RESEARCH PROPOSAL

A Multicenter Clinic-Based Open-Label Observational Study of Patient-Directed Transdermal Flumazenil for the Treatment of Benzodiazepine-Induced Neurological Dysfunction and Post-Acute Withdrawal Syndrome (BIND/PAWS): A Flexible Dose-Escalation Protocol for Home-Based Management

Protocol Version: 1.0 — First Draft

Status: Draft for Review

Suitable for multicenter adoption — clinic-based study

1. Background and Rationale

Benzodiazepines are among the most widely prescribed medications worldwide, used for anxiety, insomnia, seizure disorders, and muscle relaxation. While effective in the short term, long-term use frequently leads to physiological dependence. A significant subset of patients — estimated at 10 to 25% of chronic users — continue to experience debilitating symptoms long after discontinuation, a condition variously referred to as Post-Acute Withdrawal Syndrome (PAWS) or Benzodiazepine-Induced Neurological Dysfunction (BIND). The distinction between these two terms remains unsettled in the literature; BIND has been proposed to better reflect the neurological nature of the injury rather than framing it purely as a withdrawal phenomenon. For the purposes of this proposal, both terms are used interchangeably to describe the same clinical reality.

The symptoms of PAWS/BIND are wide-ranging and can be profoundly disabling, including cognitive impairment, anxiety, insomnia, sensory disturbances, muscle pain, depersonalization, and an inability to perform basic daily functions. Duration varies enormously — from weeks to many years — and severity ranges from mild inconvenience to complete incapacitation requiring around-the-clock care. Critically, the vast majority of these patients acquired their dependence iatrogenically, meaning through a legitimate prescription, and do not fit the profile of recreational drug users or addicts. This distinction matters clinically, ethically, and in terms of study design.

Flumazenil, a GABA-A receptor antagonist, has been known since the early 1990s to offer relief from protracted benzodiazepine withdrawal symptoms. Multiple studies and case reports have demonstrated its efficacy. However, despite decades of evidence, no standardized treatment protocol exists. Each clinic operates with its own approach. The overwhelming majority of published protocols rely on intravenous or subcutaneous infusion, which require hospital or clinic settings, continuous medical supervision, significant cost, and considerable burden on the patient in terms of travel and time. Furthermore, and most critically, every major study in this field has acknowledged the same fundamental limitation: the treatment window is too short. Symptoms frequently return after the infusion period ends, and there is no established mechanism to continue treatment affordably and accessibly over the weeks or months that the condition may demand.

A parallel field offers an important precedent. For over a decade, transdermal and sublingual compounded flumazenil has been used in the treatment of idiopathic hypersomnia, a condition also believed to involve pathological enhancement of GABA-A receptor activity. Trotti et al. (2016) reported on 153 consecutive patients treated with compounded transdermal flumazenil over a period of up to two years, demonstrating sustained clinical benefit in 39% of patients with a favorable safety profile. This body of experience establishes that long-term outpatient transdermal flumazenil is both feasible and safe, and that it reaches systemic circulation in therapeutically relevant concentrations.

The present proposal builds directly on this evidence. We propose that transdermal flumazenil, compounded in a standard PCCA Lipoderm base, can serve as a practical, low-cost, home-based alternative to intravenous administration for the treatment of PAWS/BIND — addressing the single most cited gap in the existing literature: treatment duration.

2. Study Objectives and Hypotheses

2.1 Primary Objective

To evaluate the safety, tolerability, and clinical effectiveness of a patient-directed, flexible-dose transdermal flumazenil protocol administered at home under remote clinical supervision in patients suffering from PAWS/BIND following iatrogenic benzodiazepine dependence.

2.2 Secondary Objectives

- To determine whether transdermal flumazenil can produce clinically meaningful symptom relief comparable to that reported in intravenous and subcutaneous flumazenil studies, without the need for inpatient or clinic-based infusion.
- To assess functional recovery outcomes including return to work, ability to perform daily activities, and quality of life over the course of treatment.
- To characterize the dose range at which patients experience symptomatic relief, given the known variability in transdermal absorption and individual neurological response.
- To establish a replicable, standardized yet flexible protocol that can be adopted across multiple clinic settings at low cost.

2.3 Hypotheses

Hypothesis 1: Transdermal flumazenil applied 4 to 6 times daily in a compounded cream base will achieve sufficient systemic absorption to produce clinically meaningful reduction in PAWS/BIND symptoms, serving as a viable alternative to intravenous administration.

Hypothesis 2: An extended, patient-directed treatment protocol — with duration determined by symptom response rather than a fixed endpoint — will produce more durable and sustained recovery than the short infusion windows reported in existing literature, reducing the rate of symptom relapse upon dose reduction.

3. Patient Selection

3.1 Inclusion Criteria

- Adults aged 18 or older
- Documented history of benzodiazepine use prescribed by a licensed physician (iatrogenic dependence only)
- Fully discontinued from benzodiazepines for a minimum of 30 days prior to enrollment
- Presenting with persistent PAWS/BIND symptoms at time of enrollment
- No current use of benzodiazepines or other GABAergic substances
- Medically stable, with no acute psychiatric or medical crisis at time of enrollment
- Motivated, informed, and willing to follow a self-directed protocol with weekly telehealth check-ins
- Capable of independent living and self-administration of topical cream
- Able to provide written informed consent
- Access to a phone or computer for telehealth follow-up

3.2 Exclusion Criteria

- Current or recent benzodiazepine use (within 30 days of enrollment)
- History of seizure disorder or identified high risk of seizure
- Active addiction to any substance including alcohol, opioids, or recreational benzodiazepine use
- Currently undergoing benzodiazepine taper or on high-dose benzodiazepines
- Pregnancy or breastfeeding
- Severe hepatic impairment (flumazenil is hepatically metabolized)
- Known hypersensitivity to flumazenil or any component of the compounded cream base
- Active severe psychiatric condition that would impair ability to self-monitor or report symptoms reliably
- Inability or unwillingness to attend initial in-person evaluation

4. Treatment Protocol

4.1 Cream Formulation and Delivery Device

Flumazenil will be compounded by a licensed research compounding supplier, specialized pharmaceutical supplier, contract manufacturing organization (CMO), or compounding pharmacy into a transdermal cream using PCCA Lipoderm as the base, dispensed in a Topi-Click 35 metered dose applicator. The Topi-Click 35 delivers exactly 0.25 mL per click, providing precise, reproducible dosing with minimal user variability. Two concentrations will be used across the course of treatment:

- Tube 1: 4 mg/mL — each click delivers 1 mg of flumazenil. This tube is used from the starting dose up to 8 mg per application.
- Tube 2: 16 mg/mL — each click delivers 4 mg of flumazenil. This tube is introduced when the patient reaches 8 mg per application, at which point the volume of Tube 1 cream becomes impractical to apply to the inner forearm.

