STATISTICAL ANALYSIS PLAN

Medication Management for Older Adults (iMAP) Randomized Controlled Trial
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Revisions to the SAP were completed before data were locked.

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STUDY SUMMARY

Title	Medication Management for Older Adults (iMAP) Trial Project
Study Design	This study is an individually randomized controlled trial with participants assigned to either the iMAP intervention or standard care (SC) in a 1:1 ratio, stratified by site and race (White vs. non-White). Follow-up assessments occur at baseline, 6 months, and 12 months.
Study Duration	12 months
Trial Sites	This study was conducted at one UNC-affiliated and one Duke-affiliated, community-based primary care practices that employed seven primary care providers (PCPs) and was a primary teaching site for medical residents.
Objective	The primary objective of the study is to evaluate whether the iMAP intervention reduces the medication-related problems (MRPs) at 6 and 12 months compared to standard care in older adults aged 65 and older.
Number of Subjects	Participants will be randomized in a 1:1 ratio to either the iMAP intervention or standard care (SC), with stratification by site and race (White vs. non-White). The estimated sample size is up to 200 participants per group, totaling 400 participants across both groups. This increased sample size ensures robust power to detect a one-unit difference in MRPs, even if the mean MRPs in the SC group are as high as 7 and 6 in the iMAP group. Power calculations were based on a clinically meaningful one-unit difference, with a 90% power level, a Bonferroni-adjusted type I error rate of 2.5%, and an expected 20% attrition rate over the 12-month follow-up period. Additionally, the study is expected to have ample power at the 6-month follow-up due to lower anticipated attrition compared to 12 months.
Main Inclusion Criteria	Adults aged >= 65 yrs Taking >=3 regularly scheduled medications (at least one of which needed to be a prescription medication) Living independently in the community, English speaking Projected life expectancy of at least 12 months Under the care of a primary care provider (PCP) at one of the two practice sites with at least one visit to this PCP in the past year. Has a telephone

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Intervention	The Individualized Medication Assessment and Planning (iMAP) program is a pharmacist-led intervention designed to optimize medication use in older adults within primary care. Through comprehensive medication reviews at baseline, 6, and 12 months, pharmacists systematically identify and resolve medication-related problems (MRPs) such as undertreatment, suboptimal dosing, and adverse drug events using a standardized classification tool. Integrated within primary care teams, iMAP facilitates collaboration between pharmacists and physicians to implement evidence-based medication adjustments
Duration of Intervention	12 months
Primary Outcome	Number of MRPs at 6 and 12 months
Primary Analysis	Reduction in medication related problems (MRPs) in the iMAP group versus standard care (SC). We will conduct the comparison of iMAP versus SC at the 0.05 significance level (0.025 for each time point). This model will include treatment group,time and interactions as fixed effects, and race, site and baseline MRP as covariates. Adjusting for covariates in a randomized controlled trial (RCT) can improve the precision of treatment effect estimates and account for any residual confounding; it also increases statistical power by reducing the unexplained variance in the outcome. For other covariates collected, sensitivity analyses will be applied during the descriptive analysis phase to correct for any potential imbalances. **Model:** Generalized linear mixed model (GLMM) for repeated measures. Assuming a Poisson distribution with log link. **Covariates:** Race, site, baseline MRP **Effect Measure:** Difference in number of MRPs between the iMAP and SC groups at 6 and 12 months.
Secondary Analyses	rate ratio of total MRPs, subgroup of MRPs: undertreatment, suboptimal dosing, inadequate medication monitoring, inappropriate drug selection, adverse drug events (ADEs), and nonadherence. ,

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1. BACKGROUND

Older adults are particularly vulnerable to medication-related problems (MRPs) due to polypharmacy and multiple chronic conditions. MRPs—including undertreatment, suboptimal dosing, adverse drug events, and nonadherence—not only jeopardize patient safety and quality of life but also drive costly hospitalizations and emergency department visits. Standard care in primary care settings often lacks the systematic, integrated approach needed to continuously evaluate and optimize complex medication regimens in this population.

