STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

A Randomized Controlled Trial of HERDA: A Culturally Adapted Pharmacist-Led Intervention to Improve Medication Adherence in Outpatients with Depression

Unique Protocol ID

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Study acronym: HERDA

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Official Study Title

A Randomized Controlled Trial of HERDA: A Culturally Adapted Pharmacist-Led Intervention to Improve Medication Adherence in Outpatients with Depression

Study Acronym

HERDA

Brief Summary

HERDA (Holistic, Evidence-based, and cultuRally adapted Depression Adherence) is a pharmacist-led intervention developed to support medication adherence among outpatients with depression in South Kalimantan, Indonesia. It combines structured counseling, behavior change strategies, pharmaceutical care, and culturally adapted educational materials to help patients identify and address difficulties in taking their prescribed medication.

The intervention incorporates the 5A Brief Counseling framework and the Transtheoretical Model (TTM), which guides counseling according to each participant's readiness to change. It also includes screening and a predefined safety pathway for suicide-related concerns, culturally adapted psychoeducation, and family or caregiver engagement when appropriate and with the participant's consent. Cultural, spiritual, and existential considerations are addressed according to individual preferences and within predefined intervention guidelines.

HERDA is delivered by trained pharmacists alongside standard psychiatric care. Participants assigned to the intervention group receive seven planned contacts over approximately four months, combining face-to-face sessions and telephone contacts. Participants assigned to the control group receive standard psychiatric care according to the study protocol.

This randomized controlled trial evaluates whether adding HERDA to standard psychiatric care improves medication adherence among outpatients with depression. The findings are intended to inform the development of evidence-based, culturally responsive pharmacist-led care for people receiving treatment for depression.

Detailed Description

Background and Intervention Development

HERDA (Holistic, Evidence-based, and cultuRally adapted Depression Adherence) is a pharmacist-led, complex intervention developed to address medication non-adherence among outpatients with depression in South Kalimantan, Indonesia. Its development incorporated evidence synthesis, theoretical integration, cultural adaptation, and a two-round modified Delphi consensus process involving relevant experts and representatives. The finalized HERDA model comprises 29 consensus-based intervention statements organized into 10 domains.

Intervention Framework and Core Components

HERDA integrates three core clinical components: Brief Counseling 5A, screening and a safety gate, and pharmaceutical care. The Transtheoretical Model (TTM) provides the behavioral framework for tailoring counseling to each participant's readiness to change.

A predefined suicide safety pathway supports the identification, assessment, and escalation of suicide-related safety concerns in accordance with the study's safety procedures. Culturally adapted psychoeducation, family or caregiver engagement, spiritual-cultural communication, and culturally adapted educational media provide contextual support. Integrated service delivery guides the implementation of these components within routine clinical care.

Intervention Delivery

The intervention is delivered by trained pharmacists who complete competency assessment before providing HERDA. Counseling is tailored to each participant's current TTM stage. Each intervention contact follows a structured sequence comprising assessment, identification or reassessment of the TTM stage, Brief Counseling 5A, stage-matched education, appropriate use of intervention materials, collaborative action planning, family or caregiver involvement when appropriate and with participant consent, and follow-up or reassessment.

Educational content may be repeated or adjusted according to participants' needs and changes in their stage of behavioral change. Such tailoring is conducted within predefined adaptation boundaries to preserve the intervention's core clinical components and support consistency across participants.

Intervention Schedule

Participants assigned to the intervention arm receive seven planned contacts over approximately four months. Face-to-face contacts occur at Visits 1, 3, 5, and 7, while telephone contacts occur at Visits 2, 4, and 6.

Visit 1 includes the baseline assessment and initial intervention contact, as specified in the study protocol. Visit 7 includes the final post-intervention assessment and the planned final intervention contact. HERDA is delivered alongside standard psychiatric care, which continues throughout the study period. The control group receives standard psychiatric care according to the study protocol.

Cultural Adaptation and Educational Materials

HERDA uses culturally adapted educational materials, including Banjar-language audiovisual education and electronic flipbooks. Cultural, spiritual, and existential considerations are incorporated according to participants' preferences and within predefined adaptation boundaries. These adaptations aim to improve the relevance and acceptability of counseling while maintaining the intervention's core clinical components and compatibility with evidence-based psychiatric care.

Family or caregiver engagement is considered when appropriate and is guided by participant consent. Cultural and spiritual perspectives are addressed respectfully and are intended to complement, rather than replace, appropriate clinical treatment.

Intervention Fidelity Monitoring and Process Evaluation

Intervention fidelity will be monitored throughout the HERDA intervention period as part of study quality assurance. Before intervention delivery, pharmacist counselors will undergo training and simulation to support standardized intervention delivery. Standardized pharmacist session logbooks, session checklists, supervision, and random internal audits will be used to document and monitor intervention implementation. Recorded indicators will include completion of scheduled intervention contacts, counseling duration, adherence to the HERDA protocol, delivery of applicable core counseling components, appropriate use of the Clinical Decision Matrix and Transtheoretical Model (TTM), use of educational materials when indicated, action planning, follow-up arrangements, patient understanding of key counseling messages, and session documentation.

Each applicable intervention component will be classified as delivered according to protocol, partially delivered, not delivered according to protocol, or not applicable. Safety-protocol compliance, protocol deviations, reasons for incomplete or modified sessions, and corrective actions, where applicable, will be documented separately. Periodic supervision and refresher training will be provided when needed to support consistent intervention delivery. Process evaluation data will be summarized descriptively to characterize intervention delivery and implementation throughout the study period. These monitoring procedures are intended to assess intervention implementation and are not measures of patient medication adherence or evidence of medication ingestion.

As a supplementary process evaluation, the acceptability and implementation of HERDA will also be explored after completion of the intervention through focus group discussions (FGDs) with pharmacist counselors, in-depth interviews with patients and family members, and a satisfaction questionnaire, as specified in the study procedures. Evaluation domains will include perceived benefits, satisfaction, experiences of receiving or delivering the intervention, implementation challenges, and recommendations for improvement. Qualitative data will be analyzed thematically, while questionnaire findings will be summarized descriptively. These findings will be used to characterize intervention acceptability and implementation and to inform interpretation of the study findings. They will be analyzed and interpreted separately from the randomized comparison of clinical and behavioral outcomes and will not constitute formal trial outcome measures.

Monitoring period: Throughout the intervention period, from V1 to V7 (Day 0 to Day 120).

Supplementary process evaluation period: After completion of the intervention, following the relevant participant visits and pharmacist intervention delivery.

Safety Procedures

Safety concerns identified during screening or follow-up are managed according to the predefined study safety procedures. Suicide-related concerns are addressed through the study's safety pathway, including escalation to appropriate clinical assessment and care when indicated. HERDA is intended to support medication adherence as part of ongoing psychiatric care and does not replace clinical assessment, prescribed treatment, or emergency care when required.

Study Objective

This randomized controlled trial evaluates whether adding the HERDA pharmacist-led, culturally adapted intervention to standard psychiatric care improves medication adherence among outpatients with depression compared with standard psychiatric care alone. The study is intended to contribute evidence on the implementation of structured, culturally responsive pharmaceutical care for people receiving treatment for depression in Indonesia.

