives, we agree with the overall conclusion that the evidence base is insufficient to draw conclusions about the effectiveness of MTM. More studies evaluating a similar intervention are needed, especially studies specific to the high risk Medicare Part D population.	So noted, thank you.

Comment #	Commentator & Affiliation	Section	Comment	Response
164	OutcomesMTM, Public Commenter	General Comments	It was noted the study approach may have been overly inclusive because it led to inclusion of studies that addressed a single disease, as long as the pharmacist reviewed all medications. Many medication therapy management interventions target a single medication or medication class, particularly adherence interventions. By reviewing only studies which included a comprehensive medication review, the generalizability of the results is significantly limited. OutcomesMTM considers the comprehensive medication review only one of many MTM intervention types.	Please see prior response on comments 30, 33, 41, 100, and 124.
165	OutcomesMTM, Public Commenter	General Comments	Lastly, the August 2013 CMS Report entitled "Medication Therapy Management in Chronically Ill Populations: Final Report" was not included in the review. We highly encourage the authors to evaluate this study for inclusion when preparing the final report.	We have included relevant results.
166	Combined Pharmacy Organization, Public Commenter	General Comments	The American Pharmacists Association (APhA), Accreditation Council for Pharmacy Education (ACPE), American Association of Colleges of Pharmacy (AACP), American Society of Consultant Pharmacists (ASCP), National Alliance of State Pharmacy Associations (NASPA), and National Community Pharmacists Association (NCPA) appreciate the opportunity to provide comments on the Agency for Health Care Research and Quality (AHRQ) draft systematic review Medication Therapy Management (MTM). As noted in the report, the impact from medication-related problems on the U.S. health care system is significant, and medication therapy management services are gaining widespread recognition as a mechanism to improve both the quality and cost of medication-related outcomes and overall health care. This AHRQ systematic review will have important implications in the marketplace, is of great importance to the pharmacy profession, and will add to the numerous studies and reports focused on the role of medication therapy management in the health care system. The insightful commentary and suggestions in the report provide important guidance for future MTM research needs.	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
167	Combined Pharmacy Organization, Public Commenter	General Comments	The comments on the draft report were informed by 22 pharmaceutical scientists and pharmacist clinicians with expertise in medication therapy management. These individuals reviewed the draft MTM report then participated in one of three 90-minute conference calls held in December. Additionally, some individuals submitted written comments to add clarifying information. From this feedback, we developed general overarching comments followed by comments on specific sections of the report. Throughout this process, we have been committed to contributing a thoughtful, detailed response on this very extensive report. We respectfully submit the following comments for consideration and offer to serve as a resource for the researchers or to clarify information provided in these comments.	So noted, thank you
168	Combined Pharmacy Organization, Public Commenter	General Comments	The complexity of medication therapy management and variability in MTM programs makes analysis of MTM effectiveness difficult. This is compounded by the lack of a standard MTM definition from which to conduct MTM research. We recognize the amount of work that was required to structure and conduct this evaluation and believe that framing the report based on the data presented and providing recommendations for future MTM research will provide significant benefit in identifying MTM elements and interventions that have the most impact on patient health and health system outcomes. We offer the following comments on the need for an MTM research framework, concerns with draft report conclusions, and challenges with MTM research funding for consideration in the development of the final report.	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
169	Combined Pharmacy Organization, Public Commenter	General Comments	The report researchers found (pages ES-15 and 95) that "the evidence base is insufficient to address the effectiveness of MTM on most outcomes." To address this, they recommend the creation of "a systematic system for classifying the different types of direct patient care services that pharmacists can provide" and "consensus guidelines for describing intervention features in publications reporting findings from evaluation studies." We wholeheartedly agree with these recommendations and urge them to be reflected in the conclusions of the report. With the inherent complexity of medication therapy management and the diversity of delivery by type of service, credential, licensure, and setting, both singularly and in combination (one expert likened this complexity to trying to conduct a systematic review of the effectiveness of primary care delivery), and the variability in terminology and approach used in published studies, it is imperative that a research framework be established and adopted that will permit more consistent and effective evaluation of published MTM research.	Conclusion revised and expanded
170	Combined Pharmacy Organization, Public Commenter	General Comments	A national MTM research framework would help to prevent broad affirmation or broad dismissal of MTM effectiveness at a higher level of granularity than is sensible (example, ruling out primary care as effective because a procedure performed by primary care has a null effect). The risk of Type II error in this report is very high (saying something doesn't work, when it does) because of the lack of research in this area resulting from: 1) a lack of a global research framework for MTM, that can parse out research by interventionist, setting of care, service and other relevant factors of success or failure and 2) a lack of funding in this area, considering the intended impact of over 3 billion prescriptions filled and $290 billion in annual costs from medication-related problems, including non-adherencei. Highlighting the need for an MTM research framework in the conclusions of the report would provide actionable guidance for those who conduct research in this important area. i 1NEHI. (2009). Thinking Outside the Pillbox: A System-wide Approach to Improving Patient Medication Adherence for Chronic Disease. Available at: www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease. Accessed January 6, 2014.	We agree that a national framework for research is a good idea, but respectfully disagree regarding the high risk of Type II error in our report. We pay close attention to a range of causal criteria before arriving at a strength of evidence grade. Issues of inconsistency, imprecision, and high study limitation are very common in the literature and lead us to a judgment of insufficient evidence, not evidence o no benefit. Drawing conclusions about the evidence of no benefit requires some confidence about consistency, directness, precision, and study quality – these instances occurred very infrequently in our analysis.

