Research Protocol

Title: Substance misuse To Psychiatric disorders for Etomidate —repetitive Transcranial Magnetic Stimulation for people with etomidate addiction: a 6-month, double-blind, randomized, sham-controlled trial (**SToP-E × rTMS**).

a. Background

Non-medical abuse of etomidate and its related analogues has raised significant concerns in East and Southeast Asia since 2023 (United Nations Office on Drugs and Crime, 2025). Etomidate, which is also known as "K-pods", "E-eggs" or "Space Oil drug" by its street names among abusers, has been the second most commonly reported substance of abuse in 2024 among drug abusers aged under 21 in Hong Kong (Narcotics Division, 2025). Concerns have grown over the increased etomidate abuse since it can cause significant mental and physical health sequelae, including adrenal cortical insufficiency, epileptic seizures, potential cognitive impairment, dependence, and even death (Martin et al., 2009; Zheng et al., 2024). To stir up the problems, no effective treatment modalities for abusers with etomidate addiction is currently available.

Etomidate and its related analogues are used as sedative/hypnotic agents intravenously during anesthesia. They cause sedation and hypnosis through its binding to the γ-aminobutyric acid type A ($GABA_A$) receptors α and β subunits in the brain, in particular selectively to the β2 and β3 subunits, enhancing the GABA agonistic function to cause neuronal inhibition (Pejo et al., 2014; Voss et al., 2008). Unlike alcohol, benzodiazepines and Z-drugs, such as zopiclone and zolpidem, etomidate can also directly activate the $GABA_A$ receptor even in the absence of GABA (Pejo et al., 2016). The GABAergic system modulates the mesolimbic dopaminergic reward neurocircuitry (Ohta et al., 2022) and low GABA levels in the prefrontal cortex (PFC) are associated with disinhibition, poor impulse control, and impaired executive function (Shyu et al., 2022), which are salient neurobehavioral mechanisms in addiction attributing to their high dependence potential. While currently there is no data on the long-term cognitive consequences of repeated etomidate exposure, the use of etomidate might alter two key aspects of reward processing modulated by dopamine: 1) delayed reward discounting or temporal discounting (Lopez-Guzman et al., 2019; Odum, 2011), that is the tendency to prefer smaller immediate rewards over larger delayed rewards; and 2) risk sensitivity or risky decision making (Konova et al., 2020), that is tendency to engage in choices with uncertain outcomes despite potential losses. Both processes are robustly associated with vulnerability to addiction and relapse risk across varieties of substances, including GABA-related substances (Amlung et al., 2017; Chen et al., 2020).

Neuromodulation interventions oriented to targeting the PFC, where substance dependence is hypothesized to occur due to the imbalance of hyperactive emotional processing in ventral PFC and hypoactive executive control in dorsal PFC have shown promising results in various substance use disorders (SUD) (Martinotti et al., 2021; McClure & Bickel, 2014; Zhang et al., 2019). Enhancement of executive control is highlighted to reduce cue-induced craving, which is one of the core features of SUD contributing to relapse in drug addiction (Ferguson & Shiffman, 2009).

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique amongst neuromodulation interventions. It utilizes an alternating magnetic field generated by a coil placed over scalp which induces electrical currents in brain tissue and modulates neuronal firing. Therapeutic applications of rTMS had been established for treatment-resistant depression, and as an adjunctive treatment modality to medications for

obsessive-compulsive disorder with the formal approvals granted by the US Food and Drug Administration (FDA) in 2008 and 2018, respectively (FDA, 2018). rTMS has also been found effective in reducing craving and substance consumption in SUD, especially in alcohol, stimulant and cannabis use (Dharavath et al., 2023; Maiti et al., 2017; Mehta et al., 2024; Sahay et al., 2025; Sahlem et al., 2024; Zhang et al., 2019). In 2021, rTMS had also received the approval from the Conformité Européenne (CE) of the European Union for treating psychoactive substance use disorder (PSUD) in adults, especially for those with stimulant use to reduce their carving and relapses (MagVenture, 2021). Recent systematic reviews and meta-analyses have looked more closely into the application of high-frequency rTMS (excitatory stimulation) to dorsolateral PFC (DLPFC) and medial PFC (mPFC) which would strengthen the executive functions and cognitive control, resulting in reduced craving and addiction (Enokibara et al., 2016; Gay et al., 2022; Maiti et al., 2017; Makani et al., 2017; Sahay et al., 2025; Zhang et al., 2019). Such beneficial effect was also found to be dose-dependent, where repeated sessions (Barr et al., 2011) and number of pulses (Zhang et al., 2019) might predict the effect size of rTMS (Sahay et al., 2025).