Research Questions and Hypotheses

Primary research question:

Among adult outpatients with depression receiving oral antidepressant medication in South Kalimantan, Indonesia, does the HERDA pharmacist-led, culturally adapted intervention, compared with usual care, improve medication adherence at the final assessment (T4)?

Primary hypothesis:

Participants allocated to the HERDA intervention group will demonstrate better medication adherence at T4 than those receiving usual care, assessed using the Medication Adherence Rating Scale (MARS-5) and pill count.

Secondary research questions and hypotheses:

1. Do participants receiving the HERDA intervention demonstrate greater improvement in depressive symptoms at the final assessment (T4) than participants receiving usual care? It is hypothesized that the HERDA group will have lower PHQ-9 scores at T4 than the usual-care group.
2. Do participants receiving the HERDA intervention demonstrate greater reductions in personal stigma at T4 than participants receiving usual care? It is hypothesized that the HERDA group will have lower personal stigma scores at T4 than the usual-care group.
3. Does the HERDA intervention result in more favorable suicidal ideation outcomes at T4 than usual care? It is hypothesized that the HERDA group will demonstrate more favorable suicidal ideation outcomes than the usual-care group.
4. Do participants receiving the HERDA intervention demonstrate greater improvement in medication-related health behavior at the final assessment (T4) than participants receiving usual care? It is hypothesized that the participants in the HERDA group will demonstrate more favorable medication-related health behavior scores at T4 than participants in the usual-care group, as measured using a previously developed and validated medication-related health behavior questionnaire.

Additional blinding during research or analysis

The trial uses an assessor-blinded design. Individual participants are randomly allocated to the HERDA intervention or usual-care group using a computer-generated allocation list prepared by a research assistant who has no clinical role in the trial. Pharmacists delivering the intervention are aware of group allocation and are therefore not blinded. The research assistant serving as the blinded outcome assessor is unaware of participants' group allocation throughout outcome data collection. To minimize unintended influences, outcome assessments are conducted using standardized instruments and procedures. The blinded outcome assessor is instructed not to seek or disclose participants' group assignments. Any accidental unblinding or protocol deviations will be documented. Data analysis will follow the prespecified analysis plan, and the extent of analyst blinding will be reported according to the procedures actually implemented.

Arm Label: HERDA Intervention Group

Arm Type: Experimental

Arm Description: Participants receive the HERDA pharmacist-led, culturally adapted intervention in addition to standard psychiatric care. The intervention consists of seven planned contacts over approximately four months, combining face-to-face sessions and telephone contacts, delivered by trained pharmacists according to the study protocol.

Arm Label: Usual Care Group

Arm Type: No Intervention

Arm Description: Participants receive standard psychiatric care according to the study protocol, without the additional HERDA pharmacist-led intervention.

Arms	Interventions
Experimental: HERDA Intervention Group Participants receive the HERDA pharmacist-led, culturally adapted intervention in addition to standard psychiatric care. The intervention consists of seven planned contacts over approximately four months, combining face-to-face sessions and telephone contacts, delivered by trained pharmacists according to the study protocol.	**Behavioral: HERDA Pharmacist-Led Culturally Adapted Intervention** HERDA is a structured pharmacist-led, culturally adapted behavioral intervention designed to improve medication adherence among outpatients with depression. It integrates Brief Counseling 5A, the Transtheoretical Model (TTM) to tailor counseling to participants' readiness to change, pharmaceutical care, culturally adapted psychoeducation, and a predefined safety pathway for suicide-related concerns. The intervention is delivered by trained pharmacists through seven planned contacts over approximately four months, comprising face-to-face sessions and telephone contacts. Educational materials include Banjar-language audiovisual content and electronic flipbooks. Family or caregiver engagement is included when appropriate and with participant consent. HERDA is delivered in addition to standard psychiatric care and does not replace prescribed treatment or clinical assessment.

Arm to Intervention Mapping

	Behavioral: **HERDA Pharmacist-Led Culturally Adapted Intervention**
Experimental: HERDA Intervention Group	☑
No Intervention: Usual Care Group	

Arm/Group
Experimental: HERDA Intervention Group **Arm Description:** Participants receive the HERDA pharmacist-led, culturally adapted intervention in addition to standard psychiatric care. The intervention consists of seven planned contacts over approximately four months, combining face-to-face sessions and telephone contacts, delivered by trained pharmacists according to the study protocol.

Arm/Group
No Intervention: Usual Care Group **Arm Description:** Participants receive standard psychiatric care according to the study protocol, without the additional HERDA pharmacist-led intervention.

Intervention
Behavioral: HERDA Pharmacist-Led Culturally Adapted Intervention **Description:** HERDA is a structured pharmacist-led, culturally adapted behavioral intervention designed to improve medication adherence among outpatients with depression. It integrates Brief Counseling 5A, the Transtheoretical Model (TTM) to tailor counseling to participants' readiness to change, pharmaceutical care, culturally adapted psychoeducation, and a predefined safety pathway for suicide-related concerns. The intervention is delivered by trained pharmacists through seven planned contacts over approximately four months, comprising face-to-face sessions and telephone contacts. Educational materials include Banjar-language audiovisual content and electronic flipbooks. Family or caregiver engagement is included when appropriate and with participant consent. HERDA is delivered in addition to standard psychiatric care and does not replace prescribed treatment or clinical assessment.

Study Design

Model Description

This is a two-arm, parallel-group randomized controlled trial involving 72 adult outpatients with depressive disorders at RSJ Sambang Lihum, South Kalimantan, Indonesia. Participants are individually randomized in a 1:1 ratio to the HERDA intervention group or the usual-care control group, with randomization stratified by depression severity and sex. The intervention group receives the HERDA pharmacist-led, culturally adapted intervention in addition to usual psychiatric care, while the control group receives usual psychiatric care alone. The intervention comprises seven planned contacts over approximately four months, including face-to-face and telephone sessions. Outcomes are assessed at baseline and prespecified follow-up visits over the four-month study period. Outcome assessors are blinded to group allocation; intervention pharmacists are not blinded.

Sampling and Data Collection Procedures

The study population consists of adult outpatients with a clinical diagnosis of depressive disorder who receive care at RSJ Sambang Lihum, South Kalimantan, Indonesia. Eligible patients are informed about the study, and written informed consent is obtained before

enrolment and study-specific data collection. The planned sample size is 72 participants. Following enrolment, participants are individually allocated in a 1:1 ratio to either the HERDA intervention group or the usual-care control group using computer-generated stratified block randomization. The randomization is stratified by depression severity and sex. The allocation sequence is prepared by a research assistant without a clinical role in the trial.

At baseline, a research assistant who is blinded to group allocation collects data on participants' sociodemographic and clinical characteristics, medication adherence, depression severity, stigma, suicidal ideation, and lifestyle factors using standardized study procedures and instruments specified in the protocol. Follow-up assessments are conducted at the prespecified time points over the four-month follow-up period.

