Background and Rationale Statement: Antidepressants (AD) are among the most prescribed medications and are often initiated with the belief that pharmacotherapy will be short term, consistent with the timelines studied in clinical trials.[1,2] However, in practice, data show that two-thirds of users have taken ADs for at least two years, and one-quarter for over a decade.[1] Despite this, up to 30–50% of these individuals may no longer meet criteria for maintenance therapy.[3] In the absence of structured discontinuation protocols, ADs are frequently continued by default rather than clinical necessity, accumulating side effects and gradually eroding trust in psychiatric care.[4,5] Withdrawal symptoms, vague guidelines, and provider uncertainty have created a system where stopping AD is far harder than starting them.[3]

When patients attempt to discontinue, withdrawal symptoms are common and frequently severe. Rates of withdrawal symptoms average around 56%, with reports as high as 86%; nearly half of those affected describe their symptoms as severe.[3] Symptoms include dizziness, insomnia, agitation, anxiety, flu-like symptoms, and in some cases, even suicidality.[2] Even with gradual tapering these effects can persist for months or longer, particularly in individuals with long-term SSRI use, challenging the assumption that withdrawal is always short-lived and highlighting the gaps in understanding AD discontinuation.[2,3,4,5] These patterns underscore the critical need for better, evidence-based discontinuation protocols to support patients through this high-risk period.

Withdrawal symptoms align with the neurobiology of Selective Serotonin Reuptake Inhibitors (SSRIs): as the brain adapts to chronic serotonergic enhancement, abrupt reductions trigger sudden neurochemical shifts.[4] Given serotonin's complex role, it is unsurprising that discontinuation can lead to a range of distressing symptoms. These are frequently mistaken for relapse due to symptom overlap.[4,5] Most AD research has used tapering periods of four weeks or less, and guidelines are vague, with recommendations to simply "taper gradually," without offering specific protocols.[3] In the absence of clear, standardized approaches, many providers default to indefinite continuation, unsure how to safely and effectively deprescribe.[4]

Long-term continuation of AD is not without consequences. Unlike acute side effects, several SSRI-related adverse effects continue, or even worsen, with time. These include emotional blunting, diminished affect, and lasting sexual dysfunction.[2,5] Though often accepted when benefits outweigh risks, such effects can become increasingly disruptive over time, straining relationships, reducing quality of life, and undermining a person's sense of self.[6]

Without viable discontinuation strategies, continued treatment has become the default, leaving patients and providers with no end in sight.

This study directly addresses the lack of clear guidance on how to taper and discontinue ADs. It will assess the feasibility, acceptability, and preliminary clinical outcomes of a pharmacist-led tapering protocol. This approach, designed to provide clearer dose transitions and minimize withdrawal symptoms, will inform a future larger, adequately powered randomized controlled trial (RCT), and has the potential to serve as a model for safe AD discontinuation.

Study Design/Justification: This study proposes Structured Proportional Tapering (SPT), a protocol to address the need for safe and effective AD discontinuation. SPT uses 10% dose reductions of the current dose every two weeks, creating an exponential reduction. SSRIs exhibit a unique relationship between dose and serotonin transporter (SERT) occupancy, making even standard 4–6 week tapers prone to abrupt neurochemical shifts and withdrawal.[4] SPT mitigates this risk through small, consistent dose reductions that align with the nonlinear pharmacology of SSRIs. This offers a scalable, real-world alternative using commercially available liquid medications, though successful implementation still requires consistent monitoring, individualized support, and medication expertise.

Pharmacists are well-positioned to fill this gap, having demonstrated success in deprescribing and collaborative psychiatric care. In one study, pharmacist-managed depression treatment improved adherence and satisfaction.[7] Another study showed that pharmacist-led interventions improved discontinuation of inappropriate medications without increasing adverse events.[8] These findings support integrating pharmacists into structured care models, making a pharmacist-led SSRI tapering protocol a logical next step.

