Supporting Statement Part A

"Evaluation of a Medication Therapy Management Program on Patient Safety in Medicare Beneficiaries at High Risk of Adverse Drug Events"

Version 10/22/2007

A. Background and Justification

1. Need for Information

1

The Agency for Healthcare Research and Quality (AHRQ) requests that the Office of Management and Budget (OMB) approve under the Paperwork Reduction Act of 1995 AHRQ's intention to collect information to improve the effectiveness and safety of medication therapy for Medicare patients. This collection is responsive to AHRQ's request for research released under its Effective Health Care Program initiative with the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network, which was created as a result of Section 1013 of the Medicare Modernization Act. This network of research centers conducts accelerated practical studies about the outcomes, comparative clinical effectiveness, safety, and appropriateness of health care items and services. The purpose is to generate new knowledge.

The enactment of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA) is an important national milestone that holds potential to increase access to medications and improve the quality of care that seniors receive. MMA expands the Medicare entitlement program to offer seniors and people living with disabilities the option of purchasing a prescription drug plan (PDP) through a new Part D benefit. An important provision in MMA is that PDPs establish a medication therapy management program (MTM) that may be furnished by a pharmacist or other health professional and is designed to assure, with respect to targeted beneficiaries, that covered drugs are appropriately used to optimize therapeutic outcomes and to reduce the risk of adverse events. Plan sponsors are directed to target beneficiaries who (a) have multiple chronic conditions, (b) are taking multiple medications, or (c) are "likely to incur" high drug expenses.

Although the Centers for Medicare and Medicaid Services, in its final regulation on the Part D drug benefit, noted that it expects the MTM programs to "become a cornerstone of the Medicare Prescription Drug Benefit", MMA regulations only broadly define MTM and allows insurance plans discretion in determining MTM programs, outcomes, and which beneficiaries to target.[1] Many unanswered questions remain about the optimal design, delivery, and acceptance of MTM services by patients and health care providers, particularly related to improving medication safety. Moreover, those elderly or disabled subpopulations that have historically had poor access to prescription drugs

may encounter unique cultural, linguistic, or other communication barriers that could limit the success of standard MTM programs. For example, a recent study of elderly Medicare beneficiaries found racial and ethnic differences in influenza vaccination rates that were largely unaccounted for by differential access to care.[2] Consequently, there is an important need to identify successful models of MTM that will benefit all groups of Medicare enrollees, are practical in community settings, can be integrated with other health services, and assure continuity of care. In addition, new research is needed to identify effective approaches to medication therapy management that integrate ethnic, cultural, and functional health-literacy considerations.

In October 2005, AHRQ convened MTM researchers and practitioners to create a plan for advancing the scientific base of medication therapy management programs and discuss the implications of MTM on priority populations, especially low-income and minority elders. In conjunction with the meeting, AHRQ funded the Chicago-area DEcIDE center to design and evaluate a pilot medication therapy management program that improves medication safety in Medicare beneficiaries. In the first year of the project, a) a report describing MTM programs offered by PDPs across the nation was written for publication, b) a preliminary MTM research protocol was developed, and c) preparations were made for approval of government-sponsored data collection as required by the Paperwork Reduction Act of 1995 (PRA) through the Office of Management and Budget (OMB). To support the scientific aims of the project and meet review criteria of OMB, the DEcIDE project was subsequently expanded to a multi-center study.

Medication Therapy Management Program

To answer the questions about optimal design, delivery, and acceptance of MTM services by elderly Medicare subpopulations and their health care providers, a randomized controlled trial has been designed. It is a prospective, multi-center trial, with partial blinding. The intervention consists of three main components:

- Medication reconciliation
- Assessment of drug related problems (DRP's)
- Resolving DRP's through a pharmacist-based intervention

The goals of the trial are to provide AHRQ with information on:

- the effects of a drug related problem list generated by a MTM clinician on patient safety
- whether an MTM program with clinician access to patient-specific information improves measures of health care quality
- whether a brief, structured MTM program, focused on patient safety, increases patient satisfaction

These research goals are based on the hypothesis that patients enrolled in a MTM program (basic MTM program), consisting of the three components above, will have fewer adverse drug events than patients in usual care. Adding access to patient-

specific information (enhanced MTM program), such as patient demographics, medical history, laboratory values, and medications, to an MTM program can further reduce adverse drug events, and by association emergency department visits and hospitalizations. Patients' receiving the enhanced MTM intervention including access to patient-specific information will have more drug related problems identified (and subsequently resolved), fewer discrepancies in their medication lists, and a higher recommendation acceptance rate by their primary care physicians than those without access to patient-specific information (basic MTM program). Furthermore, it is anticipated that patients in the intervention arms will have a higher degree of satisfaction with their medication regimen and greater overall satisfaction with their healthcare compared to patients receiving usual care.

Study Limitations

General: This study was designed to answer specific questions, as stated in the study's objectives. It should not be construed as representing the effectiveness of all MTM programs, nor that of pharmacists practicing MTM.

Setting: This study is a prospective, randomized, controlled trial (RCT) and suffers from all of the potential issues and limitations of RCTs for outcomes research. Specifically, although considerable effort has been taken to emulate a community setting, this study is being conducted in academic medical center clinics by individuals with substantial postgraduate training (residencies). These and other differences between the community and academic medical center settings may limit the study's external validity. Conducting this study in academic medical center clinics was necessary, as access to patient chart information was required to generate the clinical synopsis and to develop the "Best Possible Medication History (BPMH)." Furthermore, the clinicians may unavoidably personally know the family practice, internal medicine, and geriatric physicians with whom they are communicating drug related problems. It is possible that physician acceptance of MTM clinician recommendations may be higher (or potentially lower) than it would otherwise be depending on trust and past interactions between the clinicians.

Another potential limitation (and strength) of the study setting is that none of the involved health systems are closed systems. As a result, these health systems resemble the majority of health systems in the U.S., improving external validity. However, a limitation is that healthcare may be received by study subjects outside of the study health systems with the result that prescription drug information may not be available when developing the BPMH. Furthermore, prescribing physicians will not be involved in developing the BPMH. Therefore, charting inconsistencies and omissions may lead to a bias in estimating discrepancies between the patient's medication list and the BPMH.