There is no overlap period between tubes. The transition is clean and occurs at a single defined threshold. Cream is applied to the inner forearm at each dose, alternating arms where possible to minimize local skin irritation.

4.2 Dosing Frequency

Cream is applied 4 to 6 times per day at approximately equal intervals throughout the waking hours. The flexible frequency range accommodates individual schedules and tolerability. The goal is to approximate a steady-state plasma concentration, acknowledging that transdermal delivery will not replicate the continuity of a subcutaneous infusion but is hypothesized to be clinically sufficient for receptor normalization over an extended treatment period.

4.3 Dose Escalation Phase

- Starting dose: 1 mg per application (1 click, Tube 1)
- Each dose level is held for a minimum of 3 days before escalation
- Dose is increased by 1 mg increments
- As the dose increases, the hold period before the next escalation also increases by 1 day per step
- Maximum dose: 48 mg per day, consistent with the maximum safe dose established in the idiopathic hypersomnia literature
- Escalation is entirely patient-directed — the patient advances only when they feel ready and are not experiencing significant side effects

4.4 Therapeutic Hold Phase

When the patient begins to experience meaningful symptom relief at a given dose, that dose is held for a minimum of 3 weeks before any attempt at de-escalation. This hold period is the most critical phase of the protocol and reflects the central premise of this proposal: that the nervous system requires sustained receptor normalization over time, not a brief pharmacological intervention. The patient may choose to extend the hold period beyond 3 weeks if they feel their recovery is still progressing.

4.5 De-escalation Phase

- After a minimum 3-week therapeutic hold, the patient may begin slowly tapering the dose downward in 2 mg decrements
- Each step down is held for a minimum of 3 days before the next reduction, mirroring the escalation structure
- If symptoms return during de-escalation, the patient immediately reinstates the previous effective dose and holds for an additional week before attempting reduction again
- De-escalation is never rushed and remains patient-directed throughout

4.6 Side Effect Management

If at any point during escalation the patient experiences significant side effects — most commonly anxiety, agitation, dizziness, or insomnia — the following steps are taken:

- Return immediately to the previous tolerated dose
- Hold that dose for a minimum of 5 days before attempting escalation again
- If side effects persist, the supervising clinician is contacted via telehealth for assessment
- In the event of any serious adverse event, the patient is instructed to discontinue and seek in-person medical evaluation immediately

4.7 Overall Treatment Duration

The minimum observation period for the study is 30 days. However, the protocol is explicitly designed to extend as long as clinically necessary — potentially several months — reflecting the reality that a nervous system deregulated over years cannot be expected to normalize in days or weeks. There is no arbitrary upper time limit imposed on treatment duration, provided the patient continues to tolerate the medication and demonstrate clinical progress.

5. Study Procedures

5.1 Initial In-Person Evaluation

Prior to enrollment, each patient will attend a single in-person visit at the participating clinic. This visit serves as the gateway to the protocol and must be completed before any treatment begins. The following will be assessed and documented:

- Full medical history including duration and dosage of benzodiazepine use, taper history, and current PAWS/BIND symptoms
- Vital signs including blood pressure, heart rate, respiratory rate, and weight
- Seizure risk assessment — patients with any history of seizure disorder or identified seizure risk will be excluded at this stage
- Current medication review including any GABAergic substances
- Liver function assessment given hepatic metabolism of flumazenil
- Baseline questionnaire completion: Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), SF-36 Quality of Life scale, and the functional outcomes checklist
- Informed consent process and protocol education
- Prescription of Tube 1 through a licensed research compounding supplier or compounding pharmacy

5.2 Weekly Telehealth Check-ins

Following the initial visit, all follow-up is conducted remotely via telephone or video call on a weekly basis. Each check-in will include:

- Review of current dose and number of days held at that dose
- Symptom update — improvement, worsening, or plateau
- Side effect screening — anxiety, agitation, insomnia, dizziness, or any unexpected reactions
- Dose escalation decision — the clinician and patient jointly confirm readiness to advance, hold, or step back
- Questionnaire completion at defined intervals — BWSQ and functional checklist completed every 2 weeks, SF-36 completed monthly
- Any safety concerns are triaged and in-person follow-up arranged if needed

5.3 Patient Support Tools

- A personalized dosing chart mapping their escalation schedule with space to record daily doses, number of clicks, application times, and symptom notes
- A side effect reference card clearly listing what to watch for and exactly what to do at each step
- A simple daily symptom diary to be completed each evening and reviewed at weekly check-ins
- Clinician contact information for urgent questions between scheduled check-ins

6. Outcome Measures

6.1 Primary Outcome

The primary outcome is clinically meaningful reduction in PAWS/BIND symptom severity as measured by the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) from baseline to end of observation period. The BWSQ is a validated 20-item self-report instrument specifically designed to capture the symptom profile of benzodiazepine withdrawal, including anxiety, insomnia, perceptual disturbances, cognitive impairment, and physical symptoms.

6.2 Secondary Outcomes

Quality of Life — SF-36

The SF-36 is a widely validated 36-item general health survey measuring eight domains including physical functioning, role limitations, energy, emotional wellbeing, social functioning, and general health perception. It will be administered at baseline, monthly during treatment, and at end of observation.

Functional Outcomes Checklist

A structured functional outcomes checklist will be administered at baseline and every two weeks thereafter, capturing real-world recovery milestones including but not limited to:

- Ability to prepare meals independently
- Ability to perform basic household tasks
- Return to part-time or full-time work or studies
- Ability to drive
- Ability to socialize with family or friends
- Ability to exercise or engage in physical activity
- Ability to manage personal finances and appointments
- Overall self-rated level of independence

6.3 Safety Outcomes

- Frequency and nature of adverse events reported during weekly check-ins
- Rate of dose reduction due to side effects
- Rate of protocol discontinuation and reasons
- Any serious adverse events requiring in-person or emergency evaluation

6.4 Exploratory Outcomes

- Identification of the dose range at which patients most commonly report symptomatic relief
- Relationship between duration of original benzodiazepine use and treatment response
- Rate of symptom relapse during de-escalation phase and response to dose reinstatement
- Variability in effective dose across patients, supporting the rationale for flexible individualized dosing

7. Advantages Over Previously Published Work

7.1 The Scale of the Problem

Benzodiazepines are among the most widely prescribed medications in the world. In the United States alone, approximately 30.6 million adults report using benzodiazepines, representing more than 1 in 20 people filling a prescription each year. The problem is not confined to North America. One-year prevalence of benzodiazepine use across multiple countries ranges from 4-7% in Germany to 10% in Canada and the Netherlands, 11% in the USA, 14.5% in Sweden, and as high as 17.6% in Belgium. Current prescribing guidelines recommend benzodiazepines for no longer than 2 to 4 weeks, yet in practice long-term use is common. In France, more than 75% of users are prescribed these drugs for more than 6 months.