Comment #	Commentator & Affiliation	Section	Comment	Response
171	Combined Pharmacy Organization, Public Commenter	General Comments	The small number of studies meeting the criteria for qualitative (36/2,228) and quantitative (13/2,228) evaluation across a large number of MTM outcomes raises concerns about having a critical mass of data to conduct a large scale evaluation of MTM. This small number is compounded by the fact that where "sufficient" evidence was found to reach a conclusion (where MTM results in improvement compared to usual care or results in no improvement on specific outcomes), the studies were all rated low strength of evidence. Based on the strict inclusion criteria and small number of studies included, it seems premature to draw any overarching conclusions about the effectiveness of MTM in this report. It is clear that more research is needed to determine the true and focused effects of MTM before any conclusions should be reached, even on those factors where there is low strength of evidence found in studies.	So noted
172	Combined Pharmacy Organization, Public Commenter	General Comments	The draft report conclusions can be confusing or misleading to its intended audiences --- providers, clinicians, payers, and policymakers -- as the report can be interpreted that current efforts to integrate MTM services in new care delivery models and health care systems are not working or are ineffective. In fact, the conclusions of this draft report are inconsistent with findings in the August 2013 CMS report "Medication Therapy Management in Chronically Ill Populations: Final Report. Contract # HHSM-500-2011-00012I/TOT0001" conducted by Acumen and Westat. [accessed Jan 4 2014 at http://innovation.cms.gov/Files/reports/MTM_Final_Report.pdf]	We have clarified the results in the abstract and explained the difference between insufficient evidence and evidence of lack of effect in the executive summary. Our final results are not "inconsistent" with the CMS report – we incorporate their findings where relevant.
173	Combined Pharmacy Organization, Public Commenter	General Comments	We recommend that the findings and conclusions throughout the report be presented in a clear, understandable manner that is consistent with the strength of evidence.	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
174	Combined Pharmacy Organization, Public Commenter	General Comments	The lack of funding for large scale randomized controlled trials (RCT) evaluating the effectiveness of medication therapy management has been a longstanding challenge and is reflected by the absence of large RCTs in this systematic review. Section 3503 of the Affordable Care Act, Medication Management Services in the Treatment of Chronic Disease (currently unfunded), called for grants or contracts to eligible entities to provide medication therapy management services. An evaluation of many of the components identified by the authors of this draft report was a requirement of the grants, and if Section 3503 is funded, the grants are to be administered by AHRQ. The Center for Medicare and Medicaid Innovation (CMMI) has funded a number of important projects that include MTM, yet CMMI focuses on rapid cycle innovation metrics for measuring effectiveness that are not likely to meet the criteria required in an AHRQ systematic review. While not explicitly noted by the report authors, sufficient research funding is a high priority need for achieving the rigor of study design desired for assessing evidence of MTM effectiveness and to meet "the urgent need for actionable information" identified by the study authors in the conclusion.	We are unable to make recommendations about volume of funding needed to accomplish necessary next steps in MTM research, but have called attention to the urgent need for new research
175	Combined Pharmacy Organization, Public Commenter	Structured Abstract	If included in the final report, the structured abstract will likely be an often-read component and will serve an extremely important role. We respectfully offer the following comments/suggestions on the structured abstract:	Thank you

Comment #	Commentator & Affiliation	Section	Comment	Response
176	Combined Pharmacy Organization, Public Commenter	Structured Abstract	Results: as stated above under "Concerns with Draft Report Conclusions," the findings for MTM improvement (medication appropriateness, rate of hospitalizations among heart failure patients, and use of generic medications for patients receiving MTM from community pharmacy) or no improvement (reduction of hospitalizations in a broad range of patients and most measures of quality of life) are based on studies with low strength of evidence. Likewise the findings on four MTM intervention components and intervention features were also based on studies with low strength or insufficient evidence. As worded in the structured abstract and on pages ES 11-14 in the executive summary and pages 92-95, 102 in the full report, the findings could be misinterpreted to be definitive findings for MTM services, especially by individuals who do not have research backgrounds and may not understand the relevance of "low strength of evidence" to making definitive conclusions. We respectfully ask for additional clarification of the results presented in the structured abstract and the report (both executive summary and full report) so that they are not subject to misinterpretation.	Revised
177	Combined Pharmacy Organization, Public Commenter	Structured Abstract	Limitations: Consider incorporating some of the key limitations discussed in the paper into the structured abstract to provide context for the complexity of performing a systematic evaluation of medication therapy management.	We are unable to add sections to the structured abstract, but the conclusion now frames the bounds around the intervention.