Study Design: Since this is a study, the control group may display a Hawthorne effect since they will be aware that they are being studied. Despite receiving "usual care," more attention will be given to the control group than they would otherwise receive, with

the potential to influence both behavior and response to the measured study outcomes. Additional limitations in the study design are those associated with all survey based research. Recall bias may result in missing data such as hospitalizations, physician office visits, or even symptoms reported. Effort has been taken to minimize the impact of recall bias on the study. Having a randomized, controlled trial minimizes the impact of recall bias by distributing patients with varying cognition randomly between the treatment groups. This random distribution of subjects may still result in a smaller effect size (i.e. differences in an outcome between the groups), but all groups should be affected similarly by the bias. Also, to reduce the effect of recall bias we will assess patient outcomes twice during the study period, every 3 months. Since the outcomes we are assessing are important life events (hospitalizations, ED visits, physician office visits) or currently bothersome events (symptoms), we believe that recall bias will have a small effect.

2. Information Users

Study Settings:

The study will be conducted at three sites: the University of Illinois at Chicago (UIC), Baylor Health Care System's Geriatrics Center (BGC), and the Duke Primary Care Research Consortium (PCRC).

Patients at UIC will be recruited from the approximately 6,000 patients over 65 years of age receiving care regularly at the UIC outpatient clinics. The majority of patients seen at UIC are of African American and Hispanic descent. Many of these patients are current Medicare beneficiaries and are enrolled in the Part D benefit as being "dually-eligible" (Medicare and State Medicaid eligibility).

Baylor Health Care System (BHCS), one of the research sites and a provider of care, will enroll patients through the Baylor Geriatrics Center (BGC), a convenient neighborhood medical facility, with staff specializing in the care of older adults. More than 2,500 individuals above the age of 65 receive primary care at the center, with the majority participating in Medicare Part D programs. Recent demographic data from a sample of 575 Baylor Geriatrics Center patients shows a population that is 73 percent white, 20 percent black, 5 percent Hispanic, and 1 percent Asian. Of this patient group, 75 percent were female; mean age was 84 (± 8) years.

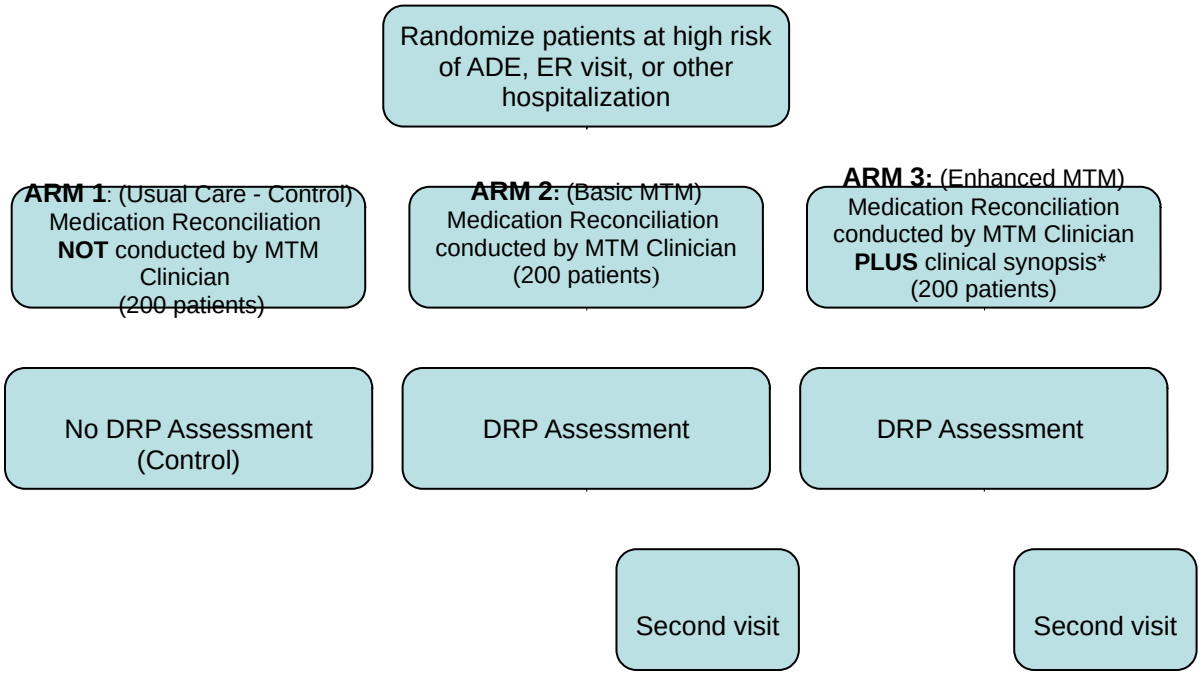
The Duke Primary Care Research Consortium (PCRC) is a primary care research network composed of academic and community practices within the Duke University Health System (DUHS) and surrounding communities, representing both urban and rural settings. The PCRC has access to over 8700 patients over 65 years of age within 2 academic primary care practices, and an additional 5600 patients age 65 or older within 5 community practices in Durham County. Recent demographic data shows the population in the Duke General Internal Medicine clinic is 54 percent white, 31 percent

black, 2 percent Hispanic or Latino, and 13 percent of other race or ethnicity. The Duke Outpatient Clinic has a population that is 23 percent white, 71 percent black, 1 percent Hispanic or Latino, and 5 percent of other race or ethnicity.

Study Arms:

Patients will be randomized to one of three arms: a usual care (control) arm, a basic MTM arm, or an enhanced MTM arm (see A1). The MTM program consists of medication reconciliation, drug related problem assessment, and an attempt by the MTM pharmacist to resolve identified drug related problems. The Institute for HealthCare Improvement defines Medication Reconciliation as "a formal process of obtaining a complete and accurate list of patient's current home medications, including name, dosage, frequency, and route. Discrepancies are brought to the attention of the prescriber, and if appropriate, changes are made to the orders." For this study, medication reconciliation is defined as a process of building a complete medication list based on the most current home prescription information and medical record information with the goal of reducing medication errors. Discrepancies will be identified as part of a formal process of DRP assessment. Discrepancies and other DRPs will be brought to the attention of the prescriber, and if appropriate, changes made to the existing medication regimen. As a minimum, medication reconciliation will be accomplished by building a list based on the patient's medication bottles. Otherwise, a complete medication reconciliation process entails assessing the available medical record, gathering the most recent medication changes as documented by physician(s), comparing information to medication bottles and updating the patient's medication list.