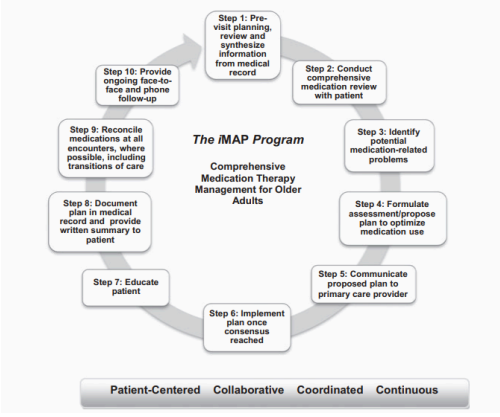
The individualized Medication Assessment and Planning (iMAP) intervention embeds a clinical pharmacist into the primary care team to provide comprehensive, 10-step medication therapy management. In a pilot study, iMAP reduced the mean number of MRPs per patient from 4.2 at baseline to 1.0 at 6 months and decreased acute health services utilization by 35%. Building on these promising results, our trial will assess whether iMAP further reduces MRPs at 6 and 12 months in a controlled trial adjusting for key covariates such as race,and clinical site.

2. AIMS

To determine whether the iMAP intervention reduces the number of MRPs at 6 and 12 months compared to standard care.

3. STUDY DESIGN

This study is an individually randomized controlled trial with participants assigned to either the iMAP intervention or standard care (SC) in a 1:1 ratio, stratified by site and race (White vs. non-White). Follow-up assessments occur at baseline, 6 months, and 12 months.
Study Phases:
Baseline: Participants are screened and enrolled based on predefined eligibility criteria. Baseline data collection includes demographic, clinical, and medication-related variables.
Intervention Group (iMAP): The intervention is led by a clinical pharmacist who provides comprehensive medication therapy management.



Control Group (Standard Care): Participants receive usual care from their primary care providers without the additional pharmacist-led intervention. For the control group, they will only

go through step 1-3 of the entire iMap process, they don't have individualized plans. And their MRPs were assessed and recommendations proposed using the previously published MRP classification tool.

Follow-up: Participants in both groups are assessed at baseline, 6 months and 12 months. Data collection includes:

- Number and types of MRPs.
- Updates to clinical and demographic data.

Key Features:

- **Randomization:** Conducted using a centralized system to ensure allocation concealment.
- **Blinding:** Due to the nature of the intervention, participants and clinical staff cannot be blinded. In addition, although pharmacists involved in developing the individualized plans cannot be blinded, pharmacists conducting MRP assessments will be blinded to limit the potential for bias. Therefore, we will have a set of blinded (doing MRP assessments) and unblinded pharmacists (developing individualized plans).
- **Data Source:** Electronic health records (EHRs), clinical assessments, and patient interviews.
- **Statistical Analysis:** Generalized linear mixed models (GLMM) for repeated measures will be used to analyze changes in MRPs over time.

4. OUTCOMES

4.1 Primary Outcome

The primary outcome is the number of medication-related problems (MRPs) identified at the 6 month, 12-month time point, measured through structured clinical assessments and electronic health records (EHRs). MRPs include undertreatment, suboptimal dosing, duration, frequency or administration, inadequate medication monitoring, inappropriate drug selection, adverse drug events, and nonadherence. The primary outcome is assessed at baseline, 6 months, and 12 months. Covariates collected at baseline include treatment group (iMAP vs. SC), site, race (White vs. non-White), age, biological sex, total number of medications, total number of prescription medications, number of healthcare utilizations in the prior year, and number of comorbid conditions. Participants who die during follow-up are censored at the time of death.

4.2 Secondary Outcomes

The secondary outcome is medication-related problem (MRP) subgroups, identified at the 6-month and 12-month time points, measured through structured clinical assessments and electronic health records (EHRs).

MRP subgroups include undertreatment, suboptimal dosing, inadequate medication monitoring, inappropriate drug selection, adverse drug events (ADEs), and nonadherence. Test all subgroups at 6 months, and 12 months.