178	Combined Pharmacy Organization, Public Commenter	Structured Abstract	Conclusions: The second sentence of the conclusion is not clear to many of the experts who reviewed the document, and there was a strong feeling that this sentence does not reflect the data in the report. Consideration should be given to incorporating into the conclusions the message that with the extent of insufficient evidence to address the effectiveness of MTM, more research that meets the rigor required of a systematic review is needed, along with resources to support that research. Likewise as stated above, calling for a national MTM research framework in the conclusions that includes consensus guidelines for describing intervention features in publications reporting findings from MTM evaluation studies would be an important actionable guidance for MTM researchers and potential research funders. (Also stated on pages ES-20, ES-21, and 101).	Revised

Comment #	Commentator & Affiliation	Section	Comment	Response
179	Combined Pharmacy Organization, Public Commenter	Introduction	Page 1, 4th paragraph, last sentence (and page ES-1). We request further clarification of this sentence that mixes aspects of the pharmacy profession's consensus MTM definition and MTM core elements service model. The broad MTM consensus definition was developed in 2004 by 11 national pharmacy organizations defining medication therapy management as a distinct service or group of services that optimize therapeutic outcomes for individual patients. ii This broad definition also delineates a range of professional activities that can be included in an MTM service according to the patient's individual needs. In 2005 and subsequently in 2008 (version 2), a service model for medication therapy management was released that established five core elements of an MTM service. iii This service model was developed by the American Pharmacists Association and National Association of Chain Drug Stores with input from an expert advisory panel and is supported by eight national pharmacy organizations. The service model is intended to be a foundational model to provide structure to MTM programs. Both of these documents plus more recent resources such as the medication management resource developed by the Patient-Centered Primary Care Collaborative are resources often used in practice in the delivery of medication therapy management. Iv ii Bluml BM. Definition of medication therapy management: development of professionwide consensus. J Am Pharm Assoc (2003). 2005 Sep-Oct;45(5):566-72. iii American Pharmacists Association; National Association of Chain Drug Stores Foundation. Medication Therapy Management inPharmacy Practice: Core Elements of an MTM Service Model. Version 2.0. March 2008. Available at: www.pharmacist.com/sites/default/files/files/core_elements_of_an_mtm_practice.pdf. Accessed January 6, 2014. iv T. McInnis, E. Webb, and L. Strand. The Patient-Centered Medical Home: Integrating Comprehensive Medication Management to Optimize Patient Outcomes, Patient-Centered Primary Care Collaborative, June 2012. Available at: www.pcpcc.org/sites/default/files/media/medmanagement.pdf. Accessed January 6, 2014.	See response to comment 20. We have added and clarified the introduction section with respect to the MTM definitions.

Comment #	Commentator & Affiliation	Section	Comment	Response
180	Combined Pharmacy Organization, Public Commenter	Introduction	Page 3, bulleted list at the top of the page with proposed features of MTM services. A multiple episode approach to medication therapy management that includes follow-up medication management and monitoring is an important component of medication therapy management is not currently reflected on the list but should be included.	A multiple-episode approach is reflected in our specifications regarding the "timing" of intervention. We excluded studies that did not include a multiple-episode approach by design, although we did not require studies to show evidence that all patients actually received more than one episode of care.
181	Combined Pharmacy Organization, Public Commenter	Introduction	Page 3, bulleted list at the top of the page. Bullet 2 lists a medication action or treatment plan developed in collaboration with the patient. Further clarification of this bullet is necessary. There are two different types of plans developed as part of an MTM service. The pharmacist develops a treatment plan or a care plan as the result of a medication therapy review. This plan will often require input from prescribers to ensure that goals of therapy are aligned. In addition, to assist patients in engaging in self-management of their medications, a patient-centered medication action plan is recommended as a core element of an MTM service. This medication action plan is developed in collaboration with the patient and prescriber if necessary and provides patients with useful actions for enhancing their medication use. It's unclear if this bullet is referring to the pharmacist's care plan or the patient's medication action plan or both. It's important to note that the patient's medication action plan is still in the adoption phase for medication therapy management services, and was just required in the Medicare Part D MTM sector in January 2013.	We have dropped the explicit requirement for an action plan in the revised report
182	Combined Pharmacy Organization, Public Commenter	Introduction	Page 7 (and page ES-3), minimum four elements characterizing MTM services. While the patient-directed medication action plan has the potential to enhance patient engagement in medication self-management and is now a required component of the Part D MTM program (as of January 2013), we question its inclusion as a minimum MTM service element for this systematic evaluation of MTM. With the medication action plan still in the adoption phase, it is unlikely to be reflected in many studies, if any, and therefore, we recommend removing it from the required interventions.	See prior response to comments 116 and 118.