Figure A1. MTM Multi-center Trial Study Arms



*clinical synopsis is an abbreviated review of the patient medical record

ADE: adverse drug event; DRP: drug related problems; ER: emergency room; MTM: medication therapy management

Arm 1: Usual Care Control Group: This group will receive no form of medication therapy management. Patients will continue to receive care from their physicians and specialists. As part of this "usual care" process, patients may have medication lists solicited by a clinic nurse or physician (or other practitioner), as may be required by accreditation bodies such as JCAHO. A formal medication reconciliation via patient interview will not be conducted by the study pharmacist.

Arm 2: Basic MTM (Basic MR plus DRP assessment): Subjects in this arm will receive medication reconciliation via patient interview alone. Patients will be asked to bring in all of their medications to their visit with the MTM clinician. The MTM clinician will interview the patient using a script (Appendix A) and document their interaction with the patient (Appendix B). Study subjects who normally receive assistance from another person, such as a spouse, adult child, or other caregiver, will be allowed to receive assistance from this person in answering the questions. At the end of the patient visit, the MTM clinician will provide the patient with a list of all of the patient's medications and directions using the form in Appendix M.

The MTM clinician will screen for DRPs using a list of questions for each drug and document any potential DRPs (Appendix C). Identified DRPs will be forwarded to the patient's primary care physician (PCP) via a faxed form (Appendix D). The pharmacist may contact the physician by phone if the identified DRP is considered urgent. The pharmacist may also refer the patient to the nearest emergency department for any emergent situations (see Appendix E for the handling of emergent situations). If a response is not obtained from the patient's primary care physician, the physician's office will be contacted by phone. The response to the pharmacist's recommendations will be recorded and changes to the patient's medication regimen will be documented by the MTM clinician and a prescription generated (if indicated). New prescriptions or changes to medications will be forwarded to the pharmacy of the patient's choice and will be communicated to the patient. An updated medication list will be generated and mailed to the patient.

Arm 3: Enhanced MTM (Enhanced MR plus DRP assessment): Patients in this arm will receive medication reconciliation via patient interview and a 2-page clinical synopsis (using the same form as in Appendix B) provided to the pharmacist by a member of the research team. The clinical synopsis will be abstracted from the patient medical record using a brief review of sections of the chart known to contain information on patient demographics, medical history, laboratory values, and medications. This brief review has been designed to emulate a request for information from a physician's office and will follow a standardized protocol outlined in the flow chart in Appendix F. It is expected that completion of this clinical synopsis will take less than 10 minutes. As with the Basic MTM intervention, study patients will be asked to bring in all of their medications to their visit with the MTM clinician. The MTM clinician will interview the patient using a script (Appendix A) and document their interaction with the patient. Differences between the clinical synopsis and information provided by the patient will be documented. At the end of the patient visit, the MTM clinician will provide the patient

with a list of all of the patient's medications and directions using the form in Appendix M.

The MTM clinician will screen for DRPs using a list of questions and information collected from the patient interview and clinical synopsis for each drug and document any potential DRP's (Appendix C). Identified DRPs will be forwarded to the patient's primary care physician (PCP) via a faxed form (Appendix D). The pharmacist may contact the physician by phone if the identified DRP is considered urgent. The pharmacist may also refer the patient to the nearest emergency department for any emergent situations (see Appendix E for the handling of emergent situations). If a response is not obtained from the patient's primary care physician, the physician's office will be contacted by phone. The response to the pharmacist's recommendations will be recorded and changes to the patient's medication regimen will be documented by the MTM clinician and a prescription generated (if indicated). New prescriptions or changes to medications will be forwarded to the pharmacy of the patient's choice and will be communicated to the patient. An updated medication list will be generated and mailed to the patient.

Information collected as part of this project will be collected from several sources by researchers from the University of Illinois at Chicago, Duke University and Baylor Health Care System. Methods of data collection are discussed in this section.

Frequency of Collection:

Enrollment/ Baseline in-person visit (all subjects). After enrollment, regardless of assigned study arm, patients will undergo a baseline study visit at their clinic site. A study investigator or trained research assistant will obtain information on demographics, medical and basic medication history (strictly from patient recall, no records will be available at the baseline visit). In a random sample of 43 enrollees in each of the intervention arms of the study, this visit will also trigger a blinded investigator (independent from the clinical pharmacist who will be doing MR or DRP assessment) to create a "gold standard medication list" by the process described below.

Initial MTM visit (intervention groups only). Participants randomized to one of the MTM intervention arms will be invited to attend a MTM study visit, conducted any time from immediately after the baseline visit to within the first 30 days of the study. During this visit, subjects will undergo a MR and DRP assessment, with the intensity of the MR and DRP assessment identical to the group to which they were originally assigned.

Follow-up in-person MTM visit (intervention groups only)**:** Participants randomized to one of the MTM intervention arms will be invited for a second MTM visit, conducted 90 to 120 days after the first MTM visit. During this visit, patients will undergo a second MR and DRP assessment, with the intensity of the MR and DRP assessment identical to the group to which they were originally assigned.

MTM Clinician Training:

MTM clinicians will receive training for this study similar to the degree of training they might normally receive in community sponsored programs operated by a typical health insurance program. The training will include:

1) An orientation to the Medicare Modernization Act, especially as it relates to Medication Therapy Management, in non-technical language. This training will include the intended purpose of the law, proposed goals of Medication Therapy Management, and a brief overview of the study's goals, as a type of Medication Therapy Management program.

2) An orientation to the patient care process outlined in the study and the forms that will be used to document patient interactions, patient record keeping, and MTM clinician – primary care provider communication and documentation.

3) A brief overview and review of managing patients who are older and have multiple chronic conditions, including providing a list of medications that generally should be avoided in elderly patients.

Respondent Identification:

The information collected cannot be completely de-identified, since it will be necessary to contact patients throughout the study for scheduling patient care visits and telephone calls. Identifiable information will be kept seperate from non-identifiable information as described in the informed consent: "Any information that could be used to identify you will be kept separate from all other health record information and linked using a code available only to the investigators."

Any data collected as part of the study can be audited by appropriate University (e.g. UIC IRB), AHRQ, and appropriate Federal agencies (only as required by law) to ensure that the study has been conducted ethically and as required by law. Audits may occur at random or when there is suspicion of improper following of approved procedures. As such, study subjects must be informed that there is a possibility that these agencies may have access to the data.

3. Improved Information Technology

Because this is a small project, investments in improved technology are not planned, nor would they be cost effective.