5. RANDOMIZATION

5.1 Method of Randomization

Randomization occurs at the participant level, with individuals assigned in a 1:1 ratio to either the iMAP intervention group or the standard care (SC) control group. To minimize confounding and ensure balanced distribution, randomization is stratified by site and race (White vs. non-White). This stratification accounts for potential differences in medication-related problems (MRPs) outcomes. A computer-generated randomization system will be used to allocate participants, ensuring an unbiased and reproducible assignment process. Participants will first be classified by site and race and then randomized within each stratum using a blocked randomization approach. The use of random-sized blocks will further ensure that balance is maintained over time while preventing predictability in group assignment. Given the updated total planned sample size of 400 participants (200 per group), randomization will be proportionally distributed across the stratified subgroups.

Given that participants will be stratified into four subgroups based on site and race, each subgroup will have its own pre-generated blocked randomization sequence. For example, if a block size of 6 is chosen, each block will contain three participants assigned to iMAP and three to SC, maintaining a 1:1 ratio. The randomization sequence for each stratum will be generated using statistical software, and participants will be sequentially assigned to the next available position within their respective block.

5.2 Allocation Concealment

Ensuring proper allocation concealment is a key component of this study to minimize selection bias and maintain the integrity of the randomization process. Several approaches will be implemented, including (1) conducting randomization only after enrollment, (2) masking recruiters and assessors, and (3) standardizing the enrollment process through rigorous training of recruitment staff. (4) Covariate adjustment will be applied in sensitivity analyses to correct for any potential imbalances.

To implement allocation concealment, sealed, sequentially numbered envelopes containing pre-determined treatment assignments will be prepared and distributed to study sites. Each envelope will contain an assignment corresponding to the randomization list, ensuring that participant allocations remain concealed until enrollment is completed. Study coordinators will be required to open envelopes sequentially and record assignments on a tracking sheet, which will be securely maintained for verification.

Pharmacists involved in the study will follow a partial blinding approach to maintain objectivity in MRP assessment. While clinical pharmacists administering the intervention cannot be blinded, the MRP outcome assessment will be blinded to minimize bias. A separate, blinded pharmacist

will independently complete Steps 1-3 of the MRP assessment, ensuring that the evaluation remains unbiased. This blinded pharmacist will not have access to participant treatment assignments. After the initial assessment, an unblinded clinical pharmacist will complete the remaining steps of the intervention process.

Additionally, regular monitoring and check-ins between study sites and the study statistician will be conducted to ensure adherence to the allocation concealment protocol. These procedures will help uphold the integrity of the study and prevent any undue influence on participant recruitment or treatment allocation.

6. SAMPLE SIZE

6.1 Preliminary Data

Preliminary data from the pilot study [1] of the iMAP intervention demonstrated a significant reduction in medication-related problems (MRPs) over six months. Specifically, the mean number of MRPs per patient decreased from 4.2 at baseline to 1.0 at six months, after adjusting for race, baseline number of medications, and pharmacist involvement. Additionally, the prevalence of MRPs decreased significantly ($p < 0.0008$) at six months compared to baseline.

6.2 Sample Size Determination for the Primary Outcome

Poisson Distribution:

For the outcome variable we can utilize a two-sample z-test to compare the mean MRPs between the iMAP and SC groups at the 12 months. Because MRPs are count data that can be assumed to follow a Poisson distribution (where the variance is approximately equal to the mean), the sample size calculation is based on comparing two Poisson rates. Using the large-sample z-test formula for comparing two Poisson rates [2], we have:

$$N = \frac{(\lambda_{\mathrm{SC}} + \lambda_{\mathrm{iMAP}}) \times (z_{1-\beta} + z_{1-\alpha/2})^2}{(\lambda_{\mathrm{SC}} - \lambda_{\mathrm{iMAP}})^2}$$

where:

$\lambda_{SC}$and λ_{iMAP}: represent the mean MRP counts in the standard care and iMAP groups respectively. For this study, we assume that a decrease in 1 MRP is meaningful, and since in the pilot study [1], the mean MRP counts per patient is 4.2 at baseline, we set $\lambda_{SC} = 4.2$ and $\lambda_{iMAP} = 3.2$, with a difference of 1 MRP. The null hypothesis is that the rate difference equals 0 (i.e., no difference), while the alternative hypothesis is that the rate difference differs from 0.