Comment #	Commentator & Affiliation	Section	Comment	Response
183	Combined Pharmacy Organization, Public Commenter	Introduction	Page 8, Table 1, second bullet on excluded interventions, 2nd sub-bullet. Integrated pharmacy services in inpatient settings were excluded from the analysis. Further clarification from the report researchers on how "inpatient" was defined would be helpful. For example, if the setting is described as a "health system," the services may be delivered through the health-system's ambulatory clinic and if they meet the criteria, should be included in the evaluation.	In this review, "inpatient" refers to acute care settings. MTM interventions delivered through ambulatory clinics of health systems were included.
184	Combined Pharmacy Organization, Public Commenter	Introduction	Page 8, Table 1, second bullet on excluded interventions, 4th and 5th sub-bullets. Disease management or care management interventions are excluded. However, if those services are delivered by a pharmacist, they are likely to include a medication therapy management approach. As an example, Kaiser Permanente coined the term "care management" for the medication-related services their pharmacists provide. We encourage the report researchers to search using the terms pharmacist and "x" disease management or care management and field test some of the results to see if these studies should be considered for inclusion in the analysis. If this approach has been used by the researchers, it is not clear in the report.	See prior response to comments 30, 41, and 100. "care management" is a generic terms used across multiple disciplines and is not unique to the pharmacy profession. If a study described as "care management" included a minimum of the three elements we defined for MTM intervention inclusion in this review, we included the study regardless of whatever terms were used to describe it.
185	Combined Pharmacy Organization, Public Commenter	Introduction	Page 8, Table 1, second bullet on excluded interventions. Recommend moving the second bullet on the types of interventions not considered MTM interventions to the bottom of the Interventions area of the table. This would provide better clarity to the table and avoid confusion as to what interventions are excluded or not.	We have revised both Table A and Table 1 to better clarify inclusion and exclusion criteria.
186	Combined Pharmacy Organization, Public Commenter	Introduction	Page 10 and 14, Setting: It's unclear whether studies examining medication therapy management services delivered in managed care or integrated health care systems are included or excluded in the evaluation. Study #6 (Borgsdorf LR) conducted in a managed care system and #9 (Ramalho de Oliveira D) conducted in a large integrated health care system are excluded for ineligible population but no further detail is provided including whether the setting impacted the exclusion. If not currently included, we recommend that these settings be included in the analysis as they are important areas where medication therapy management is delivered.	MTM interventions in managed care or integrated health care systems were included. The Borgsdorf study was excluded because the study population included patients younger than 18. The draft report mistakenly listed the Ramalho de Oliveira study as excluded due to ineligible study population. In fact, this study was excluded due to ineligible study design. However, we did identify a companion study to the Ramalho de Oliveira study in our updated search and this study was included.

Comment #	Commentator & Affiliation	Section	Comment	Response
187	Combined Pharmacy Organization, Public Commenter	Methods	Observational studies – in general, further detail on how observational studies were handled in this systematic review would be helpful. For example, were observational studies used to address gaps not met by randomized controlled trials and if yes, what were the gaps identified? In the AHRQ guidance document on observational studies, (Norris S, Atkins D, Bruening W, et al. Selecting observational studies for comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews [posted June 2010]. Rockville, MD), it is noted that "systematic reviewers disagree about the ability of observational studies to answer questions about the benefits or intended effects of pharmacotherapeutic, device, or procedural interventions." Authors suggest that observational studies not be used to address all PICOTS but instead be used to simply fill in the gaps in existing literature. It is not clear how the observational studies were used in this systematic evaluation, and further clarification would be helpful.	We have added text to the methods to indicate that we included observational studies because we anticipated, from our topic refinement work, that a review limited to trials alone would fail to yield evidence on our wide range of prespecified benefits and harms for MTM interventions as a whole and for studies evaluating the modifying effects of specific intervention and patient characteristics on outcomes of MTM interventions.
188	Combined Pharmacy Organization, Public Commenter	Methods	Page 15, Assessment of Risk of Bias of Individual Studies – further clarification on how observational studies were handled for risk of bias is also requested. In the AHRQ document referenced in the previous bullet, guidance is provided on how to proceed with assessing bias. If RCTs "do not appear to be sufficient to answer the review questions concerning benefit, then reviewers should proceed to assess the potential risk of bias in a body of observational studies used to answer gap questions. This assessment will focus particularly on issues of the natural history of the condition under study and selection and performance bias. Potential biases that vary across individual observational studies (such as detection and attrition bias) are not considered in this global assessment of observational studies, but rather are assessed at the individual study level if observational studies are included in the CER." Further clarification on whether the researchers used an approach such as this or an alternative approach would assist in understanding the role of observational studies in the evaluation.	We added text to methods describing how we evaluated trials and observational studies.