4. Efforts to Avoid Duplication

Telephone survey instruments used in this study have been developed based on other instruments used and validated by others. This study is not duplicative of another information collection.

5. Small Businesses

The collection of information under consideration in this supporting statement does not include small businesses as part of the respondent universe. Nevertheless, the protocols are designed to minimize burden on all respondents.

6. Less Frequent Collection

This request is for a one-time study. Data will be collected at baseline, three and six months. There are no legal obstacles to reduce the burden.

7. Special Circumstances

The "Authorization to Use and Disclose Health Information for Research" (see Appendix T), does not have expiration date. It is possible that the involved investigators will want to conduct additional research, with approval from AHRQ, to answer future questions that may arise from this or other similar studies. This authorization allows for other IRB-approved and AHRQ-sanctioned research to be conducted using this data and may reduce the need for additional data collection.

8. *Federal Register* Notice/Outside Consultation

The 60-day notice was published in the Federal Register on December 1, 2006 (71 (231); 69567-8). The nature of the project was discussed with an expert panel and revised accordingly. Appendix R contains a copy of the Federal Register Notice and our Responses to Public Comments

9. Payment/Gift to Respondent

Participating patients will receive a maximum of a $30 incentive to be paid at the conclusion of their participating in the trial. The incentive is in recognition of the time that the patient will spend answering questions and completing the consent and HIPAA forms. Regardless to what arm of the trial the patient participates in, they will receive $10 for completing the baseline study visit and $10 for each of the follow-up questionnaires.

10. Confidentiality

All information gathered as part of this data collection effort will be collected in accordance with the Privacy Act (FAR 52.224-1, 52.224-2). Patients will be advised that the interviews are entirely voluntary and that any information they provide will be kept confidential to the extent permitted by the Privacy Act. Patient responses will be combined and summarized with information provided by others and no individually

identifiable information will be released. In instances where the patient's identity is needed for the follow-up assessment, the information collection will fully comply with all respects of the Privacy Act. See Appendix S and T for the consent and HIPAA forms that will be submitted to each study site's IRB committees for approval.

11. Sensitive Questions

The only questions of a sensitive nature that will be asked of participants involves whether or not they are experiencing any changes in sexual function from their medications. These types of side effects are quite common, are an area of concern to many patients, and are a routine inquiry in physicians' offices after a new medication has been added or the existing dose of a medication has been changed. These responses will be used to assess for drug side effects that are unacceptable to the patient and may need to be addressed. Patients will be given the option of declining any question that they do not feel comfortable discussing with study personnel. This information will be kept in a secure location, and a format that can be linked to the patient will accessible only to the specific MTM pharmacist and principal investigator working at each site. Any data sent to the coordinating center will be de-identified.

12. Burden Estimate (Total Hours & Wages)

Total time burden estimates required of respondents to provide data required to meet the study's objectives are summarized in Table A1 below. Time required to extract data from the patient's pharmaceutical and medical records, analyze the data collected from the visits and telephone interviews, and report preparation and publication is not included in these estimates. This hour estimate also does not include cost to the subject for participating in data collection, as they are elderly Medicare enrollees.

Table A1. Respondent Hour Burden Estimates

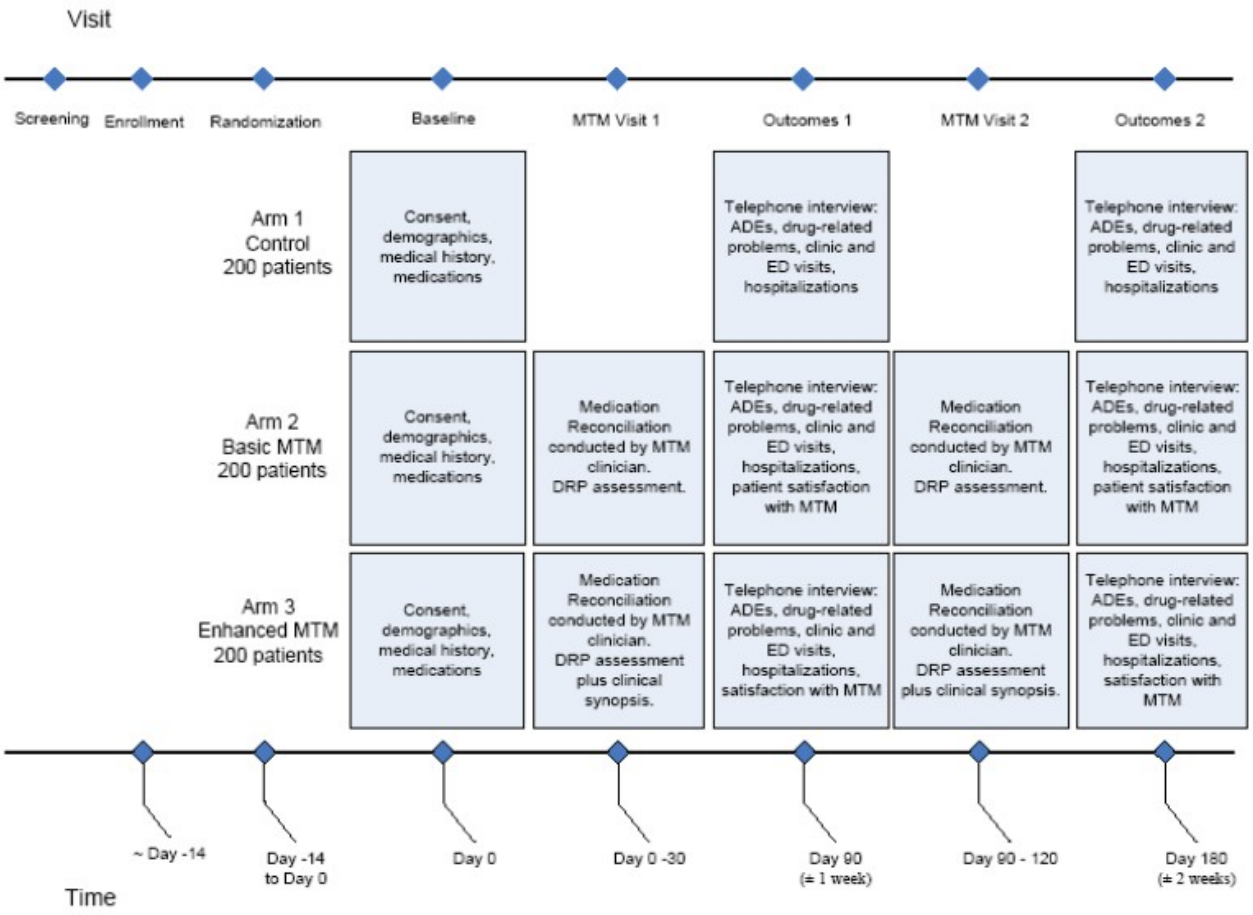
Respondents and Response Type	**Number of Respondents**	**Average responses per respondent**	**Estimated Time per Respondent (hours)**	**Estimated Total Burden (hours)**
In-person enrollment (screening, informed consent, disclosure authorization and baseline clinical interview) *(Appendix J, S, T, A)*	600	1	0.50	300
In-person MTM Visit 1 *(Appendix P)*	400	1	0.50	200
Patient Visit Log *(Appendix K)*	600	1	0.25	150
Clinical Documentation *(Appendix B)*	200	1	0.50	100
Drug Assessment *(Appendix C)*	400	2	0.50	400
Communication with Provider *(Appendix D)*	200	1	0.08	17