$\alpha = 0.025$, $\beta = 0.1$: $\alpha = 0.025$ is adjusted for 2 multiple comparisons (6 months and 12

months) using the Bonferroni correction, and since many clinical trials they choose power from 0.8 to 0.85 [3], $\beta = 0.1$, power = 0.9 is a conventional conservative threshold for power in clinical trials.

20% dropout rate: In the iMAP pilot study, over 3 months and 6 months the attrition rates were around 8% and 14%. Because we are doubling the time from 6 to 12 months, and similar 12 months studies chose 15% [3], the 20% is reasonable and conservative for a geriatric population.

Using the above formula and parameters, assuming a 1:1 randomization ratio, sample size calculations were performed using R, with the primary objective of evaluating whether the iMAP intervention leads to a significant reduction in the number of MRPs at six and twelve months compared to standard care (SC).

Although our calculations indicate that enrolling 115 participants per group (total N=230) will provide sufficient power to detect a one-unit difference, we plan to recruit up to 400 participants in total. This larger sample size ensures ample power and accommodates the possibility of higher MRP rates than originally estimated. In fact, with a sample of 400, we would still be powered to detect a one-MRP difference even if the mean MRPs rose to 7 in the SC group and 6 in the iMAP group. This makes our estimate highly conservative, providing robust protection against potential variability in the true baseline MRP rate. Additionally, we anticipate having more than sufficient power at the 6-month time point, as attrition is expected to be lower compared to 12 months. Thus, our final sample size selection ensures that the study remains well-powered across both follow-up periods, minimizing the risk of under-powering our primary analyses.

7. INTERIM MONITORING

7.1 Overview

Interim monitoring focused on patient accrual, baseline comparability of treatment groups, protocol adherence, loss to follow-up, data completeness and quality, safety, efficacy, and futility. The summary of the types of tables, listing and figures (TLFs) generated for semi-annual open and closed DSMB reports is presented in the study protocol.

7.2 Safety

Details of the safety and adverse event monitoring plan were provided in study protocol. The principal investigator was responsible for monitoring the data and assuring protocol compliance.

Unanticipated problems involving risks to subjects or others, including adverse events, were followed by a written report within five calendar days of the principal investigator becoming aware of the event to the institutional review board (IRB). The principal investigator apprised fellow investigators and study personnel of all unanticipated problems and adverse events that occurred during the conduct of this research project. The protocol's data safety monitoring board (DSMB) was informed of serious or unanticipated adverse events. Presented to the DSMB at each annual interim meeting were the following summaries by time point: AEs using the Common Terminology Criteria for Adverse Events (CTCAE) dictionary. Serious adverse events (SAEs) collected in this trial are deaths, hospitalizations, MACE, and falls requiring hospitalization. Event counts, numbers and proportions of patients with events, frequency distributions, and event rates per 100 person-years of follow-up (PYF) for each of these categories will be reported to the DSMB. These reports were presented across treatment arms in aggregate in an 'open meeting' with the study team present, followed by an unblinded presentation of these data by treatment arm to the DSMB by the unblinded statistician.

8. ANALYTIC PLAN

8.1 Overview

The analysis of the primary and secondary outcomes will be according to the principle of intent-to-treat, i.e., participants will be analyzed according to their original treatment assignment regardless of adherence to protocol. All analyses will include the participant as the unit of analysis. SAS 9.4, and the latest version of R (currently 4.0.2) software will be used for all analyses.

8.2 Comparability of Treatment Groups

To assess the comparability of the iMAP and standard care groups at baseline, we'll analyze demographic and clinical characteristics using summary statistics and visual methods. Randomization aims to balance these characteristics; however, if imbalances are detected, sensitivity analyses will adjust for these discrepancies. Since randomization was stratified by study site and race, these will be included as covariates in all analyses.