Sample Size

The initial sample size was calculated for comparing two independent proportions of medication adherence between the intervention and control groups. Based on the study by Pillai et al. (2021), the anticipated medication adherence proportions were 66.8% in the intervention group ($P_1 = 0.668$) and 31.1% in the control group ($P_2 = 0.311$). The sample size calculation used a two-sided significance level of 5% ($\alpha = 0.05$; $Z\alpha/2 = 1.96$) and a statistical power of 80% ($\beta = 0.20$; $Z\beta = 0.84$).

Using the formula for comparing two independent proportions, the estimated minimum sample size was approximately 30 participants per group, yielding 60 participants in total for the primary analysis. The recruitment target was set at 36 participants per group, resulting in a total planned sample of 72 participants, to allow for potential loss to follow-up during the four-month study period.

The unit of analysis is the individual participant. Participants will be individually randomized in a 1:1 ratio to either the HERDA intervention group or the usual-care control group. The planned sample size is equal across both groups, with 36 participants in each group. The target is to retain approximately 30 evaluable participants per group at the final assessment (T4). The planned recruitment target is 72 participants in total.

Participants and Eligibility Criteria

Participants and Eligibility Criteria

The study population comprises adult outpatients with a clinical diagnosis of depressive disorder who receive care at the study site and are prescribed oral antidepressant medication. Participants must meet all inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

1. Adults aged 18 years or older.

2. A clinical diagnosis of depressive disorder based on DSM-5 criteria, as documented in the medical record.
3. Currently prescribed oral antidepressant medication.
4. Able to understand study information and communicate in Bahasa Indonesia or Banjar.
5. Able to use an Android mobile phone.
6. Willing and able to participate in study procedures and provide written informed consent.

Exclusion Criteria

1. Organic brain disorders or intellectual disabilities that impair the ability to understand study information, provide informed consent, or participate in study procedures.
2. Severe comorbid conditions that may interfere with safe participation, including psychotic disorders, substance addiction, severe stroke, severe heart disease, severe diabetes-related complications, or other severe chronic conditions deemed unsuitable for participation by the treating physician.
3. Inability to understand the study materials or hearing impairment that prevents effective communication or completion of study assessments.
4. Any other condition that, according to the study protocol and clinical assessment, prevents safe participation in the intervention or completion of outcome assessments.

Eligible outpatients will be screened before enrollment. Written informed consent will be obtained before any study-specific procedures are performed.

Intervention Procedures

The HERDA intervention procedures comprise three integrated components:

1. TTM-Based Intervention Algorithm: A structured process for assessing behavioral readiness, identifying barriers, selecting counseling strategies, and adapting the intervention to the participant's current needs.
2. Educational Media Selection Matrix: An operational guide for selecting flipbooks, videos, reminder calendars, and additional educational materials according to the identified behavioral stage and barriers.
3. HERDA eCRF Documentation Form: A standardized electronic record for documenting assessments, intervention decisions, educational media delivered, participant responses, intervention fidelity, and follow-up plans.

Participants in the intervention group receive pharmacist-led brief counseling based on the 5A approach, supported by an electronic flipbook and culturally adapted audiovisual educational materials reflecting the language, values, and local context of the Banjar community.

The intervention is delivered by trained pharmacists through face-to-face and telephone contacts over four months. The planned pathway comprises seven principal visit or contact points (V1–V7), beginning with baseline assessment at T0 and ending with the final assessment at T4.

The educational materials cover depression and its symptoms, antidepressant treatment, medication adherence, management of adverse effects, family support, stigma, suicidality, relapse warning signs, and strategies for improving medication adherence and healthy behaviors.

The detailed content, sequence, duration, and delivery mode of each contact will follow the intervention manual and the actual trial procedures.

Arm

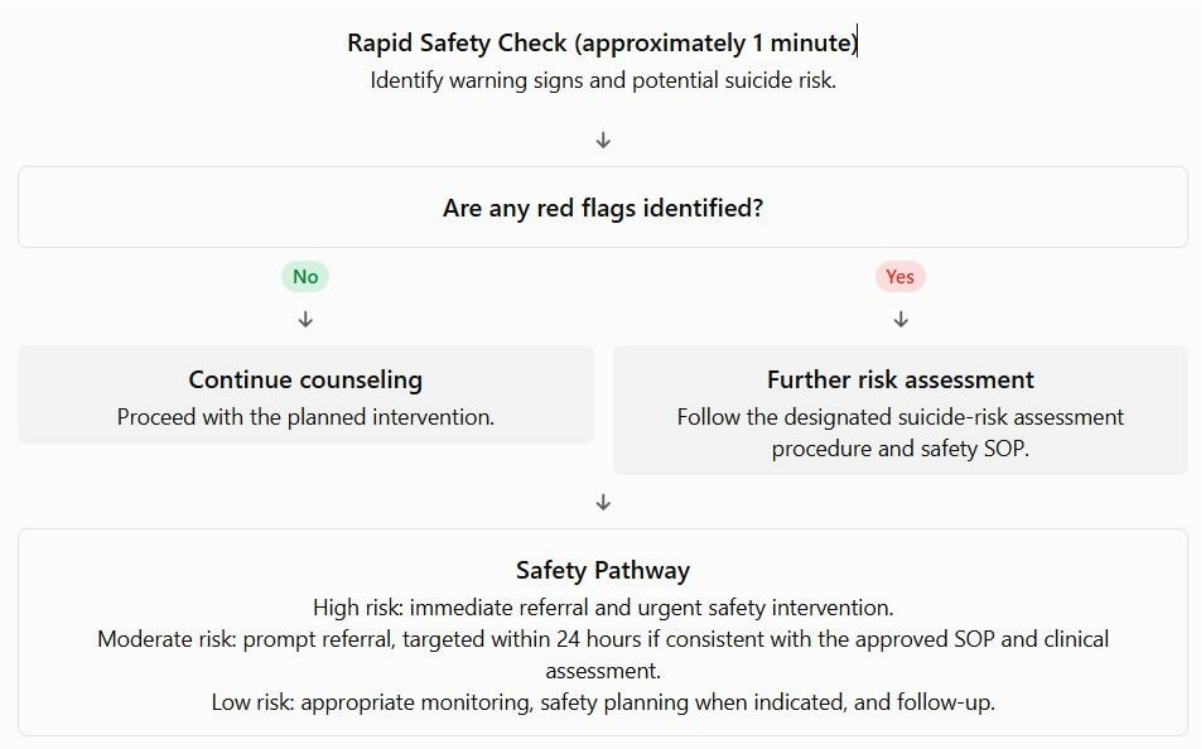
The HERDA intervention is delivered by trained pharmacists at RSJ Sambang Lihum over a four-month period through seven scheduled contacts. Face-to-face visits are conducted at V1 (day 0), V3 (day 30), V5 (day 60), and V7 (day 120), with a maximum planned duration of 30 minutes per visit. Telephone follow-up contacts are conducted at V2 (day 15), V4 (day 45), and V6 (day 90), each lasting no more than 15 minutes. The core HERDA counseling component is designed to take approximately 15 minutes per routine contact. At baseline, interim, and final assessment visits, additional time may be required to complete research outcome measurements, which are treated as separate assessment activities. Patient safety takes priority; if suicide risk or other urgent clinical concerns are identified, the consultation may be extended and the predefined safety and referral procedures are activated.