Three month Follow-up via Telephone Survey *(Appendix G)*	600	1	0.50	300
Medical Record Audit *(Appendix L)*	86	1	0.50	43
Patient Medication Form *(Appendix M)*	400	1	0.25	100
Clinician Time Log *(Appendix N)*	6	1	0.50	3
In-person MTM Visit 2 *(Appendix P)*	400	1	0.50	200
Six month Follow-up via Telephone Survey *(Appendix G)*	600	1	0.50	300
Patient Satisfaction Telephone Survey *(Appendix O)*	600	1	0.08	48
Patient Visit Telephone Survey *(Appendix Q)*	600	1	0.25	125
Total	5,692	na	na	2,286

We have estimated it will take 30 minutes to explain the study and the informed consent process to each participant in our study. With an adult population, the time would be shorter, but because this is an elderly population that we will be working with, we anticipate that it will take 30 minutes on average. For each MTM visit, clinicians will be instructed to keep visits to 30 minutes or less. For the telephone survey, we anticipate that the average response time will be 30 minutes for each follow-up time period with this elderly population. The Patient Satisfaction questions will be asked as exit questions at the six month follow-up telephone survey.

In the flow diagram below (Figure A2), we present the different data collection instruments (Appendix's A, B, C, D, G, J, M, O, P, Q, R, S, T) that will be implemented by each study arm. Whenever possible, enrollment, randomization, baseline (Appendix A) and MTM Visit #1 (Appendix P) will occur on the same day because we are trying to minimize the travel burden on the patients. The Initial Patient Contact Letter (Appendix I) will be sent to the patient prior to the telephone screening visit (Appendix J) and the Patient Visit Log (Appendix K) will be given to the patient at enrollment for use throughout the study period. The Outpatient Medication Reconciliation Audit Tool (Appendix L) will be used by blinded investigators in a subset of intervention patients after their first MTM visit and the MTM Clinician Time Log (Appendix N) will be used by the MTM clinicians throughout the study, whenever they are interviewing or addressing patient-related issues.

Figure A2 Data Collection Flow by Study Arm



Study Arm	Screening	Randomi-zation	Baseline	MTM Visit 1	Telephone Outcome 1	MTM Visit 2	Telephone Outcome 2
Control	J	S T	P	-	G	-	G
Basic MTM	J	S T	P	A B (from interview) C D M	G O Q	A B C D M	G O Q
Enhanced	J	S	P	A	G	A	G

MTM		T.		B (from chart and interview) C D M	O Q	B C D M	O Q

Table A2. Timing of Instrument Implementation by Study Arm (Appendix's A, B, C, D, G, J, M, O, P, Q, R, S, T**)**

13 Annual Cost Burden to Respondents or Record Keepers

This is an elderly population that for the most part will not be missing any paid employment time to participate in the trial and respond to our questions, thus we have not projected any burden costs to the respondents. There will not be any costs for capital equipment or operational expenses.

14. Cost to Federal Government

The total estimated one-time cost of this trial to the federal government is $1,400,000. This funding will be used to support the cost of refining the protocol, training study team staff, implementation of the interventions, data collection, analyses and reporting. The major costs are from the salary and fringe benefits for the research teams across three study sites to conduct the trial, and the direct costs for the telephone interviews, travel and incentives. The study teams at each of the sites have developed a working relationship and a shared commitment to minimizing the burden of the trial on the clinic and its staff. Intervention staff will be sensitive and flexible to schedules and requirements of care practices within each of the clinics.

15. Change in Burden

Not applicable. This is a new clearance.

16. Publication and Tabulation Dates

Little is known about the impact of community-based DRP identification and its impact on patient safety measures such as reduced hospitalizations and mortality. The purpose of this study is to test the effects of two different methods of MR and DRP assessment by pharmacists on patient safety in community dwelling Medicare beneficiaries above the age of 65. If successful, this study will expand the science base for designing MTM programs and serve as a model for heath insurance plans and others who are implementing MTM programs as a component of Medicare Part D.

The study endpoint is defined by passage of 6-months following enrollment rather than specific events. Frequency of specific events will be monitored over this time period (summarized in Table A3 below).

Table A3: MTM Study Data Collection & Intervention Schedule *(Data will be obtained for enrollees unless indicated)*

Activity	**Enrollment** Day -14 to 0	**Baseline** Day 0	**MTM Visit 1** Day 0-30	**Outcomes Assessment 1** Day 90 *(± 1 week)*	**MTM Visit 2** Day 90-120	**Outcomes Assessment 2** Day 180 *(± 2 weeks)*
Patient identification and contact	**X**					
Consent		**X**				
Demographics		**X**				
Medical History		**X**				
Medications		**X**				
Randomization		**X**				
MR and DRP assessment			**X**		**X**	
Communication of DRPs to PCP			**X**		**X**	
Adverse Drug Events, DRPs, Clinic visits, ED, Hospitalizations				**X**		**X**
Patient satisfaction with MTM *(intervention arms only)*				**X**		**X**
Time for MR, DRP *(Pharmacist)*			**X**		**X**	
Create 'gold standard' medication *list (subset of 86 non-control patients)*			**X**			
Compare with MTM intervention medication lists			**X**			

DRP: drug related problems; ED: emergency department; MR: medical record, MTM: medication therapy management; PCP: primary care provider

Data Collection:

Study-related data will be collected from two main sources: 1) information collected from the two MTM visits (intervention groups only), occurring between days 0-30 and days 90-120; and 2) information collected from two follow-up telephone surveys (all three study groups), occurring at day 90 (+/- 1 week) and at day 180 (+/- 2 weeks). Subjects will be allowed to have assistance from a caregiver for the MTM visits, but only if that caregiver is routinely involved in assisting the subject in taking their medicines. Assistance will not be allowed for the telephone surveys.

