Evaluation of a Medication Therapy Management Program in Medicare Beneficiaries at High Risk of Adverse Drug Events: Study Methods

Andrew L. Masica, MD, MSc; Daniel R. Touchette, PharmD, MA; Rowena J. Dolor, MD, MHS; Glen T. Schumock, PharmD, MBA; Mary Ann Kliethermes, PharmD; Philip T. Rodgers, PharmD; Jennifer L. Craft, PharmD, BCPS; Young-Ku Choi, PhD; Linda J. Lux, MS; Scott R. Smith, PhD

Abstract

Little is known about the effectiveness or optimal design of medication therapy management (MTM) programs as mechanisms for improving patient safety, motivating this multicenter trial sponsored by the Agency for Healthcare Research and Quality. Six hundred subjects at high risk of adverse drug events (ADEs) will be enrolled across three study sites. The study is designed as a randomized controlled trial with three arms. The control group (Arm 1) will receive usual care and have no MTM visits. Intervention groups (Arms 2 and 3) will undergo two MTM visits with a pharmacist over 6 months. The main safety outcomes are the number of ADEs, hospital admissions, and emergency room visits at 90 and 180 days, which will be compared among all three study arms. Additional safety outcomes include measures of MTM process and delivery. This paper details the methods of this study evaluating the impact of community-based MTM on enhancing patient safety.

Introduction

Pharmacotherapy is central to the medical care of individuals over age 65, a population that consumes more than 30 percent of all prescriptions.[1] Of these patients, approximately 50 percent take five or more medications regularly, and 12 percent take at least 10 medications regularly.[2] The pervasiveness of therapeutic drug use in community-dwelling elderly has major implications for patient safety. A cohort study of Medicare enrollees in the ambulatory clinic setting demonstrated an adverse drug event (ADE) rate of 50.1 per 1,000 person-years, with 38 percent of the events categorized as severe, life threatening, or fatal.[3] Furthermore, each ADE in ambulatory patients older than 65 is estimated to cost an average of $1,300 in additional health care expenditures.[4] Key factors predisposing elderly patients to ADEs include age-related changes in physiology and drug metabolism; polypharmacy (use of five to seven medications regularly doubles the risk for an ADE; use of eight or more medications regularly triples this risk); number of comorbidities; and visits to multiple physicians.[5, 6, 7]

Addressing risk factors for ADEs in an outpatient population is challenging. Ambulatory care is largely decentralized in multiple independent practices, and as such, pharmacotherapy quality and safety initiatives implemented in hospitals or long-term care facilities often do not translate well to community health care settings. One approach to managing pharmacotherapy in the ambulatory elderly has focused on inappropriate prescribing based on the Beers list, which indicates medications thought to pose an undesirably high risk of adverse effects in geriatric populations.[8]

In isolation, identifying specific drugs to avoid is not sufficient for improving safety.[9] Failure to prescribe potentially useful medications in the elderly may be equally or even more harmful. For example, a recent study indicated that patients with diabetes who were older and had more comorbidities were less likely to receive intensification of pharmacologic therapy than were younger patients, despite similarly poor glycemic control.[10] Likewise, beta-blockers and lipid-lowering drugs are apparently underused in elderly patients with cardiovascular disease.[11, 12] Further areas of concern in pharmacotherapy for community-dwelling elderly include erroneous prescription writing, deficiencies in drug education given to patients, inadequacies of ADE detection systems, and suboptimal monitoring for medication toxicity.[13, 14]

Given these conditions, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003[15] (MMA) included a drug benefit and required that prescription drug plans and Medicare Advantage plans offering prescription drug coverage have a medication therapy management (MTM) program for those beneficiaries who meet certain risk criteria. The law describes MTM as "a program of drug therapy management that may be furnished by a pharmacist and that is designed to assure, with respect to targeted beneficiaries ... that covered part D drugs under the prescription drug plan are appropriately used to optimize therapeutic outcomes through improved medication use, and to reduce the risk of adverse events, including adverse drug interactions."[16] Pharmacies (both chains and those associated with health care systems), managed care organizations, State Medicaid programs, disease-specific clinics, and third-party insurers have all successfully employed various forms of MTM.[17, 18, 19, 20]

