STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Effect of Clinical Pharmacist-Led Pharmaceutical Care on Medication Adherence, Beliefs About Medicines, and Health-Related Quality of Life in Adults With Major Depressive Disorder: A Randomised Controlled Trial

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Principal investigator / academic supervisor	Prof. Mesut Sancar
Research investigator	Ayşe Seda Kanmaz Demircioğlu
Study type	Randomised, parallel-group, open-label, controlled interventional study

PART A — STUDY PROTOCOL

1. Background and rationale

Major depressive disorder (MDD) frequently requires sustained antidepressant pharmacotherapy. Medication-related concerns, adverse effects, treatment burden and inconsistent use may impair adherence and perceived health. Clinical pharmacists may address these challenges through systematic medication review, individualised education, monitoring and collaboration with treating psychiatrists. The study evaluates whether adding structured pharmaceutical care to routine psychiatric management improves patient-reported adherence, medication beliefs and health-related quality of life.

2. Objectives and hypotheses

The principal study objective is to compare antidepressant medication adherence between patients receiving structured clinical pharmacist-led pharmaceutical care plus usual psychiatric care and patients receiving usual psychiatric care alone. Additional objectives are to evaluate beliefs about medicines and health-related quality of life over six months.

The analysis framework examines whether intervention participants have a higher probability of achieving a MARS-5 score ≥24 at Month 3 and Month 6, whether mean MARS-5 scores change differently over time between arms, and whether BMQ-T and EQ-5D-3L/EQ-VAS trajectories differ between arms.

3. Study design and setting

Single-site, two-arm, 1:1 randomized, parallel-group, open-label controlled study at the Marmara University psychiatry outpatient service in Türkiye. The planned follow-up duration for each participant was six months, with in-person outcome assessment at baseline, approximately Day 90 and approximately Day 180.

4. Eligibility criteria

Inclusion criteria	Exclusion criteria
Adults aged 18–65 years	History of bipolar disorder or other psychotic psychiatric disorder
Diagnosis of MDD according to DSM-IV or DSM-5 criteria	Drug or substance dependence
Antidepressant treatment for at least one month	Cancer
	Pregnancy

5. Recruitment, informed consent and allocation

Potentially eligible patients attending psychiatric outpatient appointments were assessed for inclusion and exclusion criteria. Patients were informed about study procedures, and written informed consent was obtained before participation. A researcher not otherwise involved in clinical implementation

generated the computer-based random allocation sequence. Participants were assigned to intervention or control in a 1:1 ratio. Blinding of participants and care providers was not feasible given the nature of counseling and follow-up.

6. Study interventions

6.1. Clinical pharmacist-led pharmaceutical care plus usual psychiatric care (intervention)

Participants received routine psychiatrist-led management and a six-month structured pharmacist intervention. At the initial visit, the pharmacist documented medication history, comorbidities, concomitant products, self-reported adherence, potential drug-related problems and treatment concerns. Individualised education addressed antidepressant purpose and expected onset, administration and timing, management of adverse effects, medication interactions, avoidance of unsupervised discontinuation and the importance of regular use. A patient-specific pharmaceutical care plan was developed and updated as needed, with communication to the psychiatrist for clinically significant issues.

Follow-up contacts were planned approximately every 15 days by telephone; the later Methods section also refers to telephone calls or messages. During follow-up, the pharmacist reviewed adherence barriers, adverse effects, drug-related problems and progress toward care goals. In-person reassessments were conducted at Month 3 and Month 6.

6.2. Usual psychiatric care (control)

Control participants continued their usual psychiatrist-led assessment and treatment without the additional structured pharmacist follow-up during the six-month study period.

7. Outcome measures

Outcomes were assessed at baseline, day 90 and day 180. The primary reporting outcome is the proportion of participants achieving a MARS-5 total score ≥24 at day 90. Secondary outcomes include the corresponding day 180 proportion, longitudinal MARS-5 total scores, four BMQ-T subscales, EQ-5D-3L index and EQ-VAS.