Comment #	Commentator & Affiliation	Section	Comment	Response
189	Combined Pharmacy Organization, Public Commenter	Methods	In addition, regarding the item bank used from RTI to evaluate risk of bias in observational studies: o Item #12 (Did execution of the study vary from the intervention protocol proposed by the investigators and therefore compromise the conclusions of the study?) – how did the report researchers take into consideration that the pharmacist doesn't have authority in many of instances to actually make the intervention happen (only to make recommendations to prescriber or patient to follow up with prescriber at the next visit)? o Item #21 (Are confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?) - were the manuscripts' bias levels assigned due to the lack of clarity by the authors to describe what proportion of the time the "protocol intervention" was actually done per protocol vs. unable to determine?	We wish to clarify what we considered to be the "intervention." We evaluate fidelity to the MTM protocol as the MTM intervention is typically defined, that is, whether or not those involved in conducting the CMR, providing education, offering followup, and coordinating care, followed through on those tasks. Patient uptake of recommendations is an outcome, in our view, rather than an aspect of the intervention. In other words, we did not judge uptake of pharmacists' recommendation by the physician or the patient. We did not ask item 21. Our instrument and detailed responses for each item is available in the Appendices.
190	Combined Pharmacy Organization, Public Commenter	Results	Page 26, Anticoagulation: There are an extensive number of studies on pharmacist managed anticoagulation yet only one study is evaluated. We request that the report researchers clarify whether studies of pharmacist managed versus usual care anticoagulation clinics are included in the review and whether studies conducted in hospital ambulatory clinics were included. One study for consideration is: Hall D, Buchanan J, Helms B, et al. Health Care Expenditures and Therapeutic Outcomes of a Pharmacist-Managed Anticoagulation Service versus Usual Medical Care. Pharmacotherapy. 2011;31(7):686–94.	The Hall study was identified through our search. Our review excludes studies of anticoagulation services, as this is a very narrowly defined type of MTM service.

Comment #	Commentator & Affiliation	Section	Comment	Response
191	Combined Pharmacy Organization, Public Commenter	Results	Pages 26-33, Diabetes, Cholesterol, and Hypertension. We have the same concerns with these 3 conditions as expressed in the previous bullet on anticoagulation and request clarification on the same questions. For example, consider the following studies considered in the evaluation of hypertension and diabetes: o Carter BL, Rogers M, Daly J, Zheng S, James PA. The potency of team-based care interventions for hypertension: a meta-analysis. Arch Intern Med. 2009;169:1748 –1755. o Brummel AR , Soliman AM , Carlson AM , de Oliveira DR . Optimal diabetes care outcomes following face-to-face medication therapy management services. Popul Health Manag . 2013;16:28–34.	See prior response to comments 30 and 117 regarding the scope of the review. Although we recognize that disease management is one of the types of services that fall under the consensus definition of MTM, this review was not framed from the perspective of pharmacist-delivered disease management interventions. However, disease management interventions that included at a minimum the three elements we identified as intervention criteria would have been included. We identified the Brummel 2013 study in our updated search and it was included. The Carter 2009 study was not identified by our search, but we screened it for inclusion and it was excluded for Ineligible intervention
192	Combined Pharmacy Organization, Public Commenter	Discussion	Page 95 (and page ES-14), KQ 5 Harms of MTM Interventions: The evaluation yielded no evidence on the majority of harm types detailed in the PICOTS yet the last sentence in this section refers to “prespecified harms” and then lists all of the harms from the PICOTS chart. This struck our experts as negative in tone and marked a different approach than the summaries for the other key questions where general information was provided without a comprehensive detailing of all aspects reviewed. We ask that consideration be given to presenting this section in a similar manner to the other key question summaries.	In fact, we treat KQ 5 exactly as we have treated the other KQ. For KQ 2, we list all available findings and note that we did not find evidence on goals of therapy or patient engagement. The fact of the matter is that we found a lot more information on benefits and almost nothing on harms
193	Combined Pharmacy Organization, Public Commenter	Discussion	Page 97, Implications for Practice: We appreciate the implications raised in this section as they are of great importance within the context of the transforming health care system. The level of integration of MTM into routine health care and whether MTM services should be positioned as a contributor to improvements in processes of care, health status and costs or whether MTM interventions can be discreetly attributed are important areas that need more examination. Likewise the impact of both patient and physician engagement on the effectiveness of MTM is well-recognized within the pharmacy profession as being critical to MTM success.	So noted.