The core components of MTM entail patient education, improved adherence to medication, determining patterns of prescription drug use, and detection of ADEs. MTM programs are typically provided by pharmacists, although this is not mandated by the MMA. The value of this approach in the ambulatory setting has been demonstrated in several studies. One randomized controlled trial found that comprehensive chart review by a consultant pharmacist with subsequent modification of a patient's medication regimen led to 1.5 fewer medications.[21] Pharmacist-physician collaboration facilitated resolution of drug-related problems (DRPs) in a Medicaid population receiving four or more medications.[22] Utilization of an electronic prescription database and an alert system for high-risk medications, followed by pharmacist outreach, prompted physicians to adjust drug therapies to more appropriate agents.[23]

We do not have information on whether critical outcomes of patient safety, morbidity, and mortality can be influenced by MTM program participation.[24] Also, issues of MTM program design—such as visit frequency, mechanisms of patient-to-pharmacist and pharmacist-to-physician communication, and optimizing ADE prevention—require further elucidation. To begin to address these questions, it is essential to undertake a prospective multicenter study with well defined patient safety outcomes. This paper details the methods of an Agency for

Healthcare Research and Quality (AHRQ)-funded study responsive to that need. The study is being conducted as part of AHRQ's Effective Health Care program, which was established through Section 1013 of the MMA and authorized AHRQ to conduct research on the outcomes of health care items and services relevant to Medicare, Medicaid, and the State Children's Health Insurance Program.[15]

Methods

Study Overview and Specific Aims

The trial is designed as a randomized controlled study of an MTM program structured to prioritize patient safety that is being conducted at three sites. The main components of the patient safety-oriented MTM model used in this study are medication reconciliation (MR), assessment of DRPs, and resolution of identified DRPs. Two different methods of achieving these MTM components will be assessed and compared to a usual care group receiving no formal MTM in a population of elderly, community-dwelling Medicare beneficiaries at risk for DRPs. Main objectives for this study are to:

- Evaluate the effects of a DRP list generated by MTM clinicians on patient safety (measured by number of ADEs, hospitalizations, and emergency room [ER] visits).
- Determine if an MTM program with clinician access to patient-specific information improves measures of patient safety (such as fewer discrepancies in medication lists) and health care quality.
- Determine whether a structured MTM program focused on patient safety increases patient satisfaction.

Study Sites, Population, and Enrollment Criteria

Three health care systems with affiliated ambulatory clinics representing geographic and demographic diversity will participate in the trial. The University of Illinois at Chicago (UIC) is the study's coordinating center. The majority of patients seen at UIC clinics are African American (65 percent) and Hispanic (24 percent); 10 percent are Caucasian. Baylor Health Care System (BHCS) in Dallas, TX, is enrolling patients through its senior health center. A recent sample of senior health center demographics indicated a population that was 50 percent Caucasian, 35 percent African American, 14 percent Hispanic, and 1 percent Asian. Duke University Medical Center (DUMC) in Durham, NC, is enrolling patients through its primary care network, a practice population that is 54 percent Caucasian, 31 percent African American, 2 percent Hispanic, and 13 percent of other race. Each site cares for large numbers of patients over the age of 65 (BHCS ~2,500; DUMC~8,700; UIC~6,000). From this population, more than 600 patients at each site have met preliminary screening criteria for the trial and constitute the pool for active recruitment, expediting patient accrual and study completion over a 1-year period.

Study entry criteria were determined based on elements from a literature review (indicating patient risk factors for ADEs in the ambulatory population), discussions with MTM stakeholders (Centers for Medicare & Medicaid Services, private insurers, pharmacy groups), and AHRQ's priority on targeting this trial to vulnerable elderly patients most susceptible to ADEs who

potentially would yield the highest safety benefits from MTM. Inclusion and exclusion criteria are displayed in Table 1.

Study Protocol

The study protocol was developed by investigators at each of the three sites and at AHRQ. The final protocol was approved by the institutional review boards at participating health care systems. To screen candidates for eligibility out of these large ambulatory populations, a search of each site's clinic administrative data was performed to identify patients above the age of 65 who have three or more comorbidities, two or more clinic visits, and a documented telephone number. Patients satisfying this initial screen received a letter and then a phone call inviting their participation and confirming eligibility.