A pragmatic RCT is the most appropriate design for evaluating an AD discontinuation program intended for real-world implementation. Unlike explanatory trials, which assess efficacy under ideal and tightly controlled conditions, pragmatic trials are designed to evaluate the effectiveness, feasibility, and generalizability of interventions in routine clinical practice.[9] This approach is particularly well suited to the context of AD tapering, which is often highly individualized, variable in duration, and influenced by a wide range of patient- and provider-level factors. The complexity of this process makes it essential to test interventions in settings that reflect the diversity of real-world clinical care. This trial will allow for evaluation of the discontinuation program in actual practice environments, involving diverse patient

populations and clinical workflows. It will assess outcomes that matter to patients and providers, such as withdrawal burden, re-initiation of care, and sustained discontinuation. Moreover, this trial is designed to generate practice-relevant evidence laying the groundwork for a larger, fully powered randomized trial. The design will be informed by the Pragmatic Explanatory Continuum Indicator Summary-2 framework, ensuring alignment between the trial's objectives and its applicability to real-world decision-making.[10] Given the urgent need for scalable, patient-centered solutions to AD discontinuation, a pragmatic pilot trial is the most efficient and impactful approach to develop and test this model of care.

Specific Aims: **Aim 1 (Primary):** To evaluate the feasibility of SPT vs. Standard of Care (SOC) for SSRI discontinuation by assessing recruitment, retention, and survey completion rates. **Aim 2 (Primary):** To evaluate the acceptability of SPT vs. SOC for SSRI discontinuation by assessing adherence, patient satisfaction, and provider-perceived appropriateness. **Aim 3 (Secondary):** To describe trends in clinical and humanistic outcomes, including withdrawal symptom severity, quality of life, changes in disease symptom severity, and reinstatement of SSRI's across tapering approaches. The study will be considered feasible and acceptable if it exceeds the progression criteria listed in *Table 1*.

Innovation: This study introduces a pragmatic, scalable strategy for SSRI discontinuation. First, it integrates pharmacists as primary facilitators of the tapering process, addressing a longstanding care gap. Providers often lack the time, training, and resources to guide patients through complex AD tapers. Pharmacists, with expertise in pharmacotherapy, medication management, and patient education, are uniquely positioned to fill this gap. This is one of the first pragmatic trials to formally evaluate a pharmacist-led discontinuation protocol in outpatient psychiatric care. Second, the study evaluates SPT, a novel approach offering a replicable model addressing the limitations of poorly tolerated tapers. Third, the study employs Ecological Momentary Assessment (EMA) via secure text prompts to collect real-time symptom data, allowing for responsive, patient-driven taper adjustments and minimizing recall bias. These innovations are evaluated through a pragmatic trial design that embraces the complexity of real-world care, including variability in patient characteristics and clinical workflows.

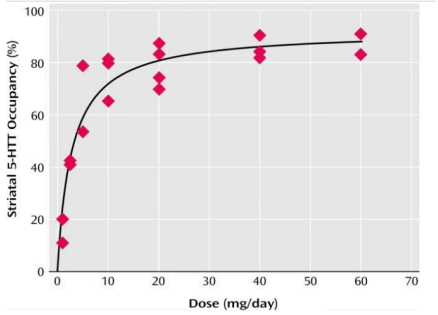
Study Significance: While the clinical and pharmacologic challenges of AD discontinuation are well recognized, this study addresses what remains underexplored: a scalable solution to AD discontinuation. If successful, it could further expand the role of pharmacists in psychiatry,

demonstrating their ability to lead patient-centered tapers, incorporate real-time symptom monitoring, and improve outcomes. Beyond ADs, this model offers a replicable approach for neurobiologically informed deprescribing. In doing so, it lays the groundwork for broader trials, guideline reform, and a shift toward structured discontinuation as a standard part of care.

Hypothesis: Structured Proportional Tapering (SPT) involving 10% dose reductions every two weeks, is a feasible and acceptable approach for SSRI discontinuation.

Literature Review and Justification: Although the challenges of AD discontinuation are well documented, limited attention has been given to tapering strategies that reflect the underlying pharmacology of SSRIs. Positron Emission Tomography studies show that SERT occupancy follows a hyperbolic curve, with small reductions at low doses causing disproportionately large drops.[4,11] For example, reducing a dose from 40 mg to 20 mg may only slightly decrease SERT occupancy, while tapering from 10 mg to 5 mg could result in a 30 percent drop or more.[4] As shown in *Figure 1*, the most abrupt shifts occur at the lowest doses.[11] These sudden changes can destabilize mood and cognition, increasing the risk of withdrawal symptoms or misdiagnosed relapse.[4]

Figure 1: Relationship between SERT occupancy and citalopram dose



Observational data supports the need for tapering strategies that account for this pharmacology. In the Netherlands, hyperbolic "tapering strips" have led to successful self discontinuation in 71% of patients, most of whom had previously failed.[12] While promising, these methods are difficult to scale due to compounding requirements and logistical complexity.