Comment #	Commentator & Affiliation	Section	Comment	Response
194	Combined Pharmacy Organization, Public Commenter	Conclusions	As stated in the general comments, the definitie statements about the effectiveness of MTM based on low strength of evidence are concerning. Absence of evidence is not the same thing as the absence of effect. We ask that the conclusions reflect the data presented in the report.	As noted in the response to comments 28 and 31, we have added a sentence detailing the difference between insufficient evidence and lack of efficacy.
195	Combined Pharmacy Organization, Public Commenter	General Comments	Thank you for the opportunity to provide comments on this important report. It is clear that more research is needed to determine the overall effectiveness of medication therapy management and specific patient populations and situations where MTM would be most beneficial. In addition, a national MTM research framework and an adequate level of funding to conduct MTM research are critical needs moving forward. We look forward to the publication of the final report and are committed to working with AHRQ and other stakeholders to address the recommendations from the final report. Please don't hesitate to contact any of the organizational staff representatives below with questions about these comments.	Thank you
196	Pete Antonopoulos, Cook County Hospital, Public Commenter	Discussion	Studies involving general patients cared by general providers (PA, NP, MD and general pharmacist) may not have a large enough effect for MTM to make a difference. However more studies must be done on select high risk- high utilization patients by higher level trained pharmacists (ie clinical pharmacist) to show a beneficial effect with MTM programs.	We have added the issue of patient risk to our call for new research with adequate sample size.
197	Khmer Health Advocates, Public Commenter	General Comments	Khmer Health Advocates is the national health organization for survivors of the Cambodian holocaust. We have continuously provided torture treatment services for survivors since 1984. Our patients are traumatized high risk with 3 or more chronic diseases including at least one serious mental health disorder. In addition, they are Limited English speaking with the majority illiterate in Khmer and English.	So noted
198	Khmer Health Advocates, Public Commenter	General Comments	We have used Medication Therapy Management as part of our clinic services for the past 5 years and pharmacists deliver MTM as part of a cross cultural team of providers. When we began the MTM program, pharmacists identified an average of 6 drug therapy problems for each of our patients. Working with Khmer speaking community health workers, they were able to alleviate 90% of the problems. Hospitalization and ER visits were reduced during this time period and scores on the Hopkins Systems Checklist were reduced by 10%. Overall, our patients were extremely satisfied with this new service and felt empowered by the process.	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
199	Khmer Health Advocates, Public Commenter	General Comments	Your study points out the difficulty in isolating the impact of a particular intervention. Clearly the whole is larger than the sum of its parts. For Khmer Health Advocates, MTM was the missing link in our service delivery model. We have gone on to include pharmacist managed medication protocols to assure that our patients are taking the right medication, at the right dose, at the right time.	Thank you for your comments. We recognize context matters but this review is also looking at effectiveness
200	Khmer Health Advocates, Public Commenter	General Comments	We recognize the importance of being able to measure the effectiveness of interventions in our community which presents multiple challenges due to the complexity of their health needs. Our work is done by cross cultural teams which mean that our outcomes cannot be discretely attributed to one member of the team. We have no doubts about the value of MTM based on our current data and feedback from our patients. Your study offers important insights into the need to collect comprehensive data but it is equally important to measure the practical aspects of MTM that offers so much for patients and service delivery models.	Thank you for your comments
201	Laura Cranston, Pharmacy Quality Alliance	General Comments	The Pharmacy Quality Alliance (PQA) appreciates the opportunity to comment on the Draft Systematic Review of Medication Therapy Management (MTM). As you may know, PQA was established with the support of former CMS Administrator, Dr. Mark McClellan shortly after the implementation of the Medicare Part D Prescription Drug benefit. PQA is a consensus-based, non-profit, multi-stakeholder organization established by a broad group of stakeholders committed to improving health care quality and patient safety through a collaborative, consensus-based process aimed at defining performance measures that focus on appropriate use of medications and pharmacy services. Organizations engaged with PQA include CMS, the FDA, as well as health plan organizations, pharmacy benefit managers, academic institutions, major pharmacy practitioner and trade groups, consumer groups, health information technology organizations, and pharmaceutical companies.	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
202	Laura Cranston, Pharmacy Quality Alliance	General Comments	Below, we provide our comments on: the small number of studies included in the review; the applicability of this systematic review to Medicare Part D MTM programs; the conclusions reached in the systematic review; and the need to support more structured research in this area in order to provide more conclusive evidence on the effect of MTM services on outcomes.	Thank you
203	Laura Cranston, Pharmacy Quality Alliance	General Comments	The broad conclusion reached in the Systematic Review is that the MTM evidence base in the literature is insufficient to address the effectiveness of MTM on most outcomes. In particular, evidence did not support benefit for most patient-centered outcomes, patient satisfaction items showed no impact from MTM programs, and MTM did not improve most measures of health related quality of life. However, when compared with usual care the outcomes demonstrated improved medication appropriateness, improved rates of hospitalization among heart failure patients, and improved use of generic medications for patients receiving MTM services from community pharmacies when compared with educational mailings.	So noted
204	Laura Cranston, Pharmacy Quality Alliance	General Comments	Also of note, there was evidence to support reduction in the mean number of adverse drug events when pharmacists had access to patient records compared with basic MTM. Importantly, evidence did not support pre-specified harms; specifically care fragmentation, patient decisional conflict, patient anxiety, increased adverse drug events, prescriber confusion, and prescriber dissatisfaction.	So noted
205	Laura Cranston, Pharmacy Quality Alliance	General Comments	The applicability of this Systematic Review based on literature review to the present MTM Program that must be offered by Medicare Part D plans is not clear. For this review, broad perspective was taken on the population and interventions evaluated; CMS Part D MTM eligibility criteria were not required. Specifically, multiple chronic conditions, multiple drugs and a minimum expenditure on prescription drugs were not required.	We have described the limitations in applicability of our report.