Table 1. Inclusion and exclusion criteria for multicenter Medication Therapy Management (MTM) trial

Inclusion criteria
• ≥65 years of age at enrollment
• Primary use of English for oral and written communication
• ≥3 comorbid conditions associated with increased health care utilization (e.g., CHF, DM, COPD, HTN)
• ≥2 visits to a physician (or advanced practice provider) at study site clinic over the past year
• ≥8 chronic prescription medications over the 6 months prior to study enrollment
• Have a telephone line available for at least 6 months
• Situation placing patient at risk for a drug related problem (DRP):
→Change in medication, new physician visit, ER visit, hospitalization, invasive procedure within last 30 days
→3 or more providers seen within 12 months
Exclusion criteria
• Terminal condition with life expectancy ≤6 months
• Previous enrollment in MTM program with medication reconciliation or assessment for DRPs within 12 months

Physician and nursing staff at each of the clinic sites can also refer patients to contact the study team directly regarding their eligibility. Patients expressing interest are instructed to come to the clinic for enrollment, randomization, and a baseline study visit. Since transportation can be a barrier for many elderly patients, attempts are made to schedule enrollment, baseline visit, and if applicable, the first MTM visit with the pharmacist at the same appointment. For patients who normally receive assistance with their medications (from a spouse, adult child, or other caregiver), this person is allowed to accompany the patient to study visits. The study flow process, including a description of visit event content and temporal relationships, is summarized in Figure 1.

Arm 1 is a control group made up of patients who receive medication counseling per their clinic's normal routine but no formal MTM from a study pharmacist. Arms 2 and 3 represent the MTM intervention groups. Arm 2 entails basic MTM, with the pharmacist performing MR and assessment for DRPs through the patient interview alone. Arm 3 involves enhanced MTM, with MR and assessment for DRPs through the patient interview and an additional two-page clinical synopsis. This synopsis is extracted from the patient's clinic chart by nonpharmacist study team personnel. It contains data on medical history, laboratory values, and medications and can be