Little is known about the effect and therapeutic applicability of rTMS for etomidate addiction or etomidate use disorder (EtUD). Nevertheless, studies on rTMS in depression over left DLPFC using high frequency stimulation and intermittent theta burst stimulation showed increases of GABA level in both DLPFC and mPFC (Diederichs et al., 2021; Dubin et al., 2016; Levitt et al., 2019). Together with the preliminary positive results from rTMS on improving GABAergic driven alcohol dependence (Harel et al., 2022), all these findings might translate the therapeutic potential of rTMS in treating the GABAergic driven addiction associated with etomidate.

Thus, here we propose the present double-blind, randomized, sham-controlled pilot study to investigate whether multiple sessions of high-frequency rTMS over left DLPFC can improve EtUD and etomidate associated cognitive biases contributing to its addiction. We will employ the same rTMS protocol researched by our group before which has shown good effects in abusers with cannabis use disorder (Chung AKK et al., 2026). With the availability of rTMS stimulators in all public psychiatric departments run under Hospital Authority, the results of this study are definitely going to provide invaluable scientific data for the potential application of rTMS as intervention for people suffering from etomidate addiction.

We assume the null hypotheses as:

1. Active rTMS and sham rTMS have similar effect in reducing etomidate addiction; and
2. Active rTMS and sham rTMS have similar effects in improving cognitive biases on delayed reward discounting and risk sensitivity in people suffering from etomidate addiction.

This study will observe the International Council for Harmonisation (ICH) guideline – Guideline for Good Clinical Practice and follow as appropriate. All study procedures adhered to the Declaration of Helsinki as well.

b. Study Objectives

I. Primary Objective:

- To compare the outcomes in participants with EtUD at four different follow-up timepoints after 20-session high-frequency *active versus sham* rTMS over four weeks on:
  i) subjective craving, amount and frequency of etomidate use; and
  ii) degree of severity in EtUD.

II. Secondary Objective:
- To determine if 20-session high-frequency rTMS can improve cognitive biases on delayed reward discounting and risk sensitivity in participants with EtUD.

c. Research Methodology

I. *Randomization and Blinding*

Participants will be randomized in 1:1 ratio to the active and sham rTMS treatment arms using computer-generated sequence with allocation concealment being maintained by a password protected computer.

The double-blinded condition in this study will be secured in three levels: 1) both the participants and the outcome assessors are blinded to the rTMS arms; 2) a special coil known as Coil Cool-B70 Active/ Placebo Bended Butterfly coil is used during the rTMS sessions. This coil is designed symmetrically on both sides to provide effective masking; and 3) scalp electrodes are applied to every participant to mimic similar skin sensations to enhance blinding.

II. *Study Phases* (Figure 1 in section ***g. Research activities to be conducted and schedule***)
This prospective intervention study has **2 phases** and will include 40 participants. They will be randomly assigned into ***2 arms***, i.e., *active rTMS* (20 participants) or *sham rTMS* (20 participants):

- *Phase 1* "**rTMS Phase**": each consented participant receives a total of **20 rTMS sessions** (either active or sham) over four weeks:
  - ***1st week*** [10 sessions]: 2 treatment-sessions per visit day for 5 consecutive days
  - ***2nd - 4th weeks*** [10 sessions]: 2 treatment-sessions per visit day for 5 days with each visit day is one day apart but not separated by more than 3 days

Total: 40 participants × 20 rTMS sessions = 800 sessions

- *Phase 2* "**Observation Maintenance Phase**": follow-up assessments for each participant starts from the completion of the last rTMS treatment session to the 6th month from baseline.

III. *rTMS Intervention*

rTMS is delivered to the participants at Queen Mary Hospital rTMS Center using MagVenture TMS system (Magnetic stimulator MagPro® X100) with Coil Cool-B70 Active/ Placebo Bended Butterfly coil.