HERDA intervention is delivered using a focused-care approach. The core pharmacist counseling component is designed to be completed within approximately 15 minutes per routine contact. Baseline, interim, and final outcome assessments may require additional time and are conducted separately from the core counseling duration. Patient safety takes priority; when suicide risk or other urgent clinical concerns are identified, the consultation may be extended and the predefined safety and referral pathway is activated.

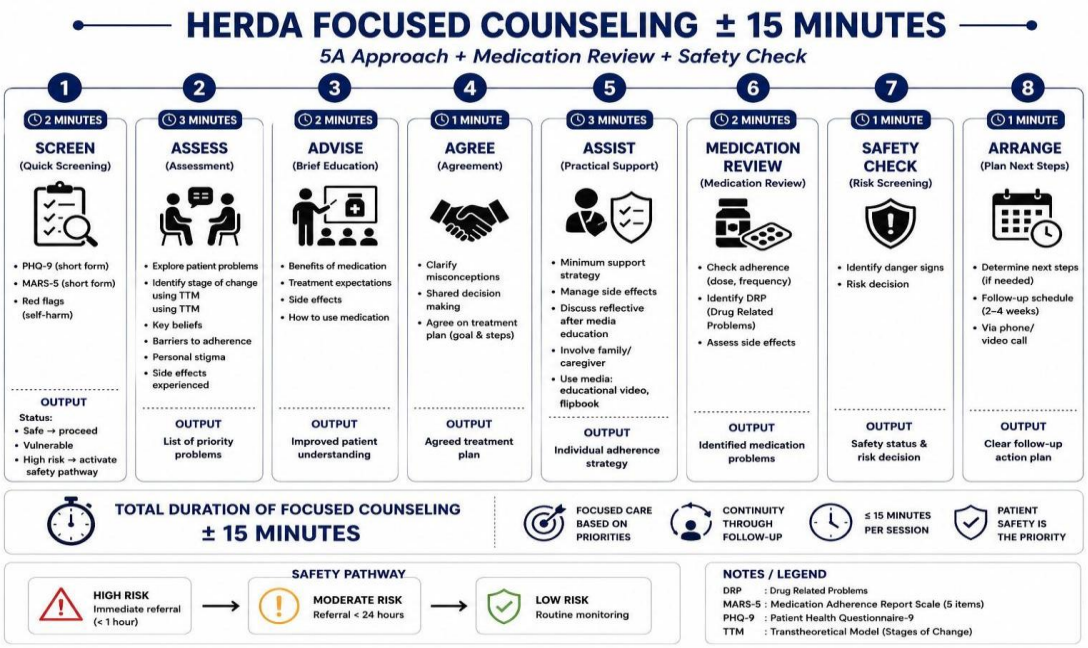


Suicide Safety Check and Escalation Pathway

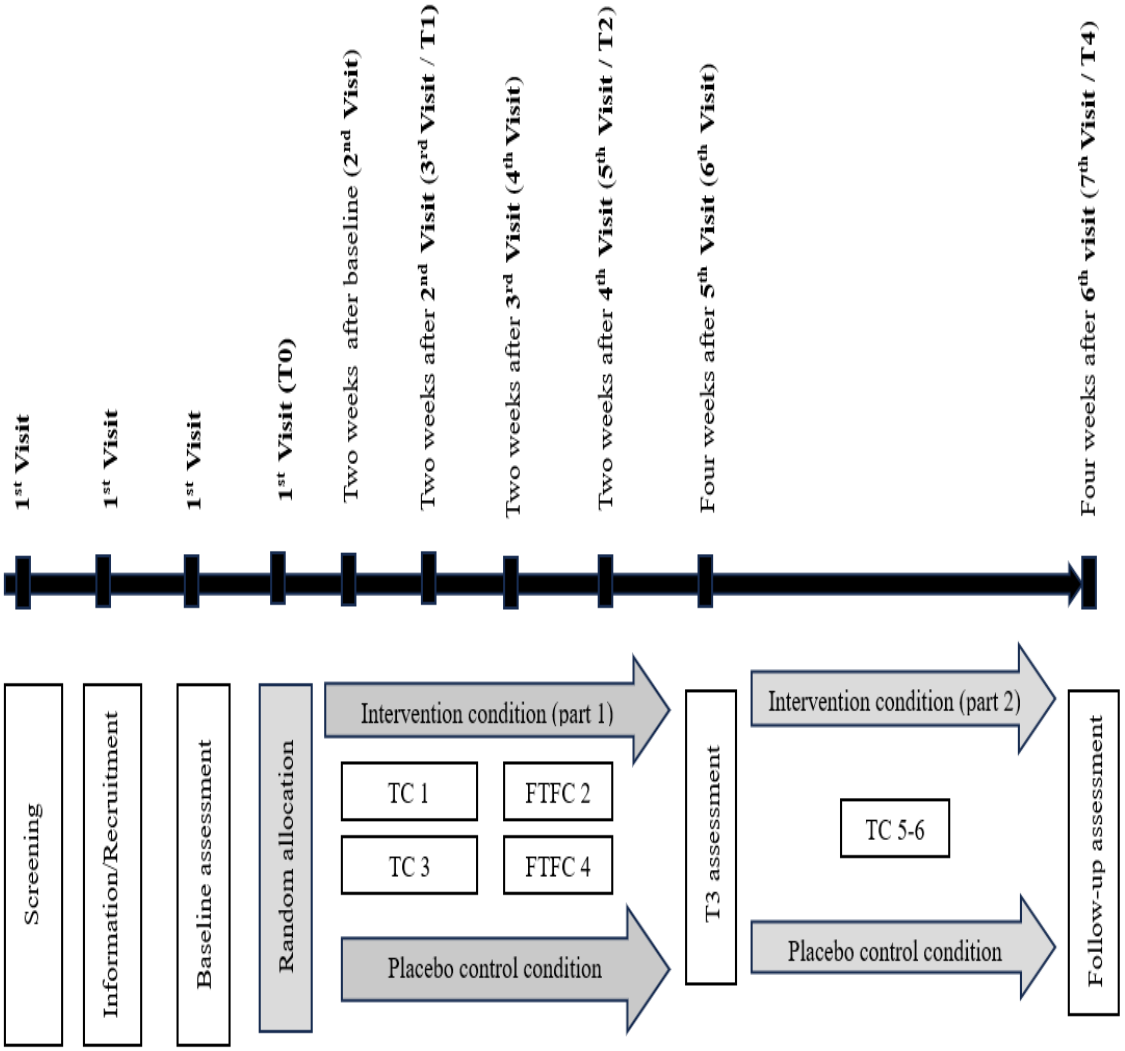
The approximately one-minute safety check is intended for rapid risk triage, not for conducting the full MINI suicide module. The MINI suicide module must be administered according to the instrument's procedures and the study's prespecified assessment schedule.



Important: If imminent suicide risk is suspected, do not delay urgent assessment or referral to complete the 15-minute counseling session. Risk classification and referral decisions must follow the approved clinical safety SOP; a one-minute check alone cannot establish that a participant is safe.



HERDA Intervention Schedule



Note: FTFC = Face-to-Face Counseling, accompanied by locally adapted educational videos reflecting the cultural wisdom of the Banjar people ("Urang Banjar") in the intervention group. The control group will receive the hospital's standard care. TC = Telephone Counseling.