Hierarchy	Outcome measure	Operational definition	Time point
Primary	MARS-5 score ≥24	Binary: MARS-5 total score ≥24 versus <24	Day 90 / Month 3
Secondary	MARS-5 score ≥24	Binary: MARS-5 total score ≥24 versus <24	Day 180 / Month 6
Secondary	Medication adherence score (MARS-5)	Continuous total score, range 5–25; group-by-time change	Baseline, Day 90, Day 180

Secondary	Medication beliefs (BMQ-T)	Specific Necessity, Specific Concerns, General Overuse, General Harm	Baseline, Day 90, Day 180
Secondary	Health-related quality of life (EQ-5D-3L)	Five-dimension health state and utility index	Baseline, Day 90, Day 180
Secondary	Self-rated health (EQ-VAS)	Visual analogue score, range 0–100	Baseline, Day 90, Day 180

7.1. Medication Adherence Report Scale (MARS-5)

MARS-5 comprises five self-report items scored 1–5; total scores range from 5 to 25, with higher scores indicating greater self-reported medication adherence. Two complementary analyses are described: (1) the continuous total score at baseline, Day 90 and Day 180, evaluated with repeated-measures ANOVA; and (2) the binary indicator of achieving a MARS-5 score ≥24 at Day 90 and Day 180, evaluated using logistic regression adjusted for baseline MARS-5 ≥24 status.

7.2. Beliefs About Medicines Questionnaire — Turkish version (BMQ-T)

The BMQ-T consists of 18 items in four subscales: Specific Necessity (5 items), Specific Concerns (5 items), General Overuse (4 items) and General Harm (4 items). Responses are recorded on a five-point Likert scale, and the four subscale scores are analysed separately. In the supplied statistical report, subscale values are reported as item-level mean scores (rather than summed subscale totals), with longitudinal group-by-time comparisons using repeated-measures ANOVA.

7.3. EuroQol 5-Dimension 3-Level (EQ-5D-3L) and EQ-VAS

The EQ-5D-3L assesses mobility, self-care, usual activities, pain/discomfort and anxiety/depression at three severity levels. The health state is converted to a utility index using the UK Measurement and Valuation of Health value set described in the later Methods. The EQ-VAS captures self-rated health on a 0–100 scale, where higher values indicate better perceived health.

8. Schedule of assessments and instruments

Procedure	Baseline	Month 3 (Day 90)	Month 6 (Day 180)	Between visits
Eligibility / informed consent	Yes	—	—	—
Random allocation	Yes	—	—	—
Medication history / pharmacist care plan	Yes (intervention)	Review	Review	As indicated

MARS-5	Yes	Yes	Yes	—
BMQ-T	Yes	Yes	Yes	—
EQ-5D-3L / EQ-VAS	Yes	Yes	Yes	—
Pharmacist adherence / safety contacts	—	—	—	Every ~15 days, intervention arm

9. Safety and participant protection

The pharmacist reviewed adverse drug reactions, drug interactions, inappropriate administration and other medication-related problems during consultations and follow-up. Clinically significant concerns were referred to the treating psychiatrist. Routine clinical treatment decisions remained with the responsible physician.

10. Ethics, confidentiality and dissemination

Ethics approval was granted by the Marmara University Institute of Health Sciences Ethics Committee on 15 October 2024 (decision no. 92). Informed consent was obtained. Study records were to be handled confidentially and reported in aggregate. The public protocol must not include patient identifiers.

PART B — STATISTICAL ANALYSIS PLAN

11. Analysis objectives and hypotheses

The analysis evaluates between-group differences in a MARS-5 score ≥24 at Day 90 (primary reporting endpoint), a MARS-5 score ≥24 at Day 180, longitudinal continuous MARS-5 scores and secondary patient-reported measures. For the binary adherence analyses, the null hypothesis is that the intervention is not associated with different odds of a MARS-5 score ≥24 after accounting for baseline adherence. For continuous longitudinal analyses, the null hypothesis is that the group-by-time interaction is zero.

12. Sample size determination

The original ethics application assumed that the proportion of adherent participants would increase from 60% under usual care to 80% under the intervention. With a two-sided α=0.05 and 80% statistical power, the minimum sample was calculated as 81 participants per arm (162 total). Allowing for approximately 15% attrition, the recruitment target was 93 participants per arm (186 total). These figures describe the original sample size plan, not the results or analyzed denominators.

13. Analysis populations

The analysis population consisted of 170 participants with completed follow-up assessments (84 in the intervention arm and 86 in the control arm). This is a completer/available-case analysis population and should not be described as an intention-to-treat population of all randomized participants.

Outcome-specific logistic regression may have a smaller evaluable denominator if data required by the model are missing; report the actual denominator for each model. The original recruitment target was 186 participants.

14. General statistical principles

Descriptive statistics comprise counts and percentages for categorical variables and means and standard deviations for continuous scores. The statistical report evaluated normality using skewness and kurtosis and employed parametric methods. It reports independent-samples t tests, ANOVA, Pearson correlation, internal-consistency reliability analysis and repeated-measures ANOVA. For longitudinal outcomes, group, time and group-by-time effects are examined; Bonferroni-adjusted pairwise comparisons are used where appropriate. Statistical tests are two-sided with $\alpha=0.05$.