This gap between recommended and actual prescribing duration is at the root of the PAWS/BIND crisis. It is estimated that 10 to 15% of patients taking benzodiazepines long-term will experience protracted withdrawal or a post-withdrawal syndrome. Given the tens of millions of long-term users worldwide, this translates to a population of sufferers numbering in the millions. In England alone, an estimated 1.5 million people are suffering from doctor-induced benzodiazepine dependency. The human and economic cost of this largely unrecognized epidemic — in lost productivity, disability, and suffering — is enormous and poorly quantified.

7.2 The Heterogeneity of PAWS/BIND Demands an Individualized Approach

One of the most striking and clinically important features of PAWS/BIND is the extraordinary variability in its presentation. Symptom duration ranges from a few weeks to many decades. Severity spans from mild and manageable inconvenience to complete incapacitation requiring around-the-clock caregiving. The symptom profile itself varies widely between individuals, encompassing cognitive dysfunction, anxiety, sensory disturbances, insomnia, depersonalization, gastrointestinal dysfunction, muscle pain, and more.

This heterogeneity is not incidental — it is a fundamental characteristic of the condition and has direct implications for treatment design. Patients who have been on low doses for months will not require the same treatment intensity as those who were prescribed high doses for decades. Individual differences in skin absorption mean that transdermal bioavailability of flumazenil will vary significantly from person to person. Sensitivity to medications, body composition, duration of nervous system dysregulation, and the degree of GABA receptor downregulation all contribute to a clinical picture that is inherently non-uniform. It is therefore not scientifically or clinically sound to assume that a single fixed dose administered over a fixed duration will be appropriate for this population.

This is the central rationale for the patient-directed flexible dose escalation design of this protocol. The hypothesis is not only that flumazenil will be effective, but that the effective dose and the required treatment duration will vary profoundly from one patient to the next. The protocol is designed to capture and accommodate that variability rather than suppress it.

7.3 Specific Advantages Over Prior Work

Treatment duration

Every major study in this field has identified short treatment windows as the primary limitation. The Italian gold standard of 8 to 10 days of intravenous infusion produces results, but symptoms frequently return because the nervous system has not had sufficient time to recalibrate. This

protocol removes the arbitrary time ceiling entirely, allowing treatment to continue for as long as clinically necessary.

Route of administration

Intravenous and subcutaneous infusions require hospital or clinic settings, trained personnel, continuous supervision, and significant cost. Transdermal flumazenil cream has been safely used for over a decade in the idiopathic hypersomnia field, with Trotti et al. demonstrating sustained benefit in outpatients over periods of up to two years. This protocol applies that same delivery method to the PAWS/BIND population for the first time in a structured protocol.

Cost and accessibility

Compounded transdermal flumazenil dispensed via a Topi-Click device is dramatically less expensive than inpatient infusion. It requires no hospital bed, no infusion nurse, and no travel beyond the initial enrollment visit. This opens the treatment to a far broader population and makes multicenter replication feasible at minimal infrastructure cost.

Lack of standardization

There is currently no agreed-upon protocol for flumazenil treatment of PAWS/BIND. Every clinic that attempts this treatment does so according to its own improvised approach, making data comparison across sites impossible. This proposal offers a structured, replicable framework that is standardized in its structure while remaining flexible in its execution — producing generalizable data for the first time.

Patient empowerment

Prior protocols treated patients as passive recipients of a fixed intervention. This protocol recognizes that PAWS/BIND patients are often deeply informed about their condition, highly motivated, and uniquely positioned to monitor their own symptom response. The self-directed escalation model is not a concession — it is a deliberate design choice grounded in the clinical reality of this population.

8. Safety Considerations and Risk Management

8.1 General Safety Profile of Transdermal Flumazenil

Flumazenil has a well-established safety profile when administered at low doses over extended periods. The idiopathic hypersomnia literature provides over a decade of real-world experience with compounded transdermal and sublingual flumazenil in outpatient settings, with no serious adverse events attributed to the medication at the doses used in this protocol. The maximum dose of 48 mg per day employed here is consistent with the upper limit established in that literature and is not being exceeded.

The patients targeted by this protocol represent a lower-risk population than those treated in most existing flumazenil studies. They are fully off benzodiazepines, medically stable, not at risk of seizure, and self-selected for motivation and independence.

8.2 Seizure Risk

The most serious potential adverse event associated with flumazenil in benzodiazepine-dependent patients is precipitation of seizure, which can occur when flumazenil rapidly displaces benzodiazepines from GABA-A receptors in patients who are still physically dependent. This risk is effectively eliminated in this protocol by the strict inclusion criterion requiring full benzodiazepine cessation for a minimum of 30 days prior to enrollment, combined with the exclusion of any patient with a history of seizure disorder or identified seizure risk.

8.3 Expected Side Effects

- Anxiety or agitation, particularly during dose escalation
- Insomnia or sleep disturbance
- Dizziness
- Skin irritation at the application site

8.4 Monitoring and Escalation of Care

- Mild side effects: step back to previous dose per protocol, monitor at next weekly check-in
- Persistent or worsening side effects despite dose reduction: telehealth assessment within 48 hours
- Any serious or unexpected adverse event: immediate discontinuation, in-person evaluation, adverse event reported and documented

8.5 Skin Safety

Patients are instructed to rotate application between both inner forearms and to report any persistent redness, irritation, or rash at weekly check-ins. In the event of significant skin reaction, the application site may be changed or treatment temporarily suspended pending clinical review.

8.6 Contraindicated Combinations

Patients will be screened at enrollment for concurrent use of any GABAergic substances including alcohol, muscle relaxants, sleep aids, anticonvulsants, and other benzodiazepines or

Z-drugs. Concomitant use of any of these substances is grounds for exclusion or discontinuation.

8.7 Pregnancy

Pregnancy is an exclusion criterion. Female patients of childbearing potential will be counseled to use reliable contraception during the treatment period.