Patient Data Collection: Demographic characteristics, history of depression, comorbidities, pill count, PHQ-9, MARS, SSSS, and MINI will be assessed at Visit 1 (baseline/Day 0), Visit 3, Visit 5, Visit 6, and Visit 7.

Figure 1. General Diagram of the Parallel Randomized Controlled Trial (RCT) Design in the HERDA Model.

HERDA Intervention Timeline

Visit	Day	Mode	Duration	HERDA / 5A Activities		Main Outputs
V1	0	Face-to-face	30 minutes	Baseline, safety assessment, identification of problems and preparation of individual counseling plan	Assess → Advise → Agree → Assist → Arrange Initial screening, TTM stage, holistic note, medication review, safety check, initial education, shared decision, action plan	Complete baseline; TTM stage; priority problems; adherence status; individual action plan; follow-up schedule
V2	15	Telephone	≤15 minutes	Early follow-up and plan enhancement	Assess → Advise → Assist → Arrange Review barriers, TTM stage, adherence, side effects, sampling support, reminders, and reinforcement	New barriers identified; strengthened adherence strategy; follow-up action plan
V3	30	Face-to-face	20–30 minutes	Evaluation T1 and intensification of intervention	Assess → Advise → Agree → Assist → Arrange MARS/pill count, safety check, medication review, action planning	T1 evaluation; adherence changes; stage changes; therapy; problems; updated action plan
V4	45	Telephone	≤15 minutes	Monitoring and reinforcement of behavior change	Assess → Assist → Arrange Review adherence, barriers, side effects, family support, follow-up plan	Reinforcement; barrier management strategy; follow-up plan
V5	60	Face-to-face	20–30 minutes	Evaluation T2 and maintenance strengthening	Assess → Advise → Agree → Assist → Arrange MARS/pill count, safety check, medication review, reinforcement	T2 evaluation; adherence changes; TTM stage changes; maintenance / updated action plan
V6	90	Telephone	≤15 minutes	Monitoring T3 and relapse prevention	Assess → Assist → Arrange Adherence check, barrier management, safety check if needed	Adherence maintained; early warning signs identified; prevention plan; follow-up schedule
V7	120	Face-to-face	30 minutes	Final assessment and maintenance planning	Assess → Advise → Agree → Assist → Arrange Comprehensive outcome finalization, safety assessment, final medication review, maintenance planning	T4/final outcome; adherence status; PHQ-9; stigma; safety status; maintenance plan; participant feedback

The intervention follows the Brief Counseling 5A framework (Assess, Advise, Agree, Assist, and Arrange), tailored to participants' needs and readiness to change using the Transtheoretical Model. V1 focuses on baseline assessment, safety screening, identification of medication-related and adherence problems, and development of an individual care plan. V2 provides early follow-up and reinforcement. V3 reviews interim outcomes and intensifies support as needed. V4 monitors adherence and reinforces behavior change. V5 evaluates progress and strengthens maintenance strategies. V6 monitors adherence and potential early warning signs of relapse. V7 includes final outcome assessment and development of a maintenance and relapse-prevention plan.

Medication adherence is assessed using the MARS-5 and pill count at the time points specified in the study protocol. Depressive symptoms, personal stigma, suicidal ideation, and Medication-related health behavior are assessed using the prespecified instruments and schedule. TTM stage and adherence barriers are reviewed during intervention contacts, while safety checks are conducted according to the protocol and whenever clinically indicated. Pharmacists delivering HERDA are aware of group allocation, whereas the research assistant responsible for outcome data collection remains blinded to allocation. Participants in the control group receive usual care. Recruitment, intervention delivery, outcome assessment, and follow-up are conducted according to the approved study protocol.

Supplementary Materials for the HERDA Intervention

A. Audiovisual Educational Videos

HERDA Video – Episode 1 Audiovisual Educational Material :
https://youtu.be/7jYAHx9hKuY?si=tL0hyfqrdLzq2Slt

HERDA Video – Episode 2 Audiovisual Educational Material :
https://youtu.be/BvbySg_L_Qo?si=tnWGpnKgiTMdDKHb

HERDA Video – Episode 3 Audiovisual Educational Material : https://youtu.be/be7D-kjvYeo?si=CqDi7alaPzKzSjxc

HERDA Video – Episode 4 Audiovisual Educational Material :
https://youtu.be/Hc6Ows4UrSE?si=hX6s1rgR1LLoZAZe

HERDA Video – Episode 5 Audiovisual Educational Material :
https://youtu.be/F494SFrB_y8?si=-CuAp_IEdZo5YUcw

HERDA Video – Episode 6 Audiovisual Educational Material :
https://youtu.be/7KbCi4acWqI?si=QanJHj027iOAtDkp

B. Educational Flipbooks

HERDA Flipbook 1: Depression Is Real Printed/Digital Educational Material
https://drive.google.com/file/d/1FH32aATMErxPazMYOp5_CzA2XRmwGWSb/view?usp=drive_link

HERDA Flipbook 2: Antidepressant Treatment, Side Effects, Drug Interactions, and Discontinuation Symptoms Printed/Digital Educational Material
https://drive.google.com/file/d/1zbN4qd0lHRbdH-gQ5WMc-NQFxZMiZCks/view?usp=drive_link

HERDA Flipbook 3: Adherence to Depression Treatment and Its Impact on Patient Recovery Printed/Digital Educational Material
https://drive.google.com/file/d/1XbgmLxwNQ8KCTOyvheUn51OlqnXBdsy4/view?usp=drive_link

HERDA Flipbook 4: The Role of Family, Success Stories of Depression Survivors, and Depression Relapse Management Printed/Digital Educational Material
https://drive.google.com/file/d/1gNfhLcRCTXLZMobyVAeEumpPVKHigdOp/view?usp=drive_link

HERDA Flipbook 5: The Burden of Depression, Stigma, and Suicide Crisis Management Guidelines Printed/Digital Educational Material https://drive.google.com/file/d/1J2FWykB3Gb86cCpU_8dmxpN_g3O-cbwo/view?usp=drive_link

HERDA Flipbook 6: Recovery and Hope – Practical Strategies Printed/Digital Educational Material https://drive.google.com/file/d/1kSQYsb9GktCDyc0giJHvMiaq1hYkrRT-/view?usp=drive_link

TTM-Guided Tailoring of the HERDA Intervention and Educational Materials

The HERDA intervention uses a stage-matched approach guided by the Transtheoretical Model (TTM). At baseline (T0), the intervention pharmacist assesses each participant's stage of change using the study-specific TTM assessment form, alongside medication adherence, depressive symptoms, personal stigma, medication-related problems, and relevant psychosocial, cultural, and spiritual factors. Clinical risk and the participant's dominant barriers to medication adherence are also assessed. The findings are documented in the HERDA electronic case report form (eCRF) and used to develop an individualized intervention plan.