206	Laura Cranston, Pharmacy Quality Alliance	General Comments	Furthermore, after applying the eligibility, and inclusion and exclusion criteria to titles and abstracts of all 2,228 identified citations, the review represented a small number – only 36 – studies. Additionally, the report states that study limitations and lack of precision of the estimates of effects limited the strength of evidence considerably.	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
207	Laura Cranston, Pharmacy Quality Alliance	General Comments	Based on these conclusions, PQA feels strongly that there is a need to develop a research framework to be used by pharmacists, which would ensure proper study design and documentation of outcomes of MTM services and programs. PQA also advocates that appropriate funding be allocated to such research efforts, so that sufficient numbers of studies can be reviewed in the future, to provide more conclusive evidence on the effect of MTM services on outcomes.	Agreed regarding the need for a research framework that is theory-driven.
			There is one additional consideration. As you are aware, in August of 2013, Acumen, LLC and its partner, Westat, Inc., under contract by the Centers for Medicare & Medicaid Services (CMS) provided their final report on the impact of MTM programs in the Medicare Part D population. In particular, this study focused on high-risk, high-cost beneficiary populations with congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and diabetes. The study evaluated the effects of MTM based on a comparison of outcomes between MTM enrollees and non-MTM enrollees. Their findings included: MTM programs improved medication adherence and quality of prescribing for CHF, COPD and diabetes patients, particularly when comprehensive medication reviews (CMRs) were provided; MTM programs initially improved the safety of drugs prescribed in new enrollees (first six months) but these positive effects had diminished or reversed by one year after enrollment; MTM programs decreased hospital utilization and costs in diabetes and CHF patients receiving CMRs but not in COPD patients; There was substantial variation in outcomes among Part D organizations. The bestperforming Part D organizations were able to improve medication adherence and quality of prescribing while keeping health care costs (including drugs) from rising; 3 MTM programs appeared to improve enrollees' adherence to drug therapies for targeted chronic medical conditions, but have smaller effects on patient adherence to therapies for non-targeted conditions; and	

Comment #	Commentator & Affiliation	Section	Comment	Response
208	Laura Cranston, Pharmacy Quality Alliance	General Comments	Based on interview responses of high-performing Part D parent organizations, the profile of an effective MTM program could be identified. Taken together, these studies add valuable information to our knowledge about the usefulness and impact of MTM. It appears that providing pharmacists with access to clinical information in addition to medication lists may lead to reductions in adverse drug events. For particular chronic diseases, heart failure in particular, MTM may result in improved medication appropriateness, patient adherence to medications and decreased rates of hospitalizations. Greater intensity of MTM services may be associated with improved outcomes; considerable differences in MTM outcomes exist among different methods of implementation and sponsors of MTM Programs.	As noted previously in this document, we have included relevant findings from this report in the updated version of our results.