Standard tapers also routinely fail in practice. In a randomized trial, only 6% of long-term AD users successfully discontinued after receiving a provider-directed tapering plan, no better than usual care, highlighting that conventional approaches are largely ineffective.[13]

Unlike models that require adjusting tapering percentages over time, SPT applies consistent proportional reductions throughout. This approach may better accommodate individual variability in withdrawal sensitivity, including symptoms that emerge early in the taper, and offers a simplified structure for both patients and providers.

Taken together, these findings suggest that structured, gradual, and individualized tapering, especially at lower doses, is essential to minimizing withdrawal symptoms and preventing misdiagnosed relapse. While hyperbolic models may offer the most precise

pharmacologic fit, their complexity limits adoption. SPT provides an alternative that retains the logic of smaller dose reductions as patients near zero, while remaining feasible in usual care.
Methods: This study is a pharmacist-led pilot pragmatic RCT evaluating the feasibility and acceptability of a SPT protocol vs. SOC. The SPT arm will taper by 10% of the previous dose every two weeks using liquid formulations for precise dosing. Participants are not expected to fully discontinue within the 52-week follow-up and may continue tapering thereafter. The SOC group will follow a traditional tapering schedule per existing clinical guidelines and research protocols, involving 50% dose reductions every two weeks with full discontinuation by week 6.[4] If participants in the SOC group are unable to discontinue by week 6 or if withdrawal is reported as severe as determined by the provider's clinical judgment, these participants are eligible to roll over to the SPT protocol, ensuring patient safety and ethical integrity.

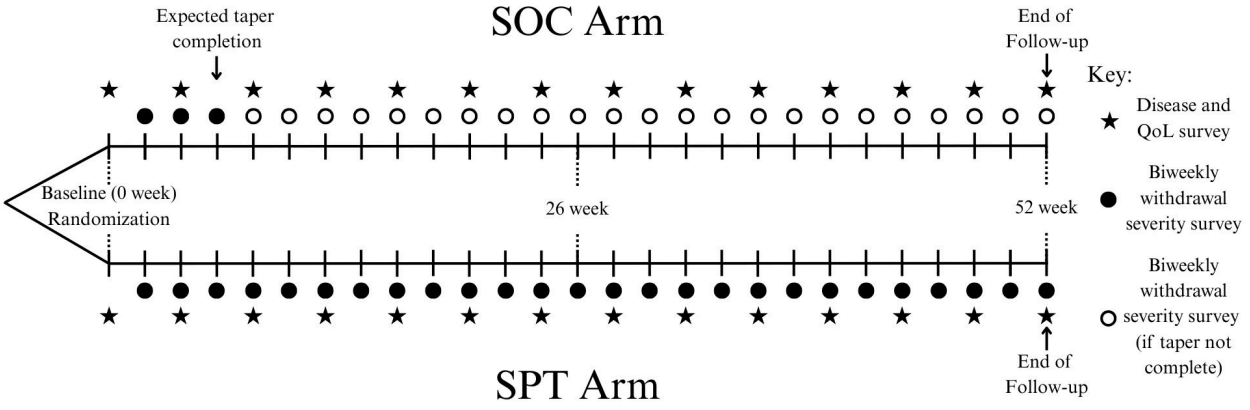
Recruitment will occur over a six-month period through referral from providers within the health system. Eligible patients will be consented, screened, and enrolled by the study team. Participants will then be randomized 1:1 to SPT or SOC. Randomization will be stratified based on duration of SSRI use (>5 or ≤5 years), as duration on SSRI is one of the greatest risk factors for withdrawal severity.[3] The follow-up period will be 52 weeks.

The approach is pharmacist-led, with psychiatric pharmacy residents implementing the tapering regimens. Dosing adjustments will be supported by psychiatric pharmacy residents in collaboration with providers. Clinic visits will continue per usual care. Pharmacy residents will prepare individualized tapering schedules based on participant-specific doses and formulations. In the SPT group, 10% dose reductions will require use of liquid formulations, as commercially available tablets do not support such fine titration. Syringes of 10 mL, 1 mL, and 0.1 mL will be provided alongside detailed instructions to ensure accurate measurement. Given the complexity of these reductions, pharmacy residents will also educate participants on drawing up and administering doses. In the SOC group, 50% dose reductions will be implemented using solid oral dosage forms and standard approximations (e.g., tablet splitting), consistent with routine clinical practice. No liquid formulations will be used in the SOC arm.