9. Ethical Considerations

9.1 Vulnerable Population and Iatrogenic Harm

The patients targeted by this protocol occupy a unique and often overlooked position in medicine. They did not seek out benzodiazepines recreationally. They were prescribed these medications by licensed physicians, frequently without adequate warning of the risks of long-term use or the potential for dependence. Many have been dismissed, misdiagnosed, or told their ongoing symptoms are psychiatric in origin rather than neurological. This ethical context obligates the medical community to take their condition seriously and to invest in developing treatments that are accessible, affordable, and respectful of their experience.

9.2 Informed Consent

Informed consent is a cornerstone of this protocol. The consent process will cover:

- The investigational nature of the protocol and its off-label use of compounded flumazenil
- The known safety profile and potential side effects
- The voluntary nature of participation and the right to withdraw at any time without consequence
- The responsibilities of the patient including accurate symptom reporting and adherence to check-in schedule
- The absence of guaranteed therapeutic benefit

9.3 Off-Label Use and Compounded Medication

Flumazenil is not currently approved by the FDA or equivalent regulatory bodies for the treatment of PAWS/BIND. Its use in this protocol is off-label, as is its compounding into a transdermal cream. Physicians participating in this study should be aware of the regulatory framework governing off-label prescribing and compounded medications in their jurisdiction. Patients will be explicitly informed of the off-label nature of the treatment during the consent process.

9.4 Patient Autonomy and Empowerment

The self-directed nature of this protocol is an ethical position as much as a practical one. PAWS/BIND patients are adults who have often spent years researching their condition, advocating for themselves in a medical system that frequently failed to recognize their suffering. This protocol explicitly honors patient autonomy by placing dose escalation and treatment duration decisions in the patient's hands, within a clearly defined safety framework and under continuous clinical supervision.

9.5 Data Privacy and Confidentiality

All patient data collected in the course of this study will be handled in accordance with applicable privacy legislation including HIPAA in the United States and equivalent frameworks in other jurisdictions. Data will be anonymized for the purposes of analysis and publication.

9.6 Multicenter Coordination and Ethics Review

As a clinic-based multicenter protocol, each participating site is responsible for obtaining approval from its relevant institutional or independent ethics review body prior to enrolling

patients. A shared protocol document will be provided to all participating sites to ensure consistency of implementation.

10. Limitations and Future Directions

10.1 Limitations of the Current Protocol

Open-label observational design

The absence of a placebo control group is the most significant methodological limitation of this protocol. Without a control arm, it is not possible to definitively attribute symptom improvement to flumazenil rather than to the natural course of recovery, the placebo effect, or the supportive structure of weekly clinical contact. This limitation is acknowledged upfront. However, the open-label design is a deliberate and justified choice for a first-generation protocol of this kind.

Transdermal absorption variability

One of the central challenges of transdermal drug delivery is the significant inter-individual variability in skin permeability and systemic absorption. This protocol does not include pharmacokinetic monitoring, meaning that actual blood levels of flumazenil will not be measured. Future studies should consider incorporating plasma level monitoring in a subset of patients.

Self-reported outcomes

All primary and secondary outcome measures in this protocol rely on patient self-report. While the instruments used are validated and widely accepted, self-reported data is inherently subject to recall bias and response bias.

No standardized compounding verification

Participating sites will source compounded flumazenil cream from local licensed research compounding suppliers or compounding pharmacies. There is no centralized quality control mechanism to verify batch consistency across sites.

Selection bias

The inclusion criteria favor highly motivated, informed, and independent patients. Findings may not generalize to PAWS/BIND patients who are more severely debilitated, less health-literate, or without access to telehealth technology.

10.2 Future Directions

- Randomized controlled trial — a placebo-controlled RCT powered to detect clinically meaningful differences in BWSQ and SF-36 scores
- Pharmacokinetic substudy — measuring plasma flumazenil concentrations at multiple time points to characterize transdermal bioavailability in this population
- Biomarker development — neuroimaging, EEG, and inflammatory marker panels as objective measures of PAWS/BIND severity and recovery
- Long-term follow-up — structured follow-up at 6 and 12 months post-treatment completion to assess durability of response
- Health economics analysis — formal cost-effectiveness comparison of home-based transdermal protocol versus inpatient intravenous approaches

11. Conclusion

Benzodiazepine-induced neurological dysfunction and post-acute withdrawal syndrome represent a significant and largely unaddressed public health crisis. Millions of patients worldwide, the majority of whom became dependent through legitimate medical prescriptions, continue to suffer debilitating neurological symptoms long after discontinuing benzodiazepines. Despite decades of evidence pointing to flumazenil as a promising treatment, the field has been held back by the same limitations since the 1990s — treatments that are too short, too expensive, too invasive, and too inaccessible to reach the patients who need them most.

This proposal offers a practical path forward. By leveraging the established safety record of compounded transdermal flumazenil, the precision dosing of the Topi-Click delivery system, and the accessibility of telehealth monitoring, we propose a protocol that is simultaneously standardized and flexible, clinically supervised and patient-directed, low-cost and replicable at scale. The self-directed dose escalation model is not a compromise — it is a recognition of the profound heterogeneity of this condition and the clinical reality that no single dose and no single duration will be appropriate for every patient.

The central innovation of this protocol is time. For the first time, a structured framework is proposed that allows flumazenil treatment to continue for as long as the patient's nervous system requires, rather than for as long as a hospital bed or infusion budget permits. This is the change that the existing literature has been calling for, explicitly and repeatedly, for thirty years.

We invite clinicians who treat this population to adopt this framework, contribute their data, and help build the evidence base that these patients deserve. The suffering is real, the mechanism is understood, the treatment exists, and the tools are available. What has been missing is a protocol. This is that protocol.

Appendix A — Illustrative Dose Escalation Schedule

The following table illustrates a smooth escalation to 6 mg x 4 daily, therapeutic hold, and de-escalation to zero. Actual patient timeline will vary.