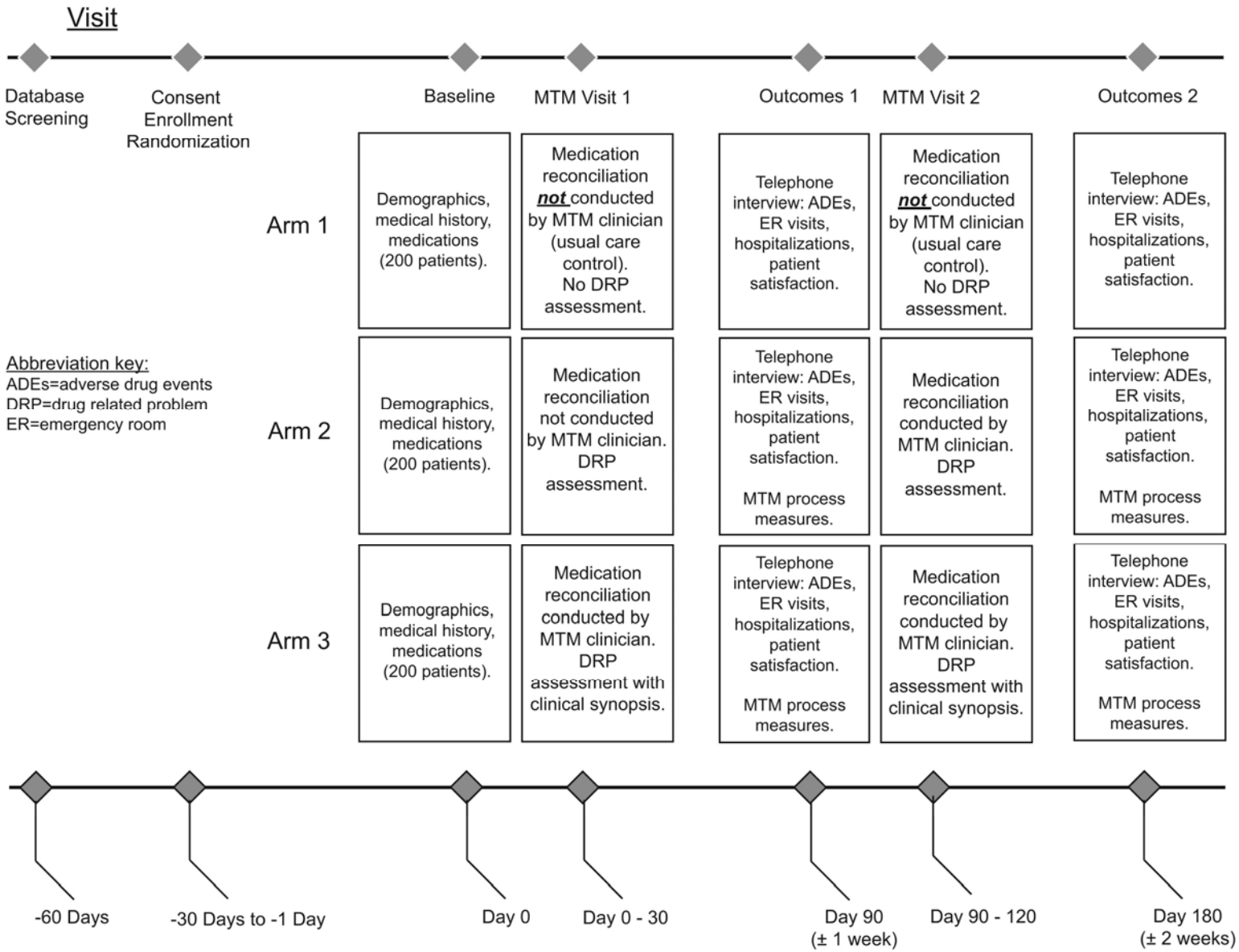

Figure 1. Medication Therapy Management (MTM) trial study flow.

completed in less than 15 minutes. Specifics of patient-pharmacist interaction and the tools used to facilitate information exchange during the MTM visits are detailed in Table 2.

Implementation of the MTM intervention was standardized through a 90-minute training session given to participating study pharmacists immediately prior to the start of enrollment. Trial design precludes blinding of either patients (they will be aware of whether or not they received the MTM intervention) or the MTM pharmacist. Study personnel conducting telephone interviews to assess outcomes at 90 and 180 days will be blinded as to patient treatment groups.

A total of 600 patients (200 per site) will be enrolled across the three sites over a 12-month study period in a 1:1:1 ratio (Arm 1: Arm 2: Arm 3) via a permuted block randomization scheme. Accrual is tracked via a computer-based enrollment log. Patients receive $10 for completion of each study phase (baseline visit, outcomes via telephone questionnaire 1, outcomes via telephone questionnaire 2), such that each participant is eligible to receive up to $30 total, regardless of study arm assignment. Reimbursement is not tied to receipt of the MTM pharmacist intervention in any way.

Outcomes, Sample Sizes, and Analysis Plan

Study outcomes, associated measurement tools, and anticipated statistical tests are displayed in Table 3. All patient data will be analyzed using an intent-to-treat plan according to original group assignment. The primary outcome of ADEs reflects the study focus on patient safety. Published reports on outpatient ADE frequency and a study using a validated ADE collection tool suggest an incidence of one to nine ADEs per patient.[3, 25] With a power of 0.80, 200 patients in each study arm (600 patients total), and statistical significance at the 0.05 level, an effect size of 10 to 25 percent relative risk reduction in ADEs from the MTM intervention compared to the usual care group should be measurable.

Even with the most conservative estimate (10 percent) in relative risk reduction of ADEs stemming from MTM, overall study accrual of 600 patients will allow detection of a statistically significant difference between groups. Furthermore, if indicated by dropout trends in a frail, elderly population, each site may enroll a few extra patients above the 200 required to achieve an adequate sample size completing the full study. Baseline rate of hospitalization or ER use within 30 days prior to study initiation will be captured during the enrollment visit. ADE occurrence and secondary safety outcomes of incident ER visitation or hospital admission over the trial period will be determined by patient self-reporting during structured telephone interviews performed (at approximately 90 and 180 days after enrollment) by study personnel independent of the MTM pharmacist (Figure 1). These safety outcomes will be compared among all three study arms.

Additional outcomes of processes of care related to different methods of MTM delivery (with or without the clinical synopsis) will be assessed between Arms 2 and 3 only (Table 3). For the medication list accuracy outcome, non-MTM pharmacist study personnel will create a “Best Possible Medication History” (BPMH) constructed from the patient’s self-reported medication list obtained at the baseline visit and complete review of available medical records, including prescription claims if applicable. Due to the intensive time resources required to create this BPMH, the medication list accuracy outcome will only be performed on a subset of MTM intervention patients in the study, 43 each in Basic (Arm 2) and Enhanced (Arm 3) MTM groups.