Baseline variables are summarized using mean and standard deviation for approximately symmetric continuous data, median and interquartile range where appropriate, and counts and percentages for categorical data. Distributional assumptions may be assessed using Shapiro–Wilk tests and graphical inspection. The original application mentioned Student t tests, Mann–Whitney U tests, paired tests, chi-square or Fisher exact tests and Pearson/Spearman correlation as appropriate. Two-sided tests with a nominal significance level of 0.05 were planned. Secondary analyses are exploratory unless a multiplicity adjustment was prespecified.

15. Primary outcome: Proportion of participants achieving MARS-5 ≥24 at Day 90

At Day 90, the binary outcome is whether the participant achieved a MARS-5 total score ≥24. Treatment group is the main predictor. The logistic model includes baseline MARS-5 ≥24 status as an adjustment variable. The analysis estimates the adjusted odds ratio with its 95% confidence interval and a two-sided p-value. The numerator, denominator and percentage reaching the threshold are reported by arm in the results, not in this protocol. Model convergence and sparse outcome cells should be checked.

The binary-threshold analysis is distinct from the continuous repeated-measures analysis. Baseline-adjusted logistic regression evaluates the threshold outcome at each follow-up. The categorical analysis also includes an alternative threshold of exactly 25 points, exact paired McNemar tests for within-arm changes, and generalised estimating equations (GEE) for longitudinal binary outcomes, including group-by-time interaction. Estimates will be reported with 95% confidence intervals and two-sided p- values.

16. Secondary outcome analyses

16.1. Proportion achieving a MARS-5 score ≥24 at Day 180

The binary MARS-5 ≥24 indicator at Day 180 is analyzed analogously to Day 90, with treatment group as the main predictor and baseline adherence status as a covariate. Arm-specific percentages, adjusted odds ratios, 95% confidence intervals and p values are reported in the results publication or registry results module, not in this protocol.

16.2. Continuous MARS-5 total scores

The continuous MARS-5 total score (range 5–25) is assessed at baseline, Day 90 and Day 180. A repeated-measures analysis of variance evaluates the effects of treatment group, time and the group ×

time interaction. Descriptive means and standard deviations at each time point and within-arm changes may be reported. Assumptions, including sphericity where relevant, should be assessed and any correction identified. The repeated-measures analysis and the dichotomised logistic models are distinct, complementary approaches; neither substitutes for the other.

16.3. BMQ-T, EQ-5D-3L and EQ-VAS

The four BMQ-T subscale mean scores, EQ-5D-3L utility index and EQ-VAS (0–100) are evaluated at baseline, Day 90 and Day 180. Repeated-measures ANOVA examines group, time and group-by-time interaction effects. Where applicable, Bonferroni-adjusted within-group comparisons describe differences between assessment occasions. Scale-specific descriptive statistics and inferential results are reserved for the results report.

Outcome	Scale / type	Primary comparison
Participants achieving MARS-5 ≥24, Day 90	Binary (≥24)	Baseline-adjusted logistic regression
Participants achieving MARS-5 ≥24, Day 180	Binary (≥24)	Baseline-adjusted logistic regression
MARS-5 score, three visits	Continuous (5–25)	Repeated-measures ANOVA, group × time
BMQ-T subscales	Subscale mean scores	Longitudinal group/time comparison
EQ-5D-3L index	Utility index	Longitudinal group/time comparison
EQ-VAS	Continuous (0–100)	Longitudinal group/time comparison

17. Missing data and sensitivity analyses

The overall six-month follow-up analysis population includes 170 participants (84 intervention; 86 control). Outcome-specific analyses will use participants with available valid data for the relevant measure. For the binary MARS-5 analyses, model-specific denominators must be reported accurately and cannot be assumed to equal the overall sample. No unverified imputation or intention-to-treat analysis is claimed.

18. Statistical software and reporting

Statistical analyses were performed using IBM SPSS Statistics version 26.0, as documented in the statistical analysis report. The repeated-measures ANOVA framework, independent-samples comparisons, correlations and reliability analyses are described there. The MARS-5 ≥24 logistic models are described as a separate analysis. No observed effect estimates, p-values or results tables are included in this protocol. Binary MARS-5 analyses additionally use baseline-adjusted logistic regression, exact McNemar tests, and generalised estimating equations, as described in the separate categorical analysis report.

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