- ***Active rTMS arm***: the treatment protocol for participants receiving active rTMS stimulations adhere to the European Union CE cleared stimulation settings for PSUD, using the following stimulation parameters:

Cool-B70 A/P Bended Butterfly Coil	
Stimulation site	Left dorsolateral prefrontal cortex (DLPFC) (located by Beam_F3 method)
Frequency	15 Hz
Pulse per train	60
Inter-train pause	15 seconds

Stimulation trains	40
Total pulses	2400
Duration	13 minutes
Hand Motor Threshold	100%

- ***Sham rTMS arm***: negligible magnetic field is generated from the "Placebo" side of the coil during rTMS.

IV. *Cognitive Bias Assessment*

Two behavioral paradigms elucidate how etomidate worsen and active rTMS interventions may restore cognitive processes in participants over time:

- ***Delayed reward discounting*** (DRD): The DRD task repeatedly presents participants with decision pairs between a smaller-sooner and a larger-later monetary amount (e.g., HKD$50 now vs. $80 in 10 days). These decisions impose a tension between time immediacy (i.e., sooner is better) and reward magnitude (i.e., more is better), and higher selection of the smaller-sooner option indicates greater time impulsivity. Computationally, time impulsivity is captured by a hyperbolic discounting function: SV=V/(1+kD), where SV denotes the subjective value, V denotes the original value amount, D denotes the number of days delayed, and k represents the discount rate. The hypothesized outcome is higher discount rates k in etomidate abusers at baseline, with a potential dose-dependent decrease in k among active rTMS group participants who favorably respond to rTMS treatments. Faster average reaction times of choosing the impulsive option is also expected to predict clinical outcomes.

- ***Risk sensitivity***. The risky decision-making task repeatedly presents participants with decision pairs between a smaller-safe and larger-risky monetary amount (e.g., $50 with 100% probability vs. $100 with 50% but with a risk of $0 with 50%). These decisions impose a tension between risk (i.e., safer is better) and reward (i.e., more is better) and higher selection of the risky options indicates greater risk tolerance. Computationally, risk tolerance is captured by a risk sensitivity parameter (α) from the prospect theory: SV=pV^α, where p represents the probability of reward and α controls the curvature of the subjective value function. When $\alpha > 1$ suggests preferences for risk, $\alpha < 1$ suggests aversions for risks, and $\alpha = 1$ indicates indifference. The hypothesized outcome is greater risk tolerance α among the etomidate abusers at baseline, with a potential dose-dependent decrease in α among active rTMS group participants who favorably respond to treatments. Faster average reaction times of choosing the risky option is also expected to predict clinical outcomes.

V. *Outcome Measures and Assessment Schedules*

(Figure 1 & Table 1 in section ***g. Research activities to be conducted and schedule***)

Outcome assessments will be conducted at baseline, 1-week, the last treatment visit day during the "rTMS Phase" (i.e., 1st month), and then at 3rd and 6th months post-treatment during the "Observation Maintenance Phase".

The following outcomes are assessed during the scheduled follow-up time-points:

- **<u>Etomidate Use Disorder (EtUD) Assessments</u>**:
  i. <u>Clinical Diagnosis</u>:
    - Structured Clinical Interview for DSM-5 (SCID-5):
      - ✓ EtUD is classified by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) under "Sedative-, Hypnotic-, or Anxiolytic Use Disorder"
      - ✓ to ascertain the diagnosis and severity of EtUD
      - ✓ to exclude other substance use disorders as listed in the exclusion criteria

  ii. <u>Clinical Outcome Measurements:</u>
    - <u>Urine Tests for etomidate use</u>:
      - → *Urine Test Kit* (quick test kit):
        - ✓ to confirm the participants are <u>not</u> under the influence of other substance use at the time of performing rTMS
        - ✓ to correlate with the status of self-reported etomidate use
    - <u>Self-administered Questionnaires & Semi-structured Interview</u>:
      - → Self-reported use of substance interview
      - → ***Beat Drugs Fund Evaluation Question Set No.5*** to assess the frequency and amount of etomidate use over the past 30 days
      - → Severity of dependence: ***Severity of Dependence Scale*** (SDS) (Gossop et al., 1995)
      - → Craving: ***Craving Automated Scale-Substance*** (CAS-S) with higher scores indicates stronger craving (Tan et al., 2022)
      - → Withdrawal: ***Clinical Institute Withdrawal Assessment for Benzodiazepines*** (CIWA-B) (Busto et al., 1989)
      - → Anxiety Symptom Assessment: ***Beck Anxiety Inventory*** (BAI)
      - → Depressive Symptom Assessment: ***Beck Depression Inventory -II*** (BDI-II)
- **<u>Cognitive Assessments:</u>**
  i. <u>Global Cognitive Assessment</u>:
    - Global cognitive function: ***Montreal Cognitive Assessment–HK version*** (MoCA-HK) (Wong et al., 2018)
    - Psychomotor speed: ***Digit Symbol Substitution Test*** (DSST) (Jaeger, 2018)