Data collected at each study site will be forwarded to the Coordinating Center at UIC. Some data will be collected for the purposes of patient care only and will not be forwarded to the UIC Coordinating Center. Study-related data will include demographic data collected at baseline, the list of medications collected by the MTM clinician (photocopied) (Appendix B medication list), the DRP assessment sheets collected by the MTM clinician (photocopied) (Appendix C), MTM clinician time logs (Appendix N), DRP forms faxed to the study subject's primary care physicians and those returned to the MTM clinician (photocopied) (Appendix D), and patient telephone interviews at 90 and 180 days by a blinded study investigator (Appendixes G, O and Q). Data collected for patient care that double as study-related data forms will be copied at the site will have the patient name crossed out prior to forwarding to the UIC Coordinating Center. All study-related data forms will be express mailed to UIC Coordinating Center on a monthly basis. Data collected for patient care only and not being forwarded to the UIC Coordinating Center include chart synopses (Appendix B Clinical Documentation Tool) and other clinic notes generated by the MTM clinician but not included in the study-related data.

Data Analysis:

All patient data will be analyzed according to the original groups patients were randomized into using an intent-to-treat analysis plan. We anticipate that some patients will be lost to follow-up for the 90- and 180-day telephone interviews and that some patients will not return for their second MTM visit. For all analyses, an alpha of 0.05 will be considered statistically significant.

Random effects such as study site, clinician, and patient characteristics may influence study outcomes. We will consider random effects in our regression models and account for these characteristics.

We expect missing data for some patients. Whether the imputation of missing values is necessary will be checked. If it is necessary, then types of missingness (e.g., missing completely at random, MCAR; or missing at random, MAR) will be assessed. Appropriate imputation procedures will be performed in SAS "mi", "mianalyze" and SPSS's Missing Values option.

Aim 1: To evaluate the impact of a drug related problem list generated by a MTM clinician on patient safety.

Hypothesis 1.1 *(Patient Safety)*:

A drug related problem list generated by an MTM clinician having access to greater patient information (physician-generated medication list; medical conditions; and medical history) and communicated to the patients' primary care physician results in fewer adverse drug events (ADEs) than a list generated without this access or than a control group receiving no MTM.

To further clarify the differences between DRP and ADE, we present the following

diagram (Figure A3) to assist with the interpretation of this terminology. DRPs and ADEs are distinct and different concepts, occurring at different periods of time. A DRP is a potential error or other problem that may or may not already be causing harm to the patient. Identifying DRPs is a preventive measure that is expected to reduce the number of ADEs experienced by the patient. DRPs may or may not be medication errors. They are medication errors if the prescriber was not aware of the potential problem at the time of prescribing the medication. They are not medication errors if the prescriber was award of the potential problem, assessed the risk-benefit, and decided to prescribe the medication anyways (benefit outweighed risk). With DRPs the prescriber's intent is not yet known, differentiating them from medication errors. ADEs are harm that has been caused by a drug or inappropriate use of a drug. ADEs can occur even with appropriate use of medications (correct dose and no identifiable DRP), as a side effect of the medication. This type of ADE is frequently termed non-preventable ADE. ADE's can also be caused by medication errors, often termed a preventable or ameliorable ADE.

Figure A4. Differences between DRP and ADE

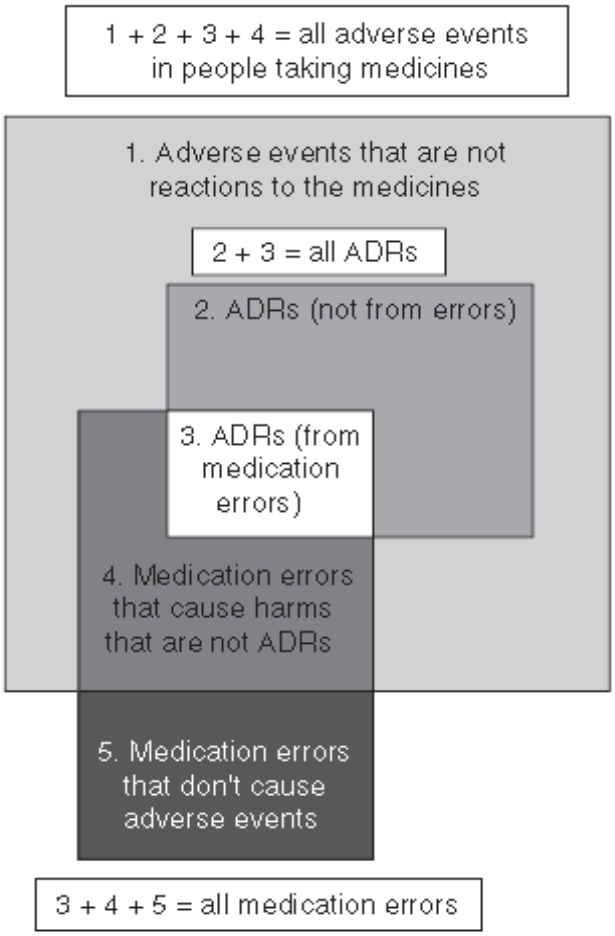


Fig. 1. A Venn diagram showing the relation between adverse events, adverse drug reactions, and medication errors; 'adverse drug events,' as defined by Bates et al.,[6] would encompass areas 2 + 3 + 4. **ADRs** = adverse drug reactions.

From: Aronson et al. 2005[19]

Outcome: This is a primary outcome. For the purposes of this analysis, ADEs are defined as harm caused by a drug or the inappropriate use of a drug.[7] Identification of ADEs will occur at 90 days and 6 months via telephone interview by a blinded study investigator. At the beginning of the study, patients will be provided a log to document ADEs, to assist with recall at the telephone interview (Appendix K). ADEs will be assessed using a tool modified from Jarernsiripornkul et al. to reflect the differences in this protocol (Appendix G).[8] The likelihood that the ADE was the consequence of a medication the patient was taking at the time the ADE occurred will be assessed using the Naranjo algorithm.[9] Only those ADEs that are considered probable or certain will be included as ADEs in the analysis.