Smooth escalation to 6 mg × 4 daily · each cell shows mg dose and (clicks)

Day	Phase	Morning	Midday	Afternoon	Evening	Total/day
— Escalation phase —						
1	Escalation	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	**4 mg**
2	Escalation	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	**4 mg**
3	Escalation	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	**4 mg**
4	Escalation	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	**8 mg**
5	Escalation	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	**8 mg**
6	Escalation	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	**8 mg**
7	Escalation	3 mg (3 clicks)	3 mg (3 clicks)	3 mg (3 clicks)	3 mg (3 clicks)	**12 mg**
8	Escalation	3 mg (3 clicks)	3 mg (3 clicks)	3 mg (3 clicks)	3 mg (3 clicks)	**12 mg**
9	Escalation	3 mg (3 clicks)	3 mg (3 clicks)	3 mg (3 clicks)	3 mg (3 clicks)	**12 mg**
10	Escalation	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	**16 mg**
11	Escalation	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	**16 mg**
12	Escalation	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	**16 mg**
13	Escalation	5 mg (5 clicks)	5 mg (5 clicks)	5 mg (5 clicks)	5 mg (5 clicks)	**20 mg**
14	Escalation	5 mg (5 clicks)	5 mg (5 clicks)	5 mg (5 clicks)	5 mg (5 clicks)	**20 mg**
15	Escalation	5 mg (5 clicks)	5 mg (5 clicks)	5 mg (5 clicks)	5 mg (5 clicks)	**20 mg**
16	Escalation	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
17	Escalation	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
18	Escalation	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg (relief)**
— Therapeutic hold phase (minimum 21 days) —						
19	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**

Day	Phase	Morning	Midday	Afternoon	Evening	Total/day
20	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
21	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
22	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
23	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
24	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
25	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
26	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
27	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
28	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
29	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
30	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
31	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
32	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
33	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
34	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
35	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
36	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
37	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
38	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
39	Hold	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	6 mg (6 clicks)	**24 mg**
— De-escalation phase (2 mg decrements) —						
40	De-escalation	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	**16 mg**

Day	Phase	Morning	Midday	Afternoon	Evening	Total/day
41	De-escalation	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	**16 mg**
42	De-escalation	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	4 mg (4 clicks)	**16 mg**
43	De-escalation	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	**8 mg**
44	De-escalation	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	**8 mg**
45	De-escalation	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	2 mg (2 clicks)	**8 mg**
46	De-escalation	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	**4 mg**
47	De-escalation	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	**4 mg**
48	De-escalation	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	1 mg (1 click)	**4 mg**
49+	Complete	0 mg	0 mg	0 mg	0 mg	**0 mg**

Total: ~48 days · Escalation days 1–18 · Hold days 19–39 · De-escalation days 40–48 · Tube 1 (4 mg/mL) used throughout.

Smooth escalation to 6 mg × 4 daily, therapeutic hold, then de-escalation to zero. Actual patient timeline will vary.

Days	Dose/app	Clicks	Doses/day	Total mg/day	Tube	Phase	Notes
1–3	1 mg	1	4	**4 mg**	Tube 1	**Escalation**	*Starting dose — observe for side effects*
4–6	2 mg	2	4	**8 mg**	Tube 1	**Escalation**	*Increase by 1 mg — hold 3 days*
7–9	3 mg	3	4	**12 mg**	Tube 1	**Escalation**	*Increase by 1 mg — hold 3 days*
10–12	4 mg	4	4	**16 mg**	Tube 1	**Escalation**	*Increase by 1 mg — hold 3 days*
13–15	5 mg	5	4	**20 mg**	Tube 1	**Escalation**	*Increase by 1 mg — hold 3 days*
16–18	6 mg	6	4	**24 mg**	Tube 1	**Escalation**	*Patient reports meaningful symptom relief*
19–39	6 mg	6	4	**24 mg**	Tube 1	**Therapeutic hold**	*Minimum 3-week hold at effective dose*
40–45	4 mg	4	4	**16 mg**	Tube 1	**De-escalation**	*Reduce by 2 mg — hold 3 days per step*
46–51	2 mg	2	4	**8 mg**	Tube 1	**De-escalation**	*Reduce by 2 mg — no symptoms return*
52–54	1 mg	1	4	**4 mg**	Tube 1	**De-escalation**	*Final step down before stopping*
55+	0 mg	—	—	**0 mg**	—	**Protocol**	*Discontinue — monitor for symptom return*

Days	Dose/app	Clicks	Doses/day	Total mg/day	Tube	Phase	Notes
						complete	

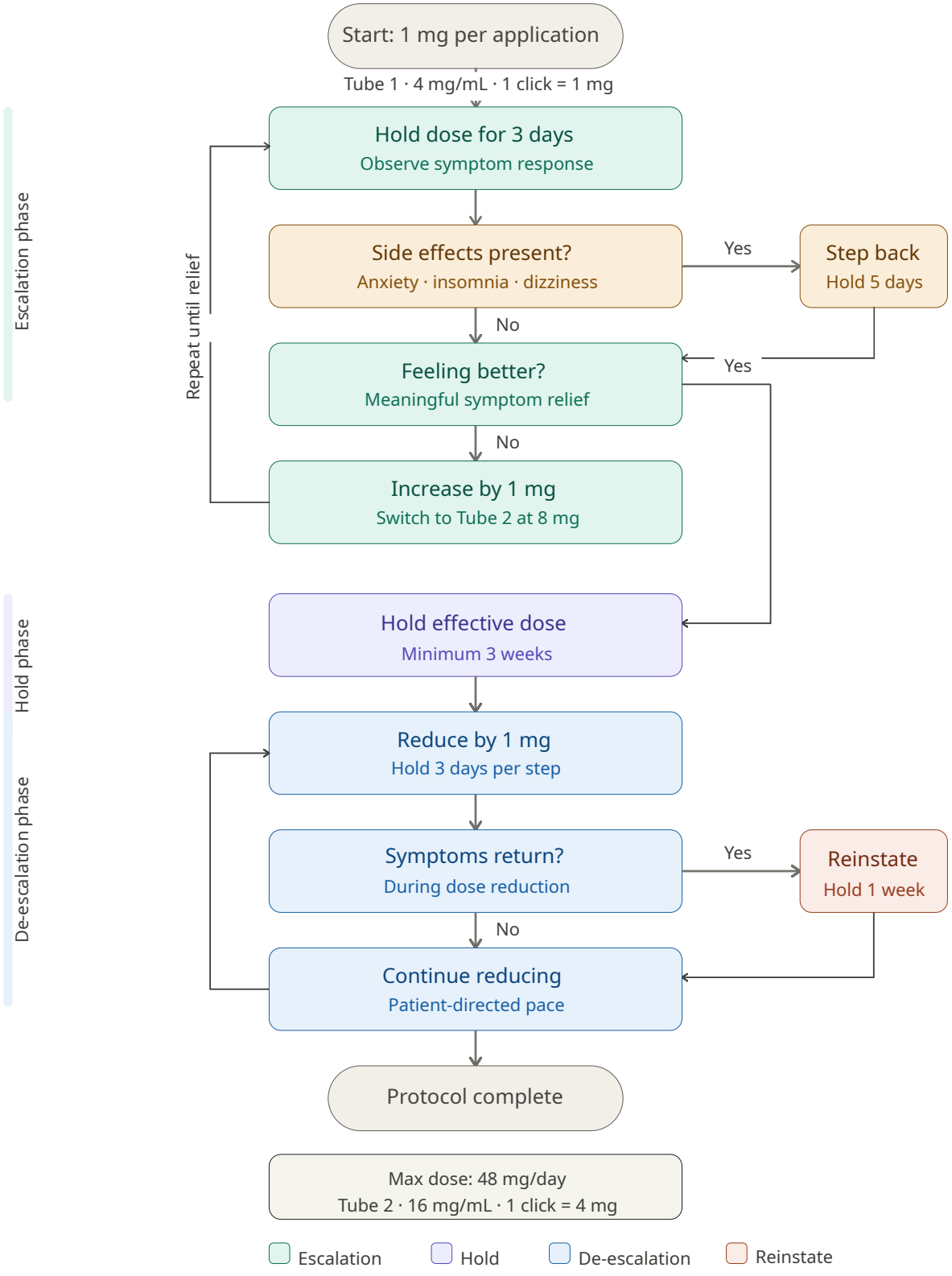
Total protocol duration (this example): ~55 days minimum · patient stays on Tube 1 throughout · Tube 2 not needed at this dose level · de-escalation uses 2 mg decrements per protocol.