  ii. <u>Cognitive Biases Assessment</u>:
    - Delayed reward discounting by the ***delay discounting task***, in which on each trial, participants decide between a smaller-sooner and large-later option to obtain monetary rewards. The task aims to directly assess participants' ability to delay gratification.
    - Risk sensitivity by the ***risk preferences task***, in which on each trial, participants decide between a smaller-safe and a larger-risky option to obtain monetary rewards. The task aims to directly assess participants' sensitivity to risk and uncertainty.

VI. *<u>Statistical Method and Data Analysis:</u>*
- Demographic data will be presented as descriptive statistics.
  → Baseline differences between participants are analyzed with either the Chi-squared statistic for categorical variables, and with Student's *t* test for continuous variables.

- Generalized linear mixed effects models will be employed as primary analytical framework to determine differences in the outcomes between the active and the sham rTMS arms over the two phases.
  - → This approach is well suited to this longitudinal, repeated-measures study design, allowing for unbalanced data and missing observations while accounting for individual variability.
  - → The main and interaction effects of two arms and time-points on all outcomes will be reported.
  - → Demographic data will be adjusted in the models as covariates should any statistical differences be detected.

All statistical analyses will be performed using R version 4.3.3 or later. Unless otherwise specified, $p < 0.05$ will be considered statistically significant.

VII. *Data Management*

Personal and research data of the participants will be managed in accordance with the following policies and arrangements:

- Personal Data: principles from the HKSAR *Personal Data (Privacy) Ordinance (Cap. 486)* will be observed, (viewed 18/8/2025, https://www.elegislation.gov.hk/hk/cap486!en-zh-Hant-HK.pdf?FROMCAPINDEX=Y)
- Research Data: principles from the *Policy on the Management of Research Data and Records,* the University of Hong Kong will be followed, (viewed 18/8/2025, http://www.rss.hku.hk/integrity/research-data-records-management)
- Data storage and confidentiality**:** Personal identifiers will be kept separately from research data and linked only by a study identification code. Paper records, including consent forms and questionnaires, will be stored in locked cabinets in a secure research office/clinical research area. Electronic records will be stored in institutional servers with access restricted to authorized study personnel. Files used for data entry, analysis, monitoring or transfer will be password-protected and/or encrypted where appropriate.
- Access to personal and study data**:** During and after the study, access to the personal and study data will be restricted to the Principal Investigator (PI), research nurse and research assistants on a need-to-know basis for study conduct, data entry, monitoring, analysis, audit and regulatory/ethics review where required. The funding organization has no rights to access the personal and study data.
- Responsibility for safekeeping**:** The PI will have overall responsibility for safekeeping of the personal and study data during and after the study. The research nurse and research assistants will handle day-to-day filing, data entry, storage and retrieval under the supervision of the PI.
- Retention period**:** Personal and study data will be kept for 10 years after completion of the study, unless a longer retention period is required by applicable regulations, institutional policy, ethics committee requirements or audit/legal obligations.
- Arrangement after the retention period**:** After completion of the aforesaid 10-year storage period, identifiable personal data, the participant identification key and study records no longer required for audit, regulatory, legal or publication-related purposes will be securely destroyed in accordance with the Policy on the Management of Research Data and Records of the University of Hong Kong. Paper

documents will be shredded or disposed of through confidential-waste procedures. Electronic files will be securely erased or deleted from active study storage and study devices where technically practicable. Only fully anonymized and non-identifiable aggregate data or study results required for publication, reporting or scientific record may be retained.

d. Number and nature of subjects involved

A total of 40 participants will be invited to join this research with 20 participants per treatment arm.

I. *Sample Size*:

Based on the applicant's publication that used the same rTMS protocol with 4-week administration schedule showing a significant post-treatment effect in reducing cannabis craving in 18 subjects (Hedges' $g = -1.38$, $p < 0.001$) (Chung AKK et al., 2026), we estimated that the current study will require at least 18 participants in the active rTMS arm to ensure an adequate power for detecting similar desirable effects in reducing craving for etomidate abusers.