Table 2. Components of medication therapy management (MTM) visits with study pharmacist

Medication therapy management activity[a]	Tool(s)
Medication reconciliation	Patient interview script; medication record (generated by pharmacist)
Assessment for drug-related problems	Pharmaceutical care network Europe drug assessment form[b]
Communication of drug-related problems to practitioners	Physician communication fax form
Medication education/review	Medication record given to patient at end of visit

a For patients in the enhanced medication therapy management group, study pharmacist will also have access to a 2-page clinical synopsis to complete these activities.

b Modification of Pharmaceutical Care Network Europe drug-related problem classification form.[26]

Table 3. Medication Therapy Management (MTM) study outcomes, measurement tools, and analysis plan

Outcome	Measurement tool(s)	Analysis plan
Safety		
Adverse drug events	Adverse drug event self-reporting script Naranjo algorithm[a]	GLMM[d]
Hospital admissions	Patient self-reporting log	GLMM
Emergency room visits	Patient self-reporting log	GLMM
Medication therapy management process		
Number of drug-related problems	Pharmaceutical Care Network Europe drug assessment form	GLMM
Medication reconciliation accuracy	"Best Possible Medication History"[b]	Mann-Whitney U
Physician acceptance of pharmacist recommendations	Physician-pharmacist communication sheet	Chi-square
Pharmacist time	Pharmacist time log	Mann-Whitney U
Number of medication therapy management interventions	Physician communication sheet	Mann-Whitney U
Satisfaction		
Patient satisfaction with pharmacotherapy	Pharmaceutical care questionnaire satisfaction survey[c]	GLMM
Patient satisfaction with overall care	Satisfaction survey	Mann-Whitney U

a Naranjo et al., 1981[27]

b www.saferhealthcarenow.ca[28]

c Gourley et al., 1998[29]

d Generalized Linear Mixed Model

Based on the limited literature describing outpatient MR, it is estimated that there will be approximately 1.5 discrepancies between the BPMH and MTM pharmacist medication list in the basic MTM group and at least 1.0 discrepancy between the BPMH and MTM pharmacist list in the enhanced MTM group.[30] The subset sample size of 86 patients will allow for detection of a difference between the two groups with a power of 0.80 at a statistical significance level of 0.05. Lastly, in all three study arms, patient satisfaction regarding both their pharmaceutical regimen and overall medical care will be evaluated with short surveys that have been validated in the outpatient setting. These assessments will allow measurement of any incremental benefit in patient satisfaction from a safety-oriented MTM program compared to medication management provided solely by clinic staff in the usual care group.

Discussion

The influence of MTM programs on patient safety in the ambulatory elderly population remains unclear, and few models have been tested in controlled settings. Likewise, elements of the MTM process that are most effective at improving communication regarding patients' medication regimens and quality of care are indeterminate. In addition to answering important research questions, this study is designed specifically to:

- Target that portion of the elderly population at highest risk for ADEs.
- Create an MTM intervention involving pharmacists, physicians, and other health care professionals that can be standardized and replicated in broader settings.
- Construct an MTM intervention that promotes patient safety.
- Provide useful clinical quality outcomes information on MTM from a multicenter clinical trial in an accelerated, 12-month period.

Within the population over age 65, there are varying levels of disease burden, frailty, and medication use.[2, 31] It is unlikely that an MTM program applied universally to all elderly ambulatory patients would be useful or cost efficient. The entry criteria for this study (Table 1) were chosen explicitly to identify patients who were frequent health care utilizers and had an elevated risk for ADEs, hospital admission, or ER visitation. In turn, the effectiveness of an MTM should be especially apparent in this group. The frequency of ADEs using this population, with multisite sampling built into the study design, will be assessed and compared to other published reports on ADEs in ambulatory settings.[3] Whether additional factors are increasing the value of MTM to individual patients, such as low health literacy, is a subject for further research beyond this investigation.