Illustrative example · smooth run · 6 mg × 4 daily · 48-day protocol

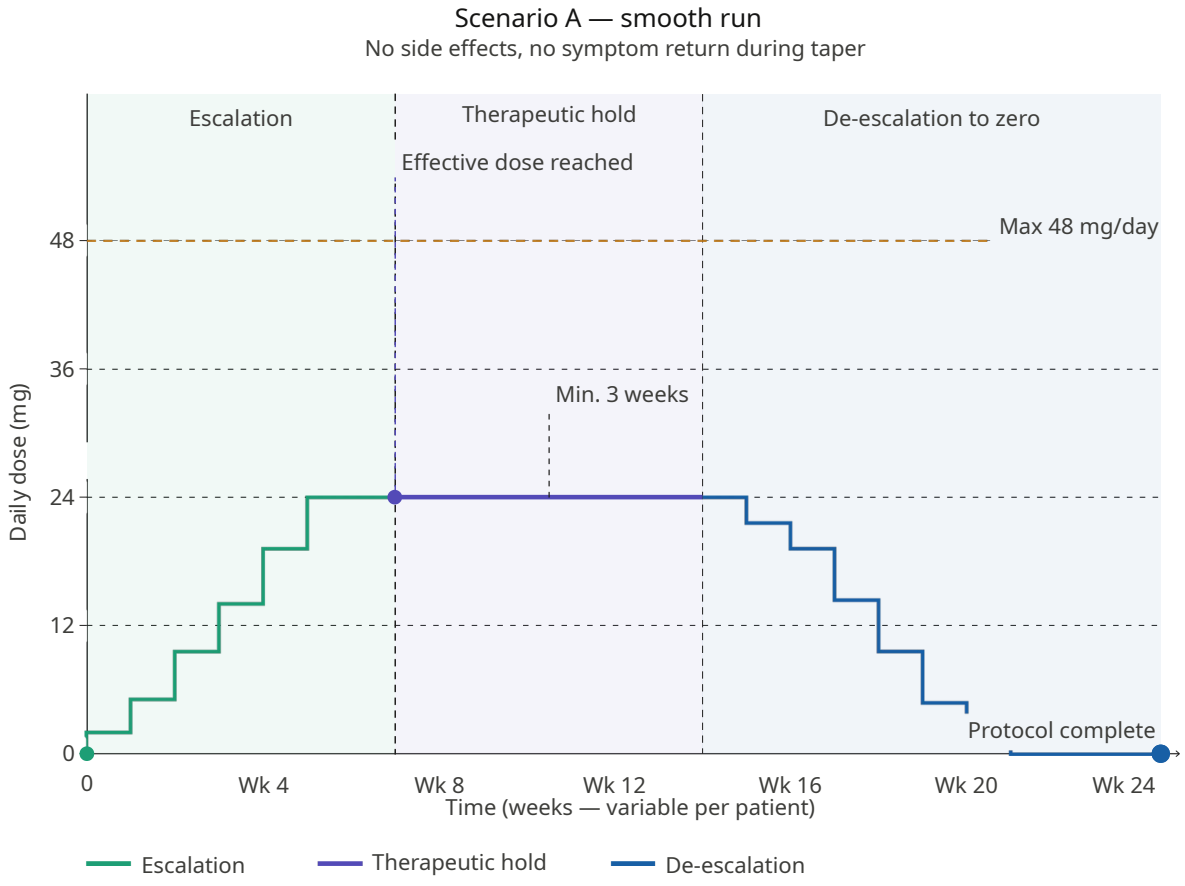
Tube	Concentration	Total mg needed	Tubes required
Tube 1	4 mg/mL · 30 mL per tube	**840 mg**	7 tubes
Tube 2	16 mg/mL · 30 mL per tube	Not required	—