II. *Inclusion and Exclusion Criteria*

- Inclusion Criteria:
  i. Age: 18-45 years old
  ii. Able to read and communicate in English and/or Chinese
  iii. Able to give informed consent and/or able to provide an informed consent from the legal guardian (if applicable)
  iv. Using ***etomidate*** and/or its related analogues as the primary psychoactive substance of abuse
  v. Suffering from etomidate addiction as defined by:
     - Etomidate Use Disorder classified under "Sedative-, Hypnotic-, or Anxiolytic Use Disorder" according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) with severity ≥ 1, or
     - Harmful Use or Dependence for etomidate classified under "Mental and behavioral disorders due to use of sedatives or hypnotics" according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), or
     - Hazardous use, harmful use or dependence classified under "Hazardous use of sedatives, hypnotics or anxiolytics" or "Disorders due to use of sedatives, hypnotics or anxiolytics" according to the Clinical descriptions and diagnostic requirements for International Classification of Diseases 11th Revision (ICD-11) mental, behavioral, and neurodevelopmental disorders.

- Exclusion Criteria:
  i. Age < 18 years old
  ii. Unable to read English or Chinese
  iii. Unable to give informed consent
  iv. Had been diagnosed with the following disorders including:

- **Neurodevelopmental Disorders**:
  - → DSM-5: Intellectual Disabilities, Communication Disorders, Specific Learning Disorder, Autism Spectrum Disorder and Motor Disorders
  - → International Statistical Classification of Diseases and Related Health Problems 11th Revision (ICD-11): Disorders of intellectual development (6A00), Developmental speech or language disorders (6A01), Autism spectrum disorder (6A02), Developmental learning disorder (6A03), Developmental motor coordination disorder (6A04), Stereotyped movement disorder (6A06), Primary tics or tic disorders (8A05.0)
- **Other** DSM-5 defined **Substance Use Disorder** greater than moderate in severity (i.e., severity score ≥4)
- **Neurocognitive Disorders** (DSM-5, or ICD-11 6D70-72 & 6D80-86)

v. Contra-indicated to undergo rTMS:
- with electronic and/or magnetic implants (e.g., pacemaker, implantable cardioverter defibrillator [ICD], cerebral shunts, cochlear implant, etc.)
- with metallic or mechanic fragments (e.g., screws, plates, stents, clips, etc.)
- pregnant
- with ***any*** known or history of neurological conditions including cerebral vascular accidents (CVA), epilepsy, brain tumor or space occupying lesion, etc.
- poorly controlled or unstable diabetes mellitus
- receiving unstable dose(s) of antipsychotics, antidepressants, benzodiazepines and/or anticonvulsants in the past 3 months

e. Plans for recruiting participants/beneficiaries

Etomidate abusers residing primarily in Hong Kong are going to be recruited from
- Substance Abuse Clinics (SACs),
- by self-referrals via our website (https://stophku.wixsite.com/website) or contact information disseminated via mass emails and promotional materials,
- by referrals from collaborating non-governmental organizations: the TWGHs CROSS Centers and the Hong Kong Federation of Youth Groups (supporting letters attached)
- by referrals from other social workers in the anti-drugs field.

To enhance recruitment and participation, each consented participant will receive $350 as travel subsidy and to compensate the registration/attendance fees after finishing each treatment session, and after completing the follow-up assessments accordingly. It should be noted that starting January 2026, the attendance fee for Hospital Authority rTMS services and the fee for medications are going up as $250 and $20 per medication, respectively (HKSAR-Gov, 2025).

In addition, to maintain the participants' adherence to the intervention schedule assigned, honorarium is going to be dispensed only in a *weekly* basis during the "rTMS phase", and at the 3rd and the 6th months during the "Observation Maintenance Phase".

f. Funding

This project is funded by the Beat Drugs Fund Regular Funding Scheme 2025 from the Beat Drugs Fund Association, Narcotics Division, Security Bureau, HKSAR. The project number is BDF 250047.