Data will be collected directly from participants, providers, and EHRs. EHRs will be used to determine patient adherence to the tapering regimen. Surveys will be used to assess various outcomes from both providers and participants. Participants will receive compensation for survey completion, with larger incentives for longer assessments. Surveys will be administered to

participants via text-messaging system Mosio, which is a Health Insurance Portability and Accountability Act compliant software designed to implement EMA by sending participants surveys directly for convenient completion. It is designed to be used with clinical trials and has direct integration with Research Electronic Data Capture (REDCap) for data storing. REDCap is a secure application that can collect and manage databases, which will be used to store all data in this study.

Figure 2: Participant Timeline



Sample size and power calculation: This pilot trial is designed to evaluate the feasibility and acceptability of a pharmacist-led AD discontinuation program, rather than to test for statistically significant differences in clinical outcomes. A total sample size of 60 participants (30 per group) aligns with pilot study guidelines and will allow for the assessment of key implementation metrics, including recruitment, retention, protocol fidelity, and adherence.[14] In addition, it will provide preliminary estimates of the proportion of patients achieving dose reduction, which can inform power calculations for a future, fully powered RCT. These estimates will also help assess the variability and potential effect size of the intervention in routine clinical practice.

The primary exploratory outcome for informing a future RCT is the proportion of patients who achieve a clinically meaningful dose reduction. For example, if the pilot reveals that 75% of patients in the intervention arm achieve dose reduction compared to 40% in the usual care arm, this would represent an absolute difference of 35 percentage points. Assuming a two-sided test with $\alpha = 0.05$ and 80% power, this effect size would require approximately 40 participants per group in a future trial. A more conservative scenario (e.g., 65% vs. 45%) would require closer to 95 per group. These projections will be refined based on the data generated from the pilot, which will serve as the foundation for designing an adequately powered trial to test the effectiveness of the intervention.

Inclusion and exclusion criteria: Inclusion criteria: adults aged 18–65 years currently prescribed an SSRI for >1 year; SSRI must be available in liquid form (citalopram, escitalopram, fluoxetine, paroxetine, or sertraline). Exclusion criteria: current psychiatric hospitalization (including detox) or acute suicidality; ongoing substance use disorder; significant cognitive or language barriers interfering with consent or survey participation; lack of access to a text-capable device; physical impairments (e.g., vision or dexterity) limiting ability to self-administer liquid doses; concurrent use of multiple serotonergic ADs (including during cross-tapering).

Table 1: Outcomes, Measurement Tools, Progression Criteria, and Assessment Schedule

Outcome	Area	Measurement	Criteria	Assesment Timeline
Primary Outcomes				
Recruitment	Quality	# Participants Enrolled	≥ 60	Ongoing through recruitment
Retention	Quality	# Completed / # Enrolled	≥ 80%	End of follow-up
Survey Completion	Quality	# Surveys Completed / # Given	≥ 70%	Throughout
Adherence	Quality	# Adherent / # Enrolled	≥ 75%	Throughout
Patient Acceptability	Quality	Mean CSQ-8 Scores & OEI	≥ 25	Cessation / End of follow-up
Provider Acceptability	Quality	Mean AIM, IAM, and FIM Scores & OEI	≥ 4	Cessation / End of follow-up
Secondary Outcomes				
Withdrawal Symptoms	Clinical	DESS	N/A	Every 2 weeks during taper
Withdrawal Burden	Humanistic	Likert	N/A	Every 2 weeks during taper
Quality of Life	Humanistic	WHO-5	N/A	Baseline + every 3 months
Dose Reduction	Clinical	# Acheiving ≥75% reduction from baseline	N/A	End of taper or follow-up
SSRI Reinstatement	Clinical	# Increasing dose ≥30% from current	N/A	Ongoing; recorded in EHR
Change in Disease Severity	Clinical	PHQ-9 & GAD-7	N/A	Baseline + every 3 months

CSQ-8 = Client Satisfaction Questionnaire-8; OEI = Open-Ended Interview; AIM = Acceptability of Intervention Measure; IAM = Intervention Appropriateness Measure; FIM = Feasibility of Intervention Measure; DESS = Discontinuation-Emergent Signs and Symptoms; Likert = 7-point scale assessing daily withdrawal burden (1 = not at all, 2 = very little, 3 = a little, 4 = some, 5 = bearable, 6 = a lot, 7 = very much); WHO-5 = World Health Organization–Five Well-Being Index; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7

Primary outcomes: **Feasibility:** recruitment (proportion of referred participants enrolled); retention (proportion completing follow-up); survey completion (proportion of scheduled surveys completed). **Acceptability:** adherence, defined as strictly following the assigned tapering regimen for the duration of follow-up, measured via EHR; patient-reported satisfaction, measured via CSQ-8; provider-rated acceptability, appropriateness, and feasibility, assessed using AIM, IAM, and FIM (both CSQ-8 and AIM, IAM, and FIM are measures with high

structural validity and reliability)[15,16]; open-ended interviews with patients and providers will explore barriers to adherence and the contextual relevance of the intervention, and will assess the conceptual adequacy and equivalence of all instruments across diverse demographics.

