1. Please upload all revised materials (appendices, supporting statement, etc.) and let me know when you've done so. I've opened ROCIS for you.

2. Please revise the burden estimates in ROCIS/ICRAS as appropriate
given the various passback questions and responses, please list all the study limitations that will be disclosed whenever results are made public.

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.

3. Please clarify how MTM will be explained in lay terms to the potential subjects to screen them for eligibility in this study. How will you differentiate between the more formal MTM you are testing here and the more general but widespread use of more informal MR practices described in the response to "KM4."

We do not intend to explain the differences between our study's MTM program and JCAHO required MR practices or existing Medicare Part D MTM program practices (which may or may not include MR). Instead, we intend to exclude patients who have had a similar intervention in the past 12 months, as outlined in the following places.

We briefly describe the study's expectations for the subjects and potential intervention (for the benefit of those subjects randomized to a non-control arm) briefly in the informed consent:

"Random Assignment and Clinic Visits

You will be randomly assigned to one of three study groups. Once you provide your written consent to participate in this research, a study investigator will choose a numbered envelope. Your study group assignment will be inside this envelope. The study investigator will not know before opening the envelope which group you will be assigned to.

All study participants will be asked to complete one entry visit and answer two telephone surveys. Depending on the group to which you are assigned, some participants may be asked to come in for two 10-30 minute meetings with a clinician, while others may not have to do so. The first (baseline) visit will be done on the same day as providing this informed consent, right after if possible. The telephone surveys will be done about three and six months later. Some study participants will also be asked to come to UIC for up to 2 more visits between the first (baseline) visit and last telephone survey. As a result of this study, we may request that your physician make changes to your medications. However, no changes will be made to your medications without both your and your physicians consent.

Baseline Study Visit

If you agree to participate in this study, you will be asked to come to a baseline study visit and must bring all of the medications that you are on to this visit. At this visit you will be asked to fill out a short survey with questions about you, your medical history, what medications you are on, and how you take these medications. Answering these questionnaires and completing the visit should take between 5 and 20 minutes."

We exclude those subjects who are not eligible because they had a similar intervention in the "Patient Telephone Screening and Invitation to Participate Script (Appendix J)" and the "Baseline Study Visit (Appendix P)":

"Have you had an interview at some time in the past year where you have been asked to bring in all of your medications to a pharmacist, nurse, doctor, or other healthcare professional and been given a list of all your medications?

YES NO"

4. Please clarify how the initial screening with pick up cultural/ethnic/linguistic barriers (response to "KM3")

In the initial screening (Patient Telephone Screening and Invitation to Participate Script – Appendix J), there are some questions which patients must answer with more than a yes/no answer. Specifically, potential study subjects must be able to provide us with the medication names off of their prescription bottles. Being able to answer all of the screening questions, without having to involve another family member or care provider (for translation purposes), will be sufficient to invite eligible patients to the baseline study visit. At the baseline study visit, potential study subjects will be asked to read and sign informed consent. By doing so, study subjects are indicating that they agree to participate in the research and are eligible for participation. The very first sentence of the informed consent document is: "You have been asked to participate in the research because you are over 65 years of age, primarily speak English, have 3 or more chronic conditions, are taking eight for more medications, have a situation that places you at risk for a drug related problem, and may be eligible to participate."

Since the intervention will be conducted in English only, indications that a potential study subject does not speak English will be considered grounds for exclusion from the study.

Comment A1: Since there is a separate HIPAA authorization subjects need to sign, this can be misleading. Would recommend either clarifying or adding the language from earlier in the consent form (highlighted).

We agree that the highlighted text improves the readability and intent of the form. This modification will be added to the informed consent.

Comments A2-A6: Will the information shared be de-identified? If not, why is it necessary to use and share identifiable data? Please clarify how and to whom the PHI will be "shared." If this is limited to the people listed in following bullet points, this should be made clear. Why does AHRQ need PHI? Please clarify whether it is these

INSTITUTIONS that will receive the data or whether it is only RESEARCHERS on this study who are affiliated with these institutions. If it is the institutions, why would institutions need this information?

This section of the Authorization to Use and Disclose Health Information is standard approved language by UIC's IRB.

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. We will be separating identifiable information 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 we collect 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, we must inform study subjects that there is a possibility that these agencies may have access to the data.

The first bullet of this section of Appendix T has been altered to clarify the intent (that the researchers can share PHI amongst each other to facilitate collection and analysis of data). This data will be shared only as described in the informed consent (and in the IRB submissions) and only as needed so as to maintain the risk of breach of confidentiality as low as possible.

Also, please clarify whether Baylor Health Care System is a third-party payor or whether they are the providers of care (e.g. the name of the university hospital).

Baylor Health Care System is the name of one of the research sites and a provider of care.

Comment A7: Please provide a justification for not including an 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.