g. Research activities to be conducted and schedule

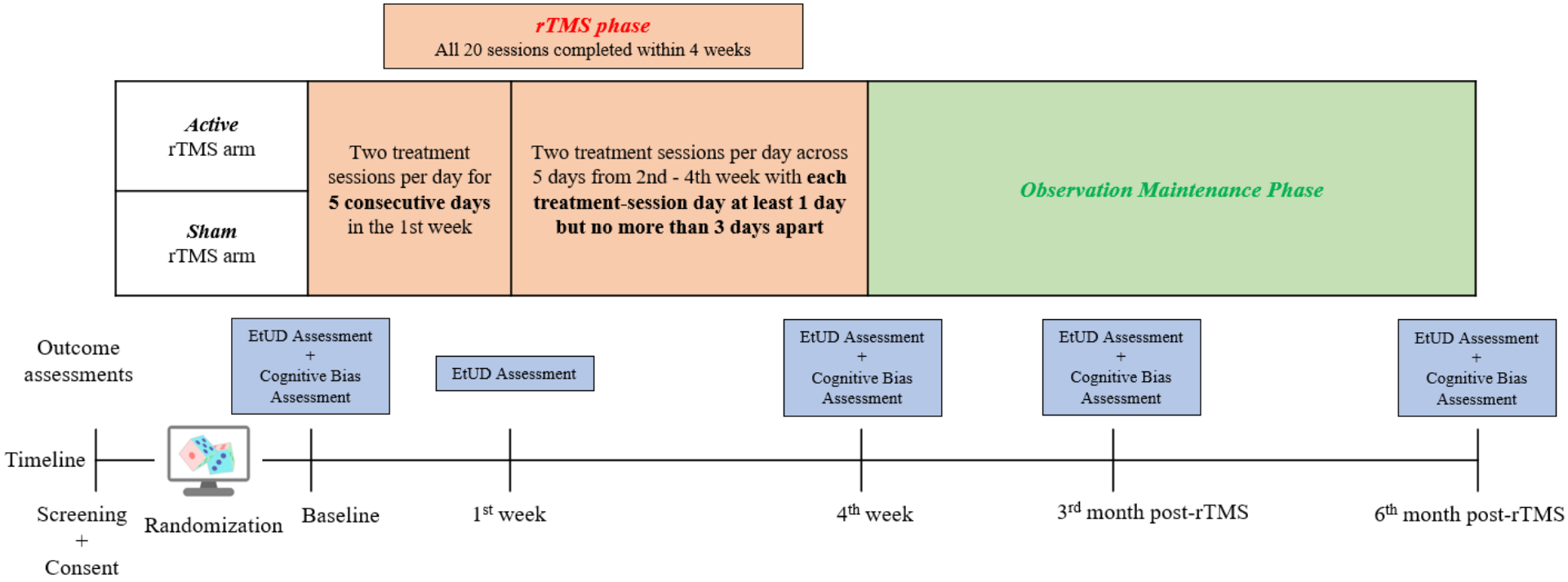

Figure 1. Treatment and outcome assessment schedule. EtUD: Etomidate use disorder

Table 1. Research outcomes and related assessment schedules to be conducted on each consented participant.

Assessment	Baseline	**rTMS Phase**				**Observation Maintenance Phase**			
		Week 1	→→→→→→→→→		Week 4	→→→→	Week 13 (3rd month)	→→→→	Week 26 (6th month)
EtUD									
Substance use interview	✓	✓			✓		✓		✓
SCID-5	✓	✓			✓		✓		✓
Urine Test	✓	✓			✓		✓		✓
BDF Question Set No. 5	✓	✓			✓		✓		✓
SDS	✓	✓			✓		✓		✓
CAS-S	✓	✓			✓		✓		✓
CIWA-B	✓	✓			✓		✓		✓
BAI	✓	✓			✓		✓		✓
BDI-II	✓	✓			✓		✓		✓
Cognitive									
MoCA-HK	✓				✓		✓		✓
DSST	✓				✓		✓		✓
Delay discounting task	✓				✓		✓		✓
Risk preference task	✓				✓		✓		✓

Note: SCID-5: Structured Clinical Interview for DSM-5, BDF: Beat Drugs Fund, SDS: Severity of Dependence Scale, CAS-S: Craving Automated Scale-Substance, CIWA-B: Clinical Institute Withdrawal Assessment for Benzodiazepines, BAI: Beck Anxiety Inventory, BDI-II: Beck Depression Inventory, MoCA-HK: Montreal Cognitive Assessment–HK version, DSST: Digit Symbol Substitution Test

h. References

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