The study team emphasized consistency and reproducibility of the MTM intervention delivered to patients, particularly since heterogeneity in current MTM practice has hindered evaluations of its efficacy. The MMA provides general principles regarding the development and administration of MTM programs, but it leaves numerous unanswered details. Geriatric and pharmacy advocacy groups offer few specifics on program implementation in their MTM consensus statement.[16] As a result, stakeholder groups involved during the early phases of trial design stressed the importance of creating an MTM intervention that would have defined parameters and could be applied broadly. Efforts were thus made to avoid practices that would require unrealistic use of time and resources from the perspectives of patients (i.e., twice monthly visits over a 6-month period are

unreasonable) and pharmacists (i.e., it would not be feasible for a community pharmacist to work without a set of visit objectives). The schedule of two MTM visits total over a 6-month period is consistent with existing MTM programs and not overly burdensome to patients or their health care providers.

Each study arm correlates with a "real-world" situation for both patients and providers. Arm 1, as the control group, represents the current state of affairs for most patients, where pharmacotherapy occurs without any formal MTM. In Arm 2, the MTM intervention occurs primarily on information obtained from patient interviews and, thus, mirrors the scenario encountered by most community-based pharmacists. Arm 3 reflects an optimized arrangement where the community-based pharmacist has access to relevant clinical information on the patient from the physician's office, which can be used to supplement the interview and guide the MTM intervention.

The general components of the study's MTM pharmacist-based intervention visits (Table 2) provide a framework for improved patient safety while still allowing each visit to be tailored according to patient needs. The clinical synopsis used in the enhanced MTM arm of the study is an example of an approach combining uniformity and practicality, while maintaining flexibility to serve individual patient needs.

In current practice, external MTM pharmacists often have little information about patients other than a record of prescriptions; access to full charts (outside of academic or Veterans Health Administration facilities) is rare. The premise of the clinical synopsis is that additional patient-specific data (e.g., list of comorbidities, formal record of allergies) will improve recognition of DRPs, facilitate patient-pharmacist communication, and promote informed decisionmaking on medication changes compared to MTM visits performed in the absence of such data. The clinical synopsis template was assembled so that members of a physician's office staff (medical assistants, nurses) could complete the form in less than 15 minutes and fax it to an outside MTM pharmacist. Some commercial pharmacies already have an analogous system in place.

Study outcomes (Table 3) are all linked to patient safety. For ADEs, hospital admissions, and ER visits, the relationship is clear. With the outcomes assessing MTM processes of care, the associations are less direct but trace back to patient safety concerns. For instance, incomplete or inaccurate MR during transitions of care is a major issue and source of adverse events.[32] Much of the previous work on MR has been conducted in inpatient settings; published data on MR in the ambulatory population (and methods to achieve outpatient MR) are sparse. This study has been designed to compare the accuracy of MR vs. a "gold standard" (the BPMH) in a subset of basic and enhanced MTM patients.[28] Although the metric is MR accuracy, improvements in this outcome should ultimately correlate with increased patient safety. Improvements in pharmacist-physician communication and total number of DRPs detected may have similar carry-over to patient safety.

The difficulty of performing large-scale clinical trials is well documented, as is the delay associated with translating effective research findings into daily patient care.[33] As MTM programs are being rolled out nationally, the demand for services has grown, and patient safety has become a heightened priority. Thus, the study investigators sensed the need to design and complete a study capable of answering focused questions within a 1-year period. The multicenter

collaboration between health care systems, pre-enrollment screening, and a protocol with a maximum of two study visits are strengths of the trial design and have fostered accrual towards the goal of 600 patients total. The geographic and demographic diversity of this MTM study population will support wider applicability of study results. Furthermore, to facilitate the uptake of elements in this MTM model found to be effective in improving patient safety, one of the end-products of the trial will be a toolkit, such that clinicians and researchers interested in instituting a similar MTM design in their own health care systems will be able to do so.

Several challenges arose while designing this study. The research team chose outcomes that would translate directly to patients and care providers (other evaluations of MTM have looked at surrogate measures, such as compliance and reductions in number of medications). It was felt that the number of deaths over the study period would be too small to demonstrate any mortality reduction with MTM, so a decision was made to pursue the more frequently occurring ADEs, ER visits, and hospitalizations as the key safety outcomes. Although the protocol was written to optimize capture of these outcomes, the potential for an insufficient number of events to demonstrate a statistically significant difference between the groups was recognized. With this in mind, elucidation of useful components of the MTM process (Table 3) was incorporated into the protocol so that the study would have residual value apart from patient safety.