Appendix B — Figures and Diagrams

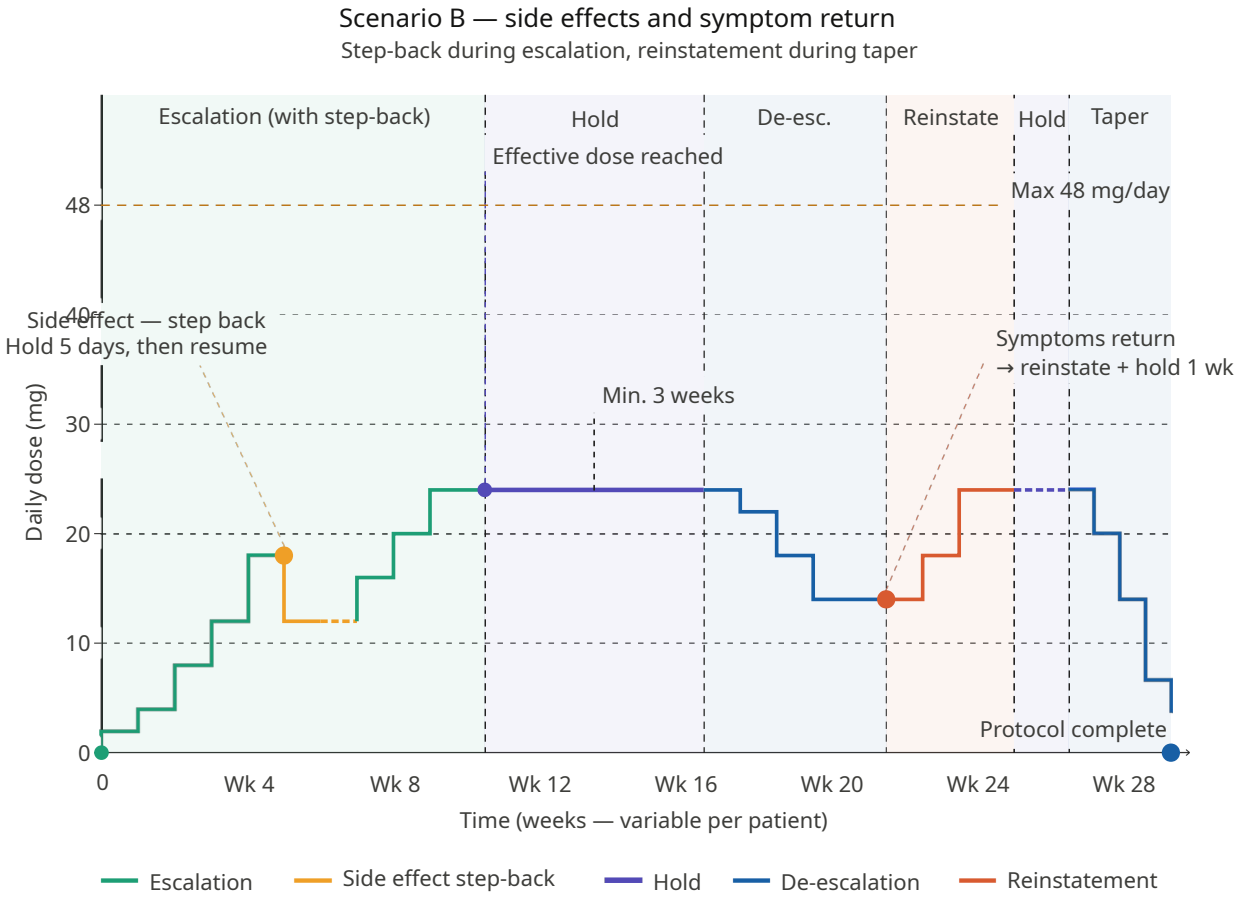
[Figure 1: Dose escalation flowchart]


Start: 1 mg per application
Tube 1 · 4 mg/mL · 1 click = 1 mg
Escalation phase
Hold dose for 3 days
Observe symptom response
Side effects present?
Anxiety · insomnia · dizziness
Yes
Step back
Hold 5 days
No
Repeat until relief
Feeling better?
Meaningful symptom relief
Yes
No
Increase by 1 mg
Switch to Tube 2 at 8 mg
Hold phase
Hold effective dose
Minimum 3 weeks
De-escalation phase
Reduce by 1 mg
Hold 3 days per step
Symptoms return?
During dose reduction
Yes
Reinstate
Hold 1 week
No
Continue reducing
Patient-directed pace
Protocol complete
Max dose: 48 mg/day
Tube 2 · 16 mg/mL · 1 click = 4 mg
Escalation
Hold
De-escalation
Reinstate

[Figure 2a: Treatment timeline — smooth run (Scenario A)]

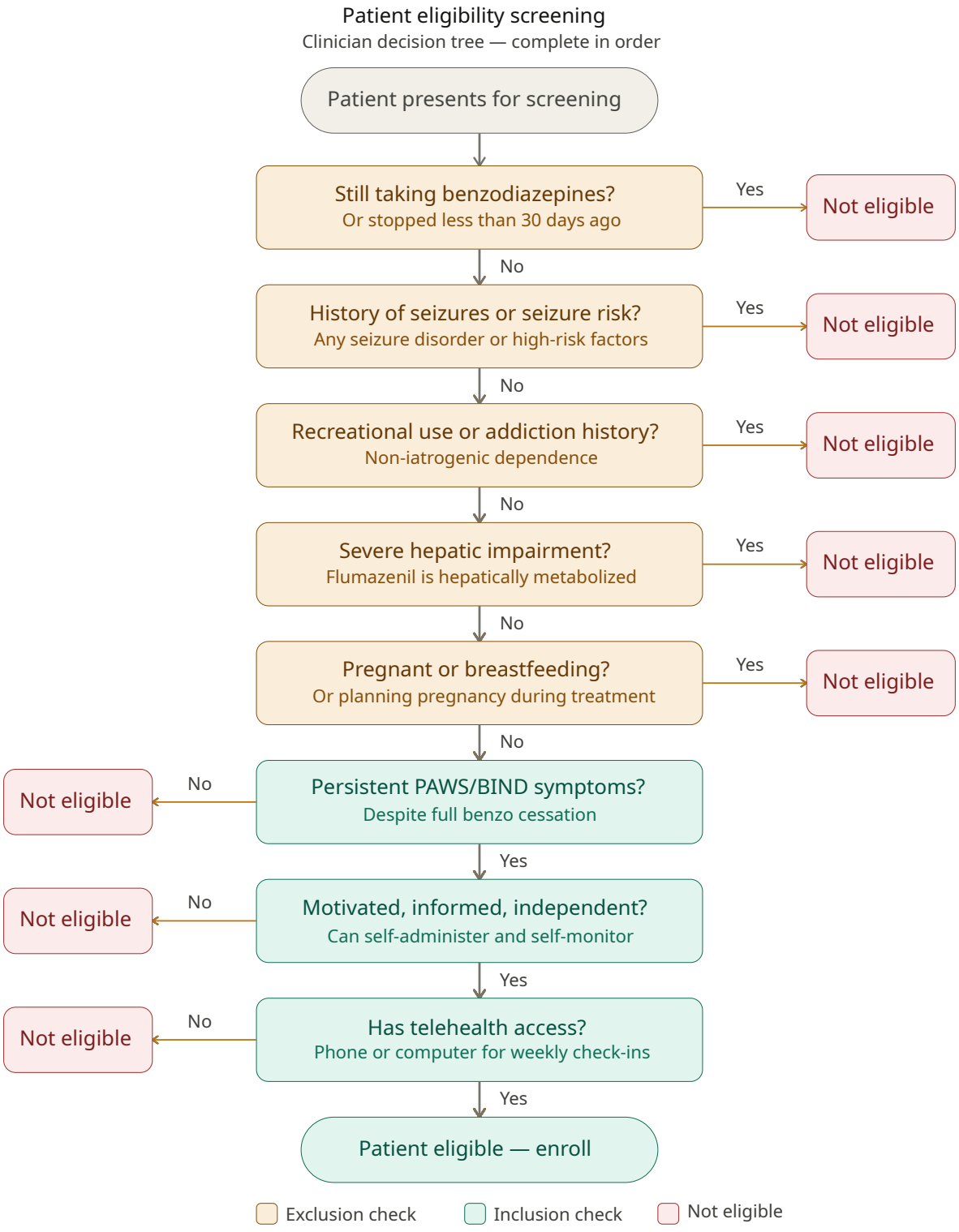


[Figure 2b: Treatment timeline — side effects and symptom return (Scenario B)]