Analysis Plan: ADEs will be summarized by treatment group and classified according to

likelihood that a medication was linked to the ADE, using the Naranjo tool.[9] The ADEs will be further classified according to whether they were preventable (medication error) or non-preventable (expected consequences of appropriate drug use) and by severity of the ADE at its worst (5 levels from minimal to very severe). The primary study endpoint will be the comparison of average number of ADEs per subject (probable or certain; preventable or non-preventable) between the three groups. The analysis will be conducted using the generalized linear mixed model (GLMM) (particularly, Poisson model) implemented in the SAS "mixed" and R.[10]

Hypothesis 1.2 *(Patient Safety)*:

A drug related problem list generated by an MTM clinician and communicated to the patient's primary care physician results in fewer emergency department (ED) visits and hospitalizations than a list generated without this access or than control.

Outcome: This is a secondary outcome. The number of ED visits and hospitalizations will be collected by a blinded study investigator at 90 and 180 days from study patients via self reporting obtained during a telephone interview. At the beginning of the study, patients will be provided a log to document ED visits and hospitalizations, to assist with recall at the telephone interview (Appendix K and Q).

Analysis Plan: Comparison of the number of ER visits and hospitalizations observed in each study arm will be made using the GLMM (particularly, Poisson model) implemented in the SAS "mixed" and R.

Aim 2: To determine if a MTM program with access to patient-specific information results in an improved process of care.

Hypothesis 2.1 *(Process Of Care)*:

A drug related problem list generated by an MTM clinician having access to greater patient information (physician-generated medication list; medical conditions; and medical history) results in identification of more drug related problems than a list generated without this access.

Outcome: This is a primary outcome. DRPs will be defined according to the PCNE Classification: as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[11] Although not explicitly stated in the PCNE Classification, our definition will include not only those events or issues related to drug administration, but also those related to a lack of necessary drug therapy.[12] The number and types of DRPs will be collected from the MTM clinician notes.

Analysis Plan: DRPs will be summarized for each of the two interventions according to the type of DRP. The primary endpoint will be the comparison of the number of DRPs between the two intervention groups. The analysis will be conducted using the GLMM

(particularly, Poisson model) implemented in the SAS "mixed" and R.

Hypothesis 2.2 *(Process Of Care)*:

A medication list generated by an MTM clinician having access to greater patient information (physician-generated medication list; medical conditions; and medical history) results in fewer discrepancies than a list generated without this access.

Outcome: This is a primary outcome. A "Best Possible Medication History" (BPMH, considered to be the gold standard medication list) will be developed for a randomly selected sample of 86 study enrollees (43 per intervention arm). Patients in both of the intervention arms of the study will undergo medication reconciliation as a component of the MTM visits, with generation of a medication list in a standardized format (Appendix B). For the random sample of patients selected for creation of the BPMH, the mean number of discrepancies (differences between the MTM intervention medication list and BPMH list) will be assessed.
We will assess the effectiveness of different methods of medication reconciliation by:

1. Creating a "BPMH" list for a randomly selected sample of 86 study enrollees (43 per intervention arm). This BPMH, serving as a gold standard, will be a list of medications (including name, dose, frequency, and route) identified from patient self-reported medications (obtained at the baseline visit) and a complete review of the patient's paper and electronic medical records, including prescription claims (if available), by a blinded investigator (see flowchart in Appendix H). It will not require any additional involvement or time from the 86 patient subset. This list will be recorded in a standardized format across all three study sites.

2. Measuring the percentage of discrepancies using each MR method (basic versus enhanced) in assessing the MTM intervention medication list compared with the "Best Possible Medication History" list using the tool in Appendix L.

    a) Mean number of undocumented intentional discrepancies
    = number (#) of undocumented intentional discrepancies divided by # of patients
    b) Mean number of unintentional discrepancies
    = # unintentional discrepancies divided by the # of patients
    c) Medication Reconciliation Success Index
    = ((# of no discrepancies + # documented intentional discrepancies / (# of no discrepancies + total # of all discrepancies)) *100.

Analysis Plan: We will compare of the mean number of undocumented intentional discrepancies and mean number of unintentional discrepancies observed in each intervention arm will be made using the GLMM implemented in the SAS "mixed" and R. The medication reconciliation success indexes of each intervention arm can typically be compared using a Mann-Whitney U test. We can further analyze these data to figure out whether the medication reconciliation success indexes of each intervention arm

have possible relationships with confounding factors by using GLMM as well. In particular, both the dependent variables here, the number of discrepancies and medication reconciliation success index (rate), can be analyzed using GLMM (Poisson model).

Hypothesis 2.3 *(Process Of Care)*: Pharmacist initiated interventions aimed at correcting drug related problems identified by an MTM clinician having access to greater patient information (physician-generated medication list; medical conditions; and medical history) will result in higher physician acceptance of these recommendations compared to recommendations generated by an MTM clinician without this enhanced access.

Outcome: This is a secondary outcome. In a previous study on outpatient medication management, pharmacist recommendations were only accepted by physicians 49% of the time.[13] We will collect physician response to MTM pharmacist recommendations regarding identified DRP's via a faxed form (Appendix D).

Analysis Plan: The proportion of physician acceptance between the two groups will be summarized and assessed by Chi-square analysis. If confounding exists, a GLMM (logistic regression) model will be used.

Hypothesis 2.4 *(Process Of Care)*: Given the availability of additional clinical information, MTM clinician time required to conduct medication reconciliation and develop a drug related problems list will be greater in the enhanced MTM format.

Outcome: This is a secondary outcome. Mean time required conducting MTM interventions and associated follow-up will be collected. MTM clinician will keep a log of time spent performing the intervention visits and subsequent interactions with patients or physicians (see Appendix N). Our interest in tracking this outcome relates to the feasibility of recreating a similar MTM intervention program in the community setting.

Analysis Plan: We will use a Student t-test (if parametric) or Mann-Whitney U test to compare the MTM clinician times between the two intervention groups at the three trial sites. A GLMM will be used if confounding exists.

Hypothesis 2.5 *(Process Of Care)*: Given the availability of additional clinical information, a greater number of medication changes will be requested by the MTM clinician and accepted by the patient's physician.