209	Laura Cranston, Pharmacy Quality Alliance	General Comments	Further, as Medicare Part C and D plan sponsors increasingly fashion their MTM Programs to addressing Star Ratings, we may see continued impact on those specific measures and the chronic diseases they monitor.	So noted
210	Laura Cranston, Pharmacy Quality Alliance	General Comments	Thank you for this opportunity to comment on the Draft Systematic Review of Medication Therapy Management.	Thank you for your comments
211	Edith A. Rosato, Academy of Managed Care Pharmacy, Public Commenter	General Comments	The Academy of Managed Care Pharmacy (AMCP) would like to thank the Agency for Healthcare Research and Quality (AHRQ) for the opportunity to comment on the *Draft Systematic Review: Medication Therapy Management*.	So noted
212	Edith A. Rosato, Academy of Managed Care Pharmacy, Public Commenter	General Comments	The Academy of Managed Care Pharmacy is a national professional association of pharmacists and other health care practitioners who serve society by the application of sound medication management principles and strategies to improve health care for all. The Academy's nearly 7,000 members develop and provide a diversified range of clinical, educational and business management services and strategies on behalf of the more than 200 million Americans covered by a managed care pharmacy benefit. It celebrated its 25th anniversary in 2013. For more news and information visit www.amcp.org.	So noted

Comment #	Commentator & Affiliation	Section	Comment	Response
213	Edith A. Rosato, Academy of Managed Care Pharmacy, Public Commenter	General Comments	AMCP believes that the report's conclusions are reasonable and could have a significant impact on the provision of MTM services and policy considerations. AMCP agrees with the study results that underscore the need for new research to define specific cohorts and MTM methods that produce the best outcomes. With the continued adoption and growth of electronic medical records and databases, certain health conditions and disease states having higher costs can be isolated to monitor for specific outcomes, including improvements in medication management. AMCP members have been actively engaged in developing and implementing further MTM research initiatives to estimate the true value of the interventions to patients and the health care system. According to a Robert Wood Johnson Research Foundation report, it is estimated that Medicare patients alone account for $26 billion each year in readmission costs, of which $17 billion was deemed to be avoidable if the right care was delivered.1 1. Robert Wood Johnson Research Foundation. The revolving door: a report on U.S. hospital readmissions, an analysis of Medicare data by the Dartmouth Atlas project. February 2013. Accessed Oct. 22, 2013. www.rwjf.org/content/dam/farm/reports/reports/2013/rwjf404178	Thank you
214	Edith A. Rosato, Academy of Managed Care Pharmacy, Public Commenter	General Comments	According to another study in North Carolina, there are similar findings for Medicaid patients.2 With the Centers for Medicare and Medicaid Services (CMS) identifying hospital readmissions as one of the top problems in the health care system and now penalizing hospitals with high rates of readmission for heart failure, heart attack, and pneumonia patients, improving the quality of transitions of care has become a top priority. Pharmacists are becoming more involved in medication management during care transitions and medication reconciliation. Given the above, AMCP believes that AHRQ should have reviewed studies pertaining to medication reconciliation interventions. 2. Jackson CT, Trygstad TK, DeWalt DA et al. Transitional care cut hospital readmissions for North Carolina Medicaid patients with complex chronic conditions. Health Affairs 2013; 32(8):1407-15.	See prior response to comments 6, 30, and 119. We agree with the reviewer that interventions at the time of care transitions, including medication reconciliation are important, and acknowledge that MTM services defined broadly can be an important component of such care. However, the scope of the review was on MTM provided to ambulatory patients to ensure studies includes were reasonably comparable. Including interventions designed for inpatient, transition, and outpatient settings would have introduced significant clinical heterogeneity. Further, we note that MTM CPT codes are not allowable by the same provider during the time period covered by care transition CPT codes suggesting that the services as defined by MTM CPT codes are not intended for post-acute care patients.

Comment #	Commentator & Affiliation	Section	Comment	Response
215	Edith A. Rosato, Academy of Managed Care Pharmacy, Public Commenter	General Comments	Additionally, the list of included studies has an average publication year of 2004. The first widely accepted definition of MTM was not established until July 2004,3 which makes it difficult for the majority of included studies to truly reflect the key elements that were defined. Furthermore, the Medicare Modernization Act of 2003 required that Medicare Part D plans reimburse for MTM services beginning in 2006.4 Therefore, the advent of MTM is still somewhat recent and has continued to evolve especially as it is coupled with increased clinical education and training for pharmacists to have more patient-centered care roles. 3. Bluml BM. Definition of medication therapy management: development of profession wide consensus. J Am Pharm Assoc. 2005;45:566–72. 4. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Public Law 108-173. www.gpo.gov/fdsys/pkg/PLAW-108publ173/content-detail.html	Agreed. The rapid pace of research in this field suggests the need for an update in the short-term.
216	Edith A. Rosato, Academy of Managed Care Pharmacy, Public Commenter	General Comments	MTM is constantly evolving and research has not conclusively indicated which services or interventions are most effective. Therefore, it is important for managed care organizations to continue to experiment with innovations with MTM programs. As highlighted by this Draft Report it is important that MTM services allow flexibility for health plans to evaluate the most effective interventions. Flexibility will allow for stronger and well-developed research initiatives and will hopefully highlight the need for appropriately funded Randomized Controlled Trials. Overall, AMCP believes it is truly important that a research framework be established and adopted to allow for a more effective evaluation of published MTM research which would be valuable to include in the Draft Report conclusions.	Agreed for the need for a research framework, which we believe should be theory-driven
217	Edith A. Rosato, Academy of Managed Care Pharmacy, Public Commenter	General Comments	Also attached is a copy of comments from an author who has published research in our peer-reviewed journal, the Journal of Managed Care Pharmacy (JMCP). We appreciate your consideration and review of our comments.	So noted, received independently