The participant's TTM stage informs the selection of the counseling strategy and educational materials, including the HERDA electronic flipbook, educational videos, and educational calendar. Participants in precontemplation receive education aimed at increasing awareness of depression and the role of antidepressant treatment, addressing misconceptions, and reducing stigma. Participants in contemplation receive counseling focused on exploring ambivalence, discussing perceived benefits and barriers, and strengthening motivation to change. Participants in preparation receive support to establish realistic medication-taking goals, develop an individualized adherence plan, and implement practical strategies. Participants in action receive reinforcement of existing adherence behaviors, problem-solving support, and assistance in managing medication-related barriers. Participants in maintenance receive support to sustain adherence, manage potential setbacks, and develop relapse-prevention strategies.

At each scheduled intervention contact, the pharmacist reviews the participant's most recent TTM assessment, current medication-taking behavior, reported barriers, and response to previous counseling. Formal TTM reassessment is conducted at the protocol-specified assessment visits, while brief reviews during telephone contacts are used to monitor progress and identify emerging needs. The intervention is adjusted when the participant progresses to another stage, remains at the same stage, or regresses to an earlier stage. Progression prompts the use of strategies and materials appropriate to the new stage; remaining at the same stage prompts reinforcement and further exploration of barriers; and regression prompts renewed counseling tailored to the participant's current stage and needs.

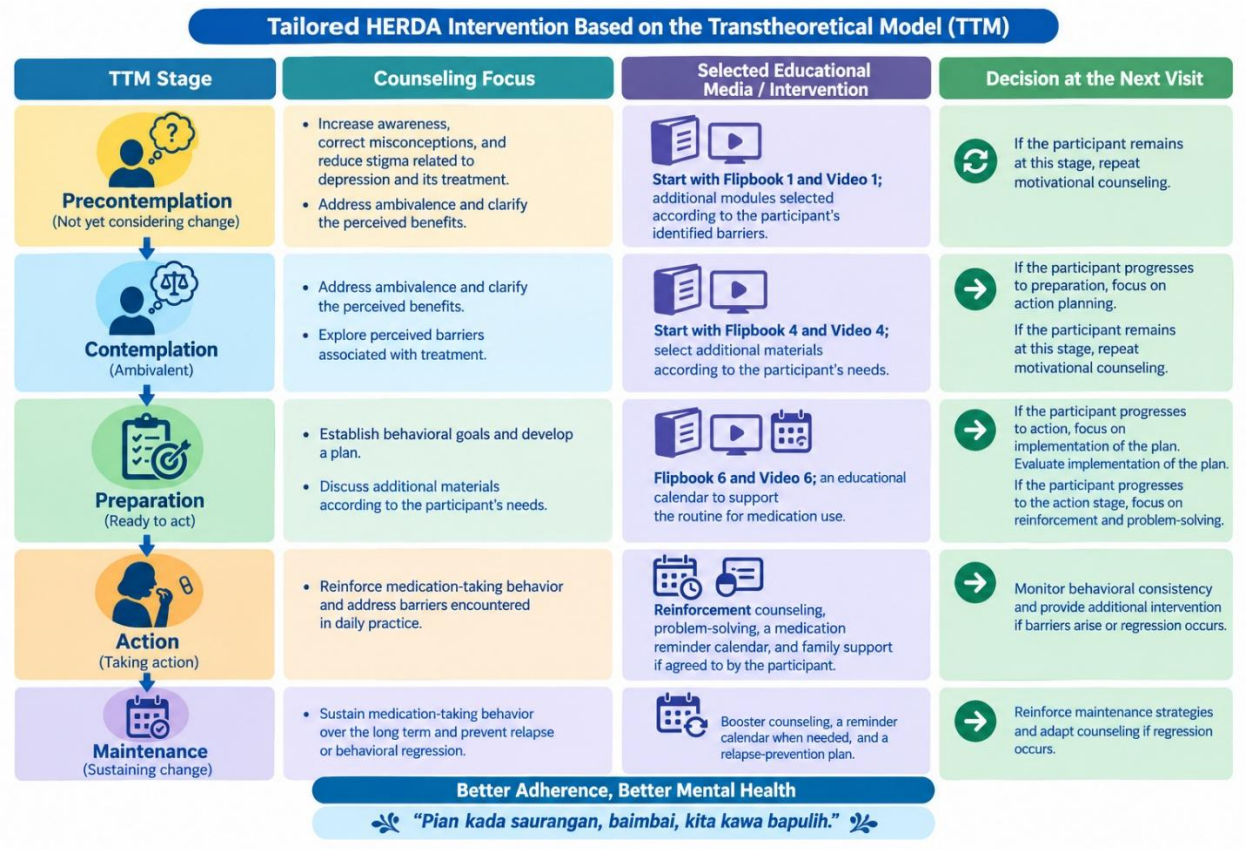
The pharmacist documents the TTM stage, identified barriers, selected counseling strategy, educational materials offered or delivered, participant response, agreed behavioral goals, and

follow-up plan in the HERDA eCRF. The actual delivery of each intervention component is recorded using the intervention log and fidelity checklist. Participants are not required to receive all six educational modules or videos; the materials delivered depend on the participant's current stage, individual needs, and the intervention algorithm. Participants in the usual-care control group receive usual care without the stage-matched HERDA intervention.

Clinical safety takes priority over educational tailoring. If a participant screens positive for suicidal ideation or other clinically significant risk, the predefined HERDA safety and referral procedures are activated. Educational material selection does not replace clinical assessment, appropriate referral, or urgent management when indicated.

Operational Matrix for Selecting Educational Media Based on the TTM

The following figure can be incorporated into the HERDA SOP or the intervention procedures appendix.



Integration of TTM Assessment into the Visit Schedule

The frequency and depth of TTM assessment should correspond to the purpose of each study visit.

Study Visit	TTM Assessment	Basis for Intervention Selection
V1 – T0 (Day 0)	Initial formal assessment	Baseline TTM stage, predominant barriers, medication-related problems, and clinical safety.
V2 (Day 15)	Brief monitoring assessment	Last documented TTM stage, response to the intervention, and current barriers.
V3 (Day 30)	Formal reassessment	Current TTM stage and evaluation of behavioral progress.
V4 (Day 45)	Brief monitoring assessment	Continuity of the behavioral plan, newly emerging barriers, and need for reinforcement.
V5 (Day 60)	Formal reassessment	Stage progression or regression, intervention needs, and maintenance strategies.
V6 (Day 90)	Brief confirmation assessment	Current behavioral status, barriers, reinforcement needs, and prevention of regression.
V7 (Day 120)	Final assessment	Final behavioral stage, reinforcement of medication adherence, and long-term maintenance planning.

Assessment of Treatment Behavior and Intervention Adaptation

The medication-related health behavior questionnaire will be administered at V1 (T0, Day 0), V3 (T1, Day 30), V5 (T2, Day 60), and V7 (T4, Day 120). At V2 (Day 15), V4 (Day 45), and V6 (Day 90), brief Transtheoretical Model (TTM)-guided monitoring assessments will be conducted to review participants' previously documented behavioral stages, identify current medication-related barriers, and guide individualized pharmacist counseling. These brief monitoring assessments will not involve administration of the full medication-related health behavior questionnaire. If a meaningful change in treatment behavior is identified, the pharmacist will reassess the participant's TTM stage according to the HERDA standard operating procedures (SOP). Assessment findings, counseling decisions, and relevant changes in behavioral stage will be documented in the HERDA electronic case report form (eCRF).