[Figure 3: Topi-Click device and forearm application — photograph]

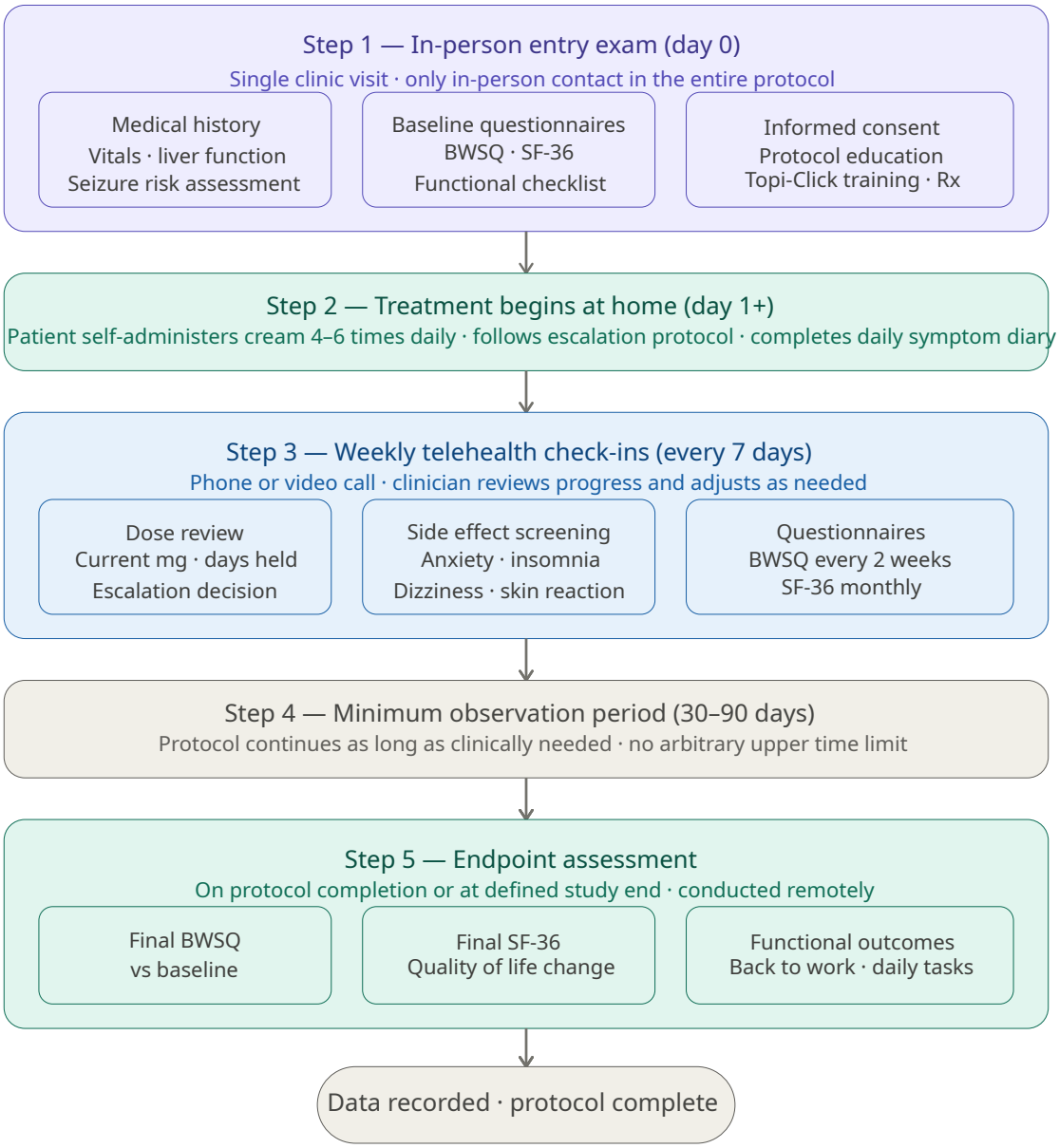
[Figure 4: Patient eligibility screening flowchart]



[Figure 5: Study procedure overview]

Study procedure overview

From enrollment to endpoint — one in-person visit, all else remote



[Figure 6: Weekly patient dosing diary]

Keep this card at home · read before starting · bring questions to your weekly check-in

EXPECTED SIDE EFFECTS

Anxiety or agitation
May occur especially during dose increases. Usually temporary.

Insomnia
Sleep disturbance during escalation is common and usually settles.

Dizziness
Mild dizziness may occur. Sit or lie down if needed.

Skin irritation
Redness or itching at application site. Alternate arms every dose.

Temporary worsening
Brief increase in PAWS symptoms during escalation is possible.

Headache
Mild headache may occur, particularly in early days of treatment.

WHAT TO DO

Mild side effects
Step back to previous dose immediately. Hold that dose for 5 days. Then try escalating again slowly.

Symptoms return during taper
Reinstate previous effective dose immediately. Hold for 1 week. Contact clinician at next check-in.

Serious or unexpected reaction
Stop cream immediately. Contact your clinician. If severe — go to emergency or call emergency services.

PROTOCOL RULES — QUICK REMINDER

ESCALATION
Increase by 1 mg every 3 days · only when feeling ready · max 48 mg/day

TUBE SWITCH
Switch from Tube 1 to Tube 2 when you reach 8 mg per application

THERAPEUTIC HOLD
When feeling better — hold that dose for a minimum of 3 weeks before tapering

DE-ESCALATION
Reduce by 2 mg every 3 days · stop if symptoms return and reinstate

CLINICIAN CONTACT

Clinician name _____

Phone / telehealth _____

Next check-in date _____

Emergency
If you experience seizure, severe confusion, chest pain, or difficulty breathing — call emergency services immediately and stop the cream.

Day	Morning Time: _____	Midday Time: _____	Afternoon Time: _____	Evening Time: _____	Symptoms / Notes
Day 1 Date: _____ Day: _____	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	
Day 2 Date: _____ Day: _____	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	
Day 3 Date: _____ Day: _____	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	
Day 4 Date: _____ Day: _____	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	
Day 5 Date: _____ Day: _____	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	
Day 6 Date: _____ Day: _____	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	
Day 7 Date: _____ Day: _____	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	☐ ___ mg ___ clicks	

Weekly check-in date _____

Clinician name _____

Clinician notes:

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