Secondary outcomes: Withdrawal symptoms, measured using the DESS checklist and a 7-point Likert scale assessing daily withdrawal burden, quality of life (WHO-5); dose reduction (≥75% from baseline); SSRI dose reinstatement: used to describe instances where patients experience a clinically meaningful increase in antidepressant dose following taper initiation (currently there is no standard or validated definition for this variable in the context of antidepressant discontinuation, as such, this will be defined as a ≥30% dose increase); change in disease severity (PHQ-9 or GAD-7).

Statistical Analysis: Frequency and percentage will be calculated for recruitment, retention, survey completion, adherence rates. Likert-scale responses will be analyzed as ordinal variables using appropriate summary statistics (e.g., medians, interquartile ranges) and graphical displays (e.g., stacked bar charts) to describe feasibility and acceptability outcomes. To compare responses across treatment groups, non-parametric tests such as the Wilcoxon rank-sum test will be used. For within-group comparisons (e.g., pre- vs. post-intervention), the Wilcoxon signed-rank test will be employed. Exploratory analyses will primarily serve to visualize symptom trajectories using mixed effects modeling and Kaplan-Meier survival analysis. The mixed effects model will assess quality of life and withdrawal symptom severity over time, change in disease severity from baseline. This accounts for repeated measures, individual variability, and missing data typical of longitudinal designs. Kaplan-Meier curves will estimate time to SSRI dose relapse. Sensitivity analyses will assess partial adherence to protocol, defined as staying within a 2 week, 4 week, and 6 week margins of their assigned tapering schedule. Subgroup analyses will include age (18-34, 35-49, and 50-65 years), sex, specific SSRI used, and duration of SSRI (1-3, 3-5, 5-10, 10+ years).

Budget Allocation: Participant compensation ($3,420) will be based on survey completion, with differing amounts for each survey completed. Assuming all 60 participants do not complete taper, there will be 26 biweekly withdrawal surveys at $1/survey ($1,560). All 60 participants will complete 13 longer surveys at baseline and every month at $2/survey ($1,560). All 60 participants will complete a satisfaction survey at completion of taper or end of follow up at $5/survey ($300). The Primary Investigator (PI) will receive $8,000, representing 10% effort for

study oversight, supervision of research assistant, and manuscript preparation. A research assistant (RA) will be employed at $16/hour for 12 hours per week over two years ($19,968), and will manage recruitment, provider communication, survey distribution, and data tracking. A statistician ($4,000) will be contracted to support data analysis of primary and secondary outcomes. Mosio will support survey delivery at $42/month for 18 months ($756). REDCap will be used for the duration of the study at $200/year for 2 years ($400). Travel funds ($5,956) are allocated for dissemination at professional conferences, including poster printing, conference registration fees, and open access journal publication. Indirect costs are budgeted at 15% ($7,500) to account for miscellaneous costs such as lab infrastructure and safety and compliance.

Table 2: Budget Allocation

Item	Cost
Participant Compensation	$3,420
Primary Investegator	$8,000
Research Assistant	$19,968
Data Analysis	$4,000
Mosio Survey Platform	$756
REDCap	$400
Travel	$5,956
Indirect Costs	$7,500
Total	$50,000

Limitations: This pilot study is designed to assess feasibility and acceptability, not efficacy. With 60 participants and no formal power calculation for clinical outcomes, it cannot determine whether SPT is more effective than SOC in reducing withdrawal symptoms or relapse. The complexity of the intervention may limit scalability, as SPT requires liquid formulations and 10% dose reductions, which may be impractical for patients without pharmacist support. Additionally, frequent biweekly surveys, particularly in the SPT arm, could contribute to survey fatigue and affect data completeness. Participants and providers are unblinded to tapering assignments, introducing potential expectancy and reporting bias. Although EMA reduces recall bias, the study still relies heavily on self-reported outcomes. Generalizability is limited by exclusion criteria that omit patients with acute suicidality, substance use disorders, non-liquid SSRIs, or alternative ADs. Recruitment via provider referral may also introduce selection bias by favoring patients perceived as better tapering candidates. Lastly, while SPT is guided by hyperbolic tapering principles, fixed 10% reductions may still be too rapid at lower doses for some individuals, particularly those more sensitive to withdrawal effects.