Control Arm/Standard Psychiatric Care/Standard Care

Description

Participants receive routine psychiatric care provided by the participating mental health service, including routine psychiatric consultation, prescribed antidepressant treatment, medication dispensing, and standard medication information according to usual practice. Participants do not receive the structured HERDA pharmacist-led intervention.

Primary Outcomes

The primary outcomes are:

1. Medication adherence measured using the five-item Medication Adherence Rating Scale (MARS-5).

Medication adherence to antidepressants will be assessed using the five-item Medication Adherence Rating Scale (MARS-5). Each item is scored from 1 (always) to 5 (never), with higher scores indicating better adherence. The total score is the sum of all five items, ranging from 5 to 25. Adherence will be classified as adherent (total score ≥23; coded as 2) or non-adherent (total score <23; coded as 1), according to the study's prespecified operational definition.

2. Medication adherence measured using pill count.

Medication adherence to antidepressants will be assessed by pill count. Adherence (%) will be calculated as [(tablets available for use during the assessment interval − tablets remaining at the end of the interval) / (prescribed tablets per day × number of days in the interval)] × 100%. Participants will be classified as adherent (80%–100%; coded 2) or non-adherent (<80%; coded 1), according to the study's prespecified criteria. Baseline pill count at V1 (Day 0) will document the initial medication supply. Adherence will be assessed over intervals ending at V3 (Day 30), V5 (Day 60), and V7 (Day 120). Dispensing records, early refills, and carryover tablets will be reconciled to account for available medication and prevent double-counting.

Secondary Outcomes

Secondary outcomes include:

1. Depressive symptom severity assessed using the Patient Health Questionnaire-9 (PHQ-9).

Depressive symptom severity will be assessed using the nine-item Patient Health Questionnaire (PHQ-9), which evaluates the frequency of nine depressive symptoms over the preceding two weeks, including loss of interest or pleasure, depressed mood, sleep disturbances, fatigue, appetite changes, feelings of worthlessness or guilt, concentration difficulties, psychomotor changes, and thoughts of death or self-harm. Each item is scored from 0 (not at all) to 3 (nearly every day), yielding a total score ranging from 0 to 27, with higher scores indicating greater depressive symptom severity. Scores will be interpreted as minimal or no depressive symptoms (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). The PHQ-9 will be administered at Visit 1 (T0, Day 0) and Visit 7 (T4, Day 120).

2. Self-stigma assessed using the Self-Stigma Scale–Short (SSS-S).

Self-stigma among patients with depression will be assessed using the nine-item Self-Stigma Scale–Short (SSS-S), as described by Wu et al. (2015). Each item is rated on a four-point Likert scale: 1 = strongly disagree, 2 = disagree, 3 = agree, and 4 = strongly agree. The total score ranges from 9 to 36, with higher scores indicating greater levels of self-stigma. Based on the study's prespecified classification, total scores will be categorized as minimal (9–15), mild (16–22), moderate (23–29), or severe (30–36). The SSS-S will be administered at Visit 1 (T0, Day 0) and Visit 7 (T4, Day 120) to assess self-stigma at baseline and at the end of the intervention period.

3. Suicide risk will be assessed using the suicidality module of the Mini-International

Neuropsychiatric Interview (MINI), ICD-10 version. The module comprises six yes/no items assessing suicidal thoughts and behaviors, including thoughts of death or wishing to be dead, thoughts of self-harm, suicidal ideation, suicide planning, and history of suicide attempts. The assessment covers the preceding month for the relevant current or recent symptoms and lifetime history for the suicide-attempt history item, according to the wording of the instrument.

Each response will be recorded separately and interpreted using the scoring algorithm specified for the MINI ICD-10 version used in the study. Suicide risk will be classified as low, moderate, or high according to the applicable combinations of responses, rather than by simply summing the number of affirmative responses. Assessments will be conducted at Visit 1 (T0, Day 0) and Visit 7 (T4, Day 120) to evaluate suicide risk at baseline and at the end of the intervention period.

The HERDA Suicide Reflex Pathway (SRP–HERDA) will be activated whenever a positive suicide-related safety signal or other concerning indication is identified during screening, counseling, follow-up, or outcome assessment. If moderate or high risk is identified, or if an acute safety concern arises at any time, routine counseling will be stopped and the participant will be promptly escalated to the responsible physician, psychiatrist, or designated mental health team in accordance with institutional procedures. For an acute safety concern, the participant will not be left alone while urgent clinical evaluation and appropriate protective measures are arranged. Family or trusted-support-person involvement will be considered in accordance with the participant's consent, immediate safety needs, confidentiality requirements, and institutional policy. Safety planning, referral, handover, and follow-up will be implemented as clinically appropriate and documented in the study records. The pharmacist's role is limited to initial recognition, safety questions within their training and scope of practice, escalation, referral coordination, and documentation; comprehensive risk assessment and clinical management will be undertaken by appropriately qualified healthcare professionals.

4. Medication-related health behavior, including relevant cognitive, affective, and behavioral domains, assessed using the study's medication-related behavior questionnaire.

Depression treatment-related knowledge, beliefs, and behaviors will be assessed using a study-specific 12-item questionnaire comprising three domains: cognitive (knowledge of depression, antidepressant treatment, risk factors, and lifestyle-related factors); affective (beliefs, attitudes, and willingness regarding antidepressant use and smoking-related risks); and behavioral (medication-carrying practices, dietary and smoking-related behavior, physical activity, and intention to discontinue antidepressants when symptoms improve). Each item will be scored as correct (+1) or incorrect (0) according to a predefined answer key, with negatively worded items scored accordingly. Domain-level findings and behavioral readiness will be interpreted according to the study's prespecified scoring criteria and Transtheoretical Model-based operational definitions. The questionnaire will be administered at V1 (T0, Day 0), V3 (T1, Day 30), V5 (T2, Day 60), and V7 (T4, Day 120).

Ethics and Registration Timing

The study has received ethics approval from the Research Ethics Committee of Sambang Lihum Mental Hospital, approval number 000.9/11562/RSJ-SAMLIH/2025, dated 15 July 2025, and Komisi Etik Penelitian Universitas Muhammadiyah Banjarmasin, approval number 660/UMB/KE/XII/2025, dated 16 December 2025.

Ethics Approval Status

Approved

Informed Consent

Written informed consent will be obtained from all eligible participants before enrollment.

Data Monitoring Committee

Yes

Sponsor

The Ministry of Higher Education, Science and Technology (KEMDIKTISAINTEK), Republic of Indonesia, through the Doctoral Dissertation Research Grant Scheme

Collaborator

Universitas Gadjah Mada – Faculty of Pharmacy

Universitas Muhammadiyah Banjarmasin– Faculty of Pharmacy

Statistical Analysis

All quantitative data will be analyzed using appropriate statistical methods according to the measurement scale, distribution, and timing of assessment. Statistical significance will be set at a two-sided p-value of less than 0.05. Effect estimates will be reported with 95% confidence intervals wherever applicable.