8.3 Analysis of Primary Outcome: MRPs

8.3.1 Primary Analysis of Primary Outcome: MRPs

Step 1: Possion Model equation:

$$log(E[MRP_{ij}]) = \beta_0 + \beta_1 Intervention_i + \beta_2 Time_{6M,j} + \beta_3 Time_{12M,j} + \beta_4 (Intervention_i \times Time_{6M,j}) + \beta_5 (Intervention_i \times Time_{12M,j}) + \beta_6 baselineMRP_i + \beta_7 Race_i + \beta_8 Site_i + b_i + \varepsilon_{ij}$$

$$b_i \sim N(0, \sigma_b^2)$$

MRP_{ij} = MRP Count for participant i at time j

$Intervention_i$ = Indicator for iMAP vs SC for participant i

$Time_j$ = Time (Categorical: 6 months, 12 months)

$(Intervention_i \times Time_j)$ = Interaction Term with the expectation that iMAP effect vary at different time points

$baselineMRP_i$ = Baseline MRP for Participant i

b_i = Participant-level random effect

$Race_i$,$Site_i$ = fixed effects for race and site.

β_0 = overall intercept (on the log scale).

ε_{ij} = error terms

Primary analyses will initially be conducted using a generalized linear mixed model (GLMM) with a standard Poisson distribution for the MRP count outcome. To check for excessive zeros, we will first create a frequency plot to visualize the data. Next, we will compare the observed number of zeros to what is expected under the Poisson assumption. If there are more zeros than expected, we will assess model fit using potential AIC and BIS along with Vuong's Test and a Likelihood Ratio Test (LRT) to see if a Zero-Inflated Poisson (ZIP) model provides a better fit. If these tests confirm zero inflation, we will use the ZIP model to properly account for the excess zeros.[16]

If overdispersion is detected, meaning the variance is greater than expected under a Poisson model, we will consider using a Negative Binomial model instead. If further adjustments are needed, we may apply transformations or explore other distributions to better fit the data.

Step 2: Contrast statement - Assessing differences between groups (tests for 6 months and 12 months)

Primary analysis:

Rate Differences for IMAP & Standard Care (SC)

- Calculation: Subtract SC's predicted MRP rates
  - RD_{6M}: $E[MRP_{SC,6M}] - E[MRP_{iMAP,6M}] = e^{\beta_0+\beta_2} - e^{\beta_0+\beta_1+\beta_2+\beta_4}$
  - RD_{12M}: $E[MRP_{SC,12M}] - E[MRP_{iMAP,12M}] = e^{\beta_0+\beta_3} - e^{\beta_0+\beta_1+\beta_3+\beta_5}$
- Confidence Intervals: delta method or bootstrapping

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- Two-Sided Hypothesis at each time point (assumption 1 MRP reduction is significant)
    - H0: iMAP's rate of MRPs is not different compared with SC (RD = 0)
    - Ha: iMAP yields a different rate of MRPs compared with SC (RD ≠ 0)
    - Wald tests (Z-test): $p < 0.025$

Analysis	Primary analysis of primary outcome: Medication-related problems (MRPs) as reported through comprehensive pharmacy review.
Analysis population	All enrolled participants
Endpoint	6-month and 12-month.
Unit of analysis	Participant
Method of analysis*	Generalized linear mixed models (GLMM) for repeated measures will be used to analyze changes in MRPs at the primary time points of 6 months and 12 months relative to the baseline, adjusting for number of MRPs at baseline, time, site and race/ethnicity. The comparison of iMAP versus Standard Care (SC) will be conducted using contrast statements for Rate Differences (RD) to specifically assess the differences in outcomes at a significance level of 0.05, adjusted for multiple comparisons. Alternatives: ZIP, neg bino → normal/other distribution with some type of transformation
Handling of missing data	MAR assumption [4] . if < 5%, ignore missing; otherwise, we will do the following: 1. Look at the pattern of missing data to look for systematic issues 2. Sensitivity Analysis. If any variable is associated with missing, adjust the model 3. Multiple Imputation
Covariates	Study site, race, baseline MRP, and time
Type I error	5% (2-sided)

Control of type I error [5]	Bonferroni correction will be applied to maintain the overall Type I error rate, dividing the alpha level by the two planned tests (primary analysis), resulting in an adjusted significance level of 0.025 for each test.
Treatment effect estimate	rate differences with 95% confidence intervals will be reported to quantify the effect of the iMAP program compared to standard care.