Study timeline: During study set up all protocols will be finalized and Mosio survey administration tool and REDCap data system will be set up. Institutional Review Board (IRB) will be submitted initially to ensure ample time for approval before recruitment. Subject recruitment and enrollment period will be 6 months to ensure enough time for providers to be

aware of the study and identify patients that would be suitable for SSRI tapering. After participants are referred, the participants will be consented and enrolled in the study, then randomized to a protocol. Once randomized, the providers will initiate the tapering protocol for the designated follow up time. Then data analysis will take place to analyze all outcomes. The PI and RA will write the manuscript for the study so the results can be disseminated.

Figure 3: Study Timeline

	Month																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Study set up																								
IRB Approval																								
Recruitment and enrollment																								
Randomization and follow up																								
Data Analysis																								
Manuscript writing																								

Study Feasibility: This pragmatic pilot trial is highly feasible within the healthcare setting, supported by established infrastructure, multidisciplinary expertise, and robust pharmacist commitment. Psychiatric pharmacy residents, trained in SSRI discontinuation and in differentiating relapse from withdrawal symptoms, will guide individualized protocol adjustments; relapse involves return of original symptoms while withdrawal symptoms involve new or atypical symptoms. Preliminary patient and provider feedback has informed the study design, indicating strong support for a pharmacist-led intervention. Real-time symptom reporting via EMA text prompts and participant incentives will further support survey response rates and patient engagement. Ongoing communication, symptom-responsive tapering, and availability of pharmacists will promote trust and continued participation. Advanced pharmacy practice experience students, under supervision, will support continued patient communication and follow-up, enhancing responsiveness and continuity of care. The multidisciplinary research team, comprising experts in clinical pharmacy, psychiatric care, and pragmatic trial design, ensures proficient trial execution and adaptability within existing clinical infrastructure, reinforcing ease of integration.

Future Impact: The impact of this trial will be to inform the design and sample size of future RCTs to test the efficacy of SPT compared with SOC. It also lays the foundation for developing SPT protocols for other high-burden drug classes, including benzodiazepines, stimulants, and sedatives, in pharmacist-led clinics that prioritize individualized, safe tapering strategies.

If successful, this study could shift clinical norms around discontinuation. Rather than viewing it as risky or unpredictable, SPT may offer a structured, evidence-based approach that health care professionals can implement confidently. Integrating EMA into routine care will demonstrate how digital symptom tracking can support timely decision-making during tapers.

Dissemination Plan: The dissemination plan includes presenting findings within the healthcare system and at national conferences such as American College of Clinical Pharmacy (ACCP), the American Psychiatric Association (APA), the American Pharmacists Association (APhA), and the American Society of Health-System Pharmacists (ASHP). The SPT protocol and findings will be published in peer-reviewed journals, such as *Journal of the American Medical Association Psychiatry*, *The Lancet Psychiatry*, or the *Journal of the American Pharmacists Association*.

In addition to traditional dissemination, access will also be provided to the tapering protocol and accompanying tools to support replication and adaptation in similar outpatient settings. Sharing these materials can help extend the study's impact beyond publication and enable other clinics to implement structured tapering approaches in real-world workflows.

Justification for Human Subject Involvement: This study will be conducted in compliance with all applicable federal regulations and institutional policies governing human subject research. All required safety and adverse reporting will be conducted in accordance with policies and procedures of the local IRB and Human Subjects Research Protection Program. Any unanticipated problems involving risk to participants will be promptly reported per regulatory requirements.

Recruitment and Informed Consent Process: Subjects will be recruited via referral from providers who determine readiness for tapering. All providers at the mental health clinic will be made aware of the study through different communication platforms such as email and recruitment brochures. Posters will also be put up around the mental health clinic to raise awareness of the study. This will occur during the subject recruitment period in order to maximize participation from providers in the clinic. All participants will be informed through explanations both verbal and written about the study and asked to provide written consent prior to any study procedures.

Data Integrity Management: Data will be stored in REDCap. To protect participant identity, Patient identifiable information and Patient health information will be stored in a

password-protected file in a secure research database only available to the research team. Each participant will be assigned a unique study identifier which will be used to collect all data collection and analyses to de-identify records. A master linking log containing names and corresponding identifiers will be maintained in a separate secure password protected file with access limited to authorized study personnel.

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