1. Instrument validity and reliability

Pearson's product–moment correlation will be used to assess item–total correlations when evaluating the validity of an eligible questionnaire, and Cronbach's alpha will be used to assess its internal consistency. These analyses will be conducted only for instruments requiring psychometric evaluation in the present study, such as a newly developed or adapted questionnaire, rather than automatically repeating validation for all established instruments. The criteria for acceptable item validity and internal consistency will be specified before analysis. For instruments previously developed and validated by other researchers, the original validation evidence and the applicability of the instruments to the study population will be documented.

2. Descriptive and preliminary analyses

Univariate analysis will summarize participants' sociodemographic and clinical characteristics and baseline outcome measures. Continuous variables will be presented as means and standard deviations when appropriate, or medians and interquartile ranges when distributions are skewed. Categorical variables will be summarized using frequencies and percentages. Data distributions will be examined using graphical methods, including histograms and Q–Q plots, and an appropriate normality test, such as the Shapiro–Wilk test, where relevant. Normality will be assessed for the relevant continuous outcomes or model residuals, rather than treating all study variables as normally distributed or non-normally distributed as a group.

3. Primary outcome: medication adherence

Medication adherence will be assessed using the Medication Adherence Rating Scale (MARS-5) and pill count at baseline and Month 4 (T4), according to the prespecified assessment schedule. The primary between-group analysis will compare medication adherence at T4 between the HERDA intervention and usual-care groups, adjusting for the corresponding baseline value. Analysis of covariance (ANCOVA) will be used for continuous outcomes when its assumptions are reasonably satisfied. An appropriate regression model will be considered if the outcome distribution or model assumptions do not support standard ANCOVA.

MARS-5 total scores and pill-count percentages will be analyzed as continuous outcomes if specified in the statistical analysis plan. In addition, medication adherence will be classified as adherent or non-adherent according to the prespecified thresholds. For MARS-5, scores below 23 will indicate non-adherence and scores of 23 or higher will indicate adherence. For pill count, adherence will be defined as 80%–100% of prescribed medication taken, while values below 80% will indicate non-adherence. Between-group differences in categorical adherence status at T4 will be assessed using an appropriate regression method, such as logistic regression adjusted for baseline adherence status, where feasible.

Between-group comparisons will assess differences in medication adherence between the HERDA intervention and usual-care groups from baseline to Month 4. Continuous MARS-5 scores and pill-count percentages will be analyzed using an appropriate baseline-adjusted between-group model, such as analysis of covariance (ANCOVA), provided the relevant model assumptions are satisfied. Changes in categorical adherence status (adherent versus non-adherent) will be summarized by group and assessment time. Between-group differences in adherence status at Month 4 will be analyzed using an appropriate categorical-data method, such as logistic regression adjusted for baseline adherence status, where feasible. Effect estimates will be reported with 95% confidence intervals. The analysis will follow the prespecified statistical analysis plan.

ANCOVA will be used to compare the Month 4 outcome between groups, adjusting for baseline MARS-5 score.

Pill-count calculation

The percentage of medication taken will be calculated using the following formula:

$$(\%) = \frac{\text{Number of tablets dispensed} - \text{Number of tablets remaining}}{\text{Prescribed number of tablets per day} \times \text{Total number of days supplied}} \times 100$$

The adherence categories will be defined as follows:

- **Adherent:** 80%–100%.
- **Non-adherent:** less than 80%.

Any pill-count percentage exceeding 100%, or any discrepancy in the number of tablets dispensed or returned, will be reviewed and handled according to a prespecified data-management rule rather than automatically classified as adherent.

4. Secondary outcomes

Secondary outcomes will include depressive symptoms measured using the Patient Health Questionnaire-9 (PHQ-9), personal stigma measured using the study-specified stigma instrument, suicidal ideation assessed using the specified MINI suicide module, and medication-related health behavior measured using the prespecified questionnaire. Where applicable, baseline-adjusted between-group analyses will be conducted at T4. Continuous outcomes will be analyzed using ANCOVA or an appropriate regression model, while categorical outcomes will be analyzed using suitable categorical-data methods. The direction of clinically favorable change will be interpreted according to the scoring rules of each instrument.

For exploratory within-group comparisons between baseline and follow-up, a paired-samples t-test may be used for continuous outcomes when its assumptions are satisfied. The Wilcoxon signed-rank test may be used when a paired non-parametric analysis is more appropriate. Unadjusted between-group comparisons may use an independent-samples t-test or the Mann–Whitney U test, as appropriate; however, these will not replace the prespecified baseline-adjusted primary analysis. Repeated measurements across multiple time points may be analyzed using a suitable repeated-measures or mixed-effects model when supported by the study design and data structure.

The MINI suicide module will be analyzed according to its prespecified categorical or clinical classification, rather than being subjected to a normality test as if it were a continuous score. The Kolmogorov–Smirnov test will not be applied indiscriminately to every instrument.

5. Analysis of repeated pill-count measurements

If pill-count adherence is measured at more than two time points, the Friedman test may be used for an exploratory within-group comparison of repeated measurements when the data and design are appropriate for this non-parametric test. If only baseline and Month 4 measurements are available, the Wilcoxon signed-rank test may be considered for an exploratory paired comparison. The Friedman test will not be used as a substitute for the primary between-group analysis of the randomized trial.

6. Graphical presentation

Boxplots may be used to display the distributions of continuous outcome measures across assessment times and treatment groups. Where appropriate, descriptive tables and plots will also present changes in categorical adherence status and other categorical outcomes. Graphical summaries will complement, rather than replace, the prespecified statistical analyses.

7. Qualitative analysis of intervention acceptability

Qualitative data from pharmacists delivering HERDA and from participating patients and family members will be analyzed thematically to explore intervention acceptability, perceived benefits, implementation challenges, and suggestions for improvement. The analysis will involve familiarization with the data, coding, development and review of themes, and interpretation of findings in relation to the implementation of HERDA. Qualitative findings will complement the quantitative results by providing insight into participants' and providers' experiences of the intervention.

Effect estimate

Between-group mean difference with 95% confidence interval and standardized effect size will be reported.

Missing data

Missing outcome data will be handled according to the prespecified statistical analysis plan.

Starting and Stopping Rules

Data collection for the HERDA randomized controlled trial began on 25 August 2026, following the required ethical approval and implementation of the study procedures. Any preliminary testing or training activities conducted before the trial will be treated as preparatory activities and will not be included in the main trial analysis unless explicitly specified in the study protocol.

Participant recruitment will continue until the planned sample of 72 participants has been enrolled, with 36 participants allocated to the HERDA intervention group and 36 to the usual-care control group. Recruitment will stop when the target sample size has been reached and all eligible participants available for enrolment have been assessed according to the prespecified eligibility criteria. Data collection and follow-up for participants already enrolled will continue according to the study schedule, even after recruitment has stopped.

Recruitment or data collection may be paused or terminated earlier if required by the responsible ethics committee, if significant safety concerns arise, or if unforeseen operational circumstances make continuation infeasible. Any early termination, changes to the recruitment target, or deviations from these rules will be documented, with the reasons reported transparently. No interim analysis of treatment effects will be used to determine when recruitment stops, unless otherwise specified in an approved protocol amendment.