Outcome: Mean number of interventions performed by the MTM clinicians in both MTM study arms. Our interest in tracking this outcome relates to capturing what occurs on the MTM clinician-physician level during MTM interactions.

Analysis Plan: The MTM clinician / physician communication fax forms have a check box for the physician to accept, reject, or alter the recommendation made by the MTM clinician (see Appendix D). We will use a Student t-test (if parametric) or Mann-Whitney U test to compare the proportion of interventions proposed versus the number accepted

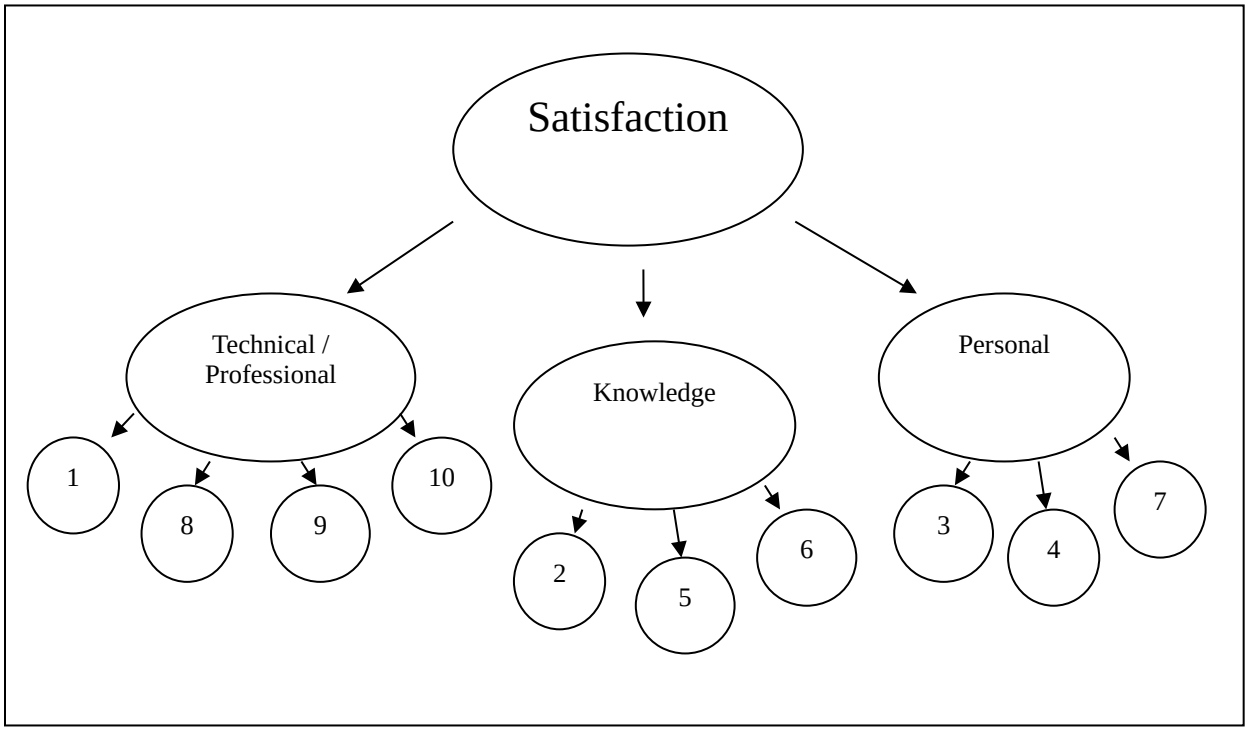
by the physician. A GLMM will be used if confounding exists.

Aim 3: **To determine whether this MTM program affects patient satisfaction.**

Hypothesis 3.1 *(Patient Satisfaction)*: Patients enrolled in an MTM program will have a higher level of satisfaction regarding the care received from their pharmacist compared to the control group, and there will be an additional increase in satisfaction among patients receiving the enhanced MTM intervention.

Outcome: Patient satisfaction with care will be assessed at the baseline and follow-up study visits using 10 items from the Pharmaceutical Care Questionnaire (see Appendix O).[14] The first 10 items of this questionnaire assessed the following three dimensions: Technical - professional; knowledge; interpersonal relationship (Figure A4).

Figure A4. 10 items from the Pharmaceutical Care Questionnaire and the Dimensions Included in these Questions:



Analysis Plan: The PCQ is a 10 questions survey with each question rated according to a 5-point Likert scale. The midpoint of the scale is equivalent to no change in patient satisfaction compared with the community pharmacy where the patient's medications are normally obtained. Each item of the PCQ will be compared independently. Negatively worded items will be reverse coded prior to comparison. We will use a Structured Equation Model (SEM) to analyze the PCQ.[15] In particular, we will use a second order factor model, which explains the relationship between patient satisfaction and the three dimensions of the questionnaire. We will also determine which aspects of

these dimensions are impacted by our intervention.

Hypothesis 3.2 *(Patient Satisfaction)*: Patients enrolled in an MTM program will have a higher level of satisfaction regarding their overall outpatient medical care compared to the control group, and there will be an additional increase in satisfaction among patients receiving the enhanced MTM intervention.

Outcome: We will measure overall patient satisfaction scores according to three questions that have been validated in the outpatient setting.

Analysis Plan: Patients will undergo a brief, 3 question survey as part of their study exit telephone interview. Questions will be assessed separately using a Mann-Whitney U test to determine if overall satisfaction with staff, care, or likelihood to recommend others were impacted by the MTM program.

Timeline for data collection, analyses and publication:

Our current plan for commencement of the trial calls for screening and enrollment to begin on November 1, 2007 or earlier. We anticipate that the baseline visits will take place within a month of enrollment and the two follow-up data points in March and August of 2008. A final report will be submitted to AHRQ on or before the end of February 2009.

Table A3. Timeline

Activity	**Expected Start Date or Completion**
Enrollment	Starting November 1, 2007
Baseline	Starting December 1, 2007
3 month Telephone Interview	Starting March 1, 2008
9 month Telephone Interview	Starting August 1, 2008
Data preparation	Completed by September 30, 2008
Analyze findings	Completed by December 31, 2008
Prepare Draft Report	Completed by January 31, 2009
Final Report/ Manuscript	Completed by February 28, 2009

17. Expiration Date

Expiration date for OMB approval of data collection will be displayed as required.

18. Certification Statement

These activities will comply with the requirements of 5 CFR 13209.9. This collection of information involves no exceptions to the second page of the 83i.

BIBLIOGRAPHY