Sensitivity analysis: This will only be conducted if baseline imbalance of covariates is found. Adjustment for baseline covariates not balanced at randomization. If we have 5% or more, we will conduct sensitivity analysis to see if adjustment for the model is needed and use multiple imputation.

8.4 Secondary Analyses

8.4.1 Rate ratio of total MRPs (as a supplement to the primary analysis)

Rate Ratios for IMAP & Standard Care (SC)

- Calculation: Exponentiate coefficients
    - iMAP vs. Standard Care at 6 Months relative to the baseline: $RR_{6M} = e^{\beta_1+\beta_4}$
    - iMAP vs. Standard Care at 12 Months relative to the baseline: $RR_{12M} = e^{\beta_1+\beta_5}$
- Confidence Intervals: Wald
- Two-Sided Hypothesis at each time point
    - H0: iMAP's rate of MRPs is not different compared with SC (RR = 1)
    - Ha: iMAP yields a different rate of MRPs compared with SC (RR ≠ 1)
    - Wald tests (Z-test): $p < 0.025$

Analysis	Secondary analysis of **total MRPs**. Test rate ratio of total MRPs as a supplement to the primary analysis.
Analysis population	All enrolled participants
Endpoint	6-month and 12-month.
Unit of analysis	Participant
Method of analysis	Same as primary analysis.

Handling of missing data	Same as primary analysis.
Covariates	Study site, race, baseline MRP, and time
Type I error	5% (2-sided)
Control of type I error [5]	Bonferroni correction will be applied to maintain the overall Type I error rate, dividing the alpha level by the two planned tests (primary analysis), resulting in an adjusted significance level of 0.025 for each test.
Treatment effect estimate	Rate ratio with 95% confidence intervals will be reported to quantify the effect of the iMAP program compared to standard care.

8.4.2 Analysis of Secondary Outcome: Subgroup of MRPs

The analysis of secondary outcomes will focus on the impact of the iMAP intervention on specific subgroups of medication-related problems (MRPs). These subgroups include **undertreatment, suboptimal dosing, inadequate medication monitoring, inappropriate drug selection, adverse drug events (ADEs), and nonadherence.**

8.4.2.1 Statistical Model

The same generalized linear mixed model (GLMM) framework used for the primary analysis will be applied to analyze each MRP subgroup individually. However, given the lower prevalence of certain subgroups, alternative models will be considered:
Binomial or multinomial logistic regression will be applied for MRP subgroups with very small counts. In this case, dds ratios (ORs) will be estimated.

Analysis	Secondary analysis of MRP subgroups: Undertreatment, suboptimal dosing, inadequate medication monitoring, inappropriate drug selection, adverse drug events (ADEs), and nonadherence.
Analysis population	All enrolled participants
Endpoint	6-month and 12-month.
Unit of analysis	Participant

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Method of analysis	Same as primary analysis. Binomial or multinomial logistic regression will be used to estimate **Odds Ratios (ORs)** for each MRP subgroup in the event of small counts. The comparison of iMAP versus Standard Care (SC) will be conducted for each subgroup separately, with ORs quantifying the likelihood of MRP occurrence under iMAP versus SC.
Handling of missing data	Same as primary outcome
Covariates	Study site, race, baseline MRP, and time
Type I error	about 5% (2-sided)
Control of type I error	A p-value of 0.01 will be used to determine significance.
Treatment effect estimate	Rate differences with 95% confidence intervals will be reported to quantify the effect of the iMAP program compared to standard care. In the event of small counts: Odds Ratios (ORs) with 95% confidence intervals will be reported to quantify the impact of the iMAP intervention on each MRP subgroup.

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