Another issue centered on the short, 6-month study timeframe. Whereas longitudinal followup over several years would be ideal to demonstrate durable improvements in outcomes, it was not practical for this study in the context of AHRQ's pressing need for information on MTM interventions as drivers of patient safety. Furthermore, periods of health care transition (from hospital to home, major procedures, from one provider to another) have been identified as high prevalence times for ADEs, hospitalization, and ER visits.[34, 35, 36] Study entry criteria seek out those patients who have undergone a recent health care transition and, in turn, are most likely to experience those outcomes, reducing the importance of long-term followup. Finally, an all-encompassing evaluation of MTM in its entirety was beyond the scope of this trial. It is hoped that investigators will use this in-depth description of an MTM program modeled on patient safety as a reference point for exploring other issues in the field.

Conclusion

Medication use is closely related to patient safety in the ambulatory elderly population. The optimal design of MTM programs for improving patient safety remains unclear. The primary aim of this trial is to assess the effectiveness of a specific MTM model in improving patient safety through reductions in ADEs. Additional measures of the MTM process relating to patient safety and providing insight into the construction of MTM programs will also be evaluated. Methods and the rationale for conducting the trial with such a design have been detailed. If indicated based on results, this MTM program has been constructed as a patient safety intervention that can be reproduced and applied broadly in the outpatient setting, and it will motivate further research.

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Individuals contributing to the study to date include: from the University of Illinois at Chicago (coordinating site), Chicago, IL: Glen T. Schumock, PharmD, MBA (Chicago-area DEcIDE center Principal Investigator); Daniel R. Touchette, PharmD, MA Economics (Study Principal Investigator); Mary Ann Kliethermes, PharmD (Co-investigator); Alexandra Perez, PharmD (Research Assistant); Katherine M. Clarke (Study Coordinator); Young-Ku Choi, PhD (Biostatistician); Jessica Tilton, Annette Pellegrino, Shiyun Kim (study pharmacists); Ariana Bautista (research assistant); from Duke University, Durham, NC: David B. Matchar, MD (Duke University DEcIDE center Principal Investigator); Rowena J. Dolor, MD (Site Principal Investigator); Philip T. Rodgers, PharmD (Co-investigator); Katie Murphy, PharmD (study pharmacist); Kathlene Chmielewski, Beth Patterson, RN (study coorindators); Luis Ballon and Lisa Clevenger (research assistants): from RTI International, Research Triangle Park, NC: Kathleen N. Lohr, PhD (RTI International DEcIDE center Principal Investigator); Linda J. Lux (Study Site Director); from Baylor Health Care System, Dallas, TX: Andrew L. Masica, MD, MSc (Site Principal Investigator); Jennifer L. Craft, PharmD, BCPS (Co-investigator); Bruce E. Koehler, MPH, S. Quay Mercer, BS, MT(ASCP), Veronica Odom, RN, Nadine Rayan, MHA (Research Assistants); Kathleen M. Richter, MS, MFA (Medical Writer); from the Agency for Healthcare Research and Quality: Scott R. Smith, PhD (Program Officer); Carmen Kelly, PharmD (Task Order Officer).

Author Affiliations

Institute for Health Care Research and Improvement, Baylor Health Care System, Dallas, TX (Dr. Masica); Department of Pharmacy, Baylor University Medical Center, Dallas, TX (Dr. Craft); Center for Pharmacoeconomic Research (Dr. Touchette, Dr. Schumock), Department of Pharmacy Practice (Dr. Kliethermes), College of Pharmacy, and Institute for Health Research and Policy, School of Public Health (Dr. Choi), University of Illinois at Chicago, Chicago, IL; Department of Internal Medicine, Duke University School of Medicine (Dr. Dolor) and Duke University Hospital (Dr. Rodgers), Durham, NC; Research Triangle Institute (Ms. Lux), Research Park, NC; and the Pharmaceutical Outcomes Research Program, Agency for Healthcare Research and Quality, Rockville, MD (Dr. Smith).

Address correspondence to: Andrew L. Masica, MD, MSc, Baylor Health Care System-Institute for Health Care Research and Improvement, 8080 N. Central Expressway-Suite 500, Dallas, TX 75206; fax: 214-265-3628; e-mail: AndrewMa@BaylorHealth.edu.

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