Accelerated Deep Transcranial Magnetic Stimulation for Smoking Cessation

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STATEMENT OF COMPLIANCE

This clinical trial will be carried out in accordance with the following:

- International Council for Harmonisation Good Clinical Practice (ICH GCP)
- Tri-Council Policy Statement 2022 (TCPS 2)
- ISO 14155:2020 for Medical Device Clinical Trials
- Personal Health Information Protection Act (PHIPA), 2004; Chapter 3 Schedule A (PHIPA) and applicable regulations
- Institutional and REB policies and procedures

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Signature of PI	Date
_____	_____
Signature of Waypoint Site-PI	Date
_____	_____
Signature of Sunnybrook Site-PI	Date

LIST OF ABBREVIATIONS

aTMS	*Accelerated Transcranial Magnetic Stimulation*
AE	*Adverse Events*
ASRM	*Altman Self-Rating Mania Scale*
CAMH	*Centre for Addiction and Mental Health*
DLPFC	*Dorsolateral Prefrontal Cortex*
DSM-V	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
FDA	*U.S. Food and Drug Administration*
FTND	*Fagerstrom Test of Nicotine Dependence*
GABA	*Gamma-Aminobutyric Acid*
GAD-7	*General Anxiety Disorder-7*
GBDP	*Global Burden of Disease Project*
HCG	*Human Chorionic Gonadotropin*
ICF	*Informed Consent Form*
MAR	*Missing At Random*
MINI	*Mini International Neuropsychiatric Interview*
MNSW	*Minnesota Nicotine Withdrawal Scale*
NIBS	*Non-Invasive Brain Stimulation*
PHQ-9	*Patient Health Questionnaire-9*
REB	*Research Ethics Board*
REDCap	*Research Electronic Data Capture*
RMT	*Resting Motor Threshold*

RPN	*Research Practice Nurse*
rTMS	*Repetitive Transcranial Magnetic Stimulation*
TASS	*TMS Adult Safety Screening Questionnaire*
TLFB	*Timeline Follow-Back*
TMS	*Transcranial Magnetic Stimulation*
TCQ-SF	*Tobacco Craving Questionnaire-Short-Form*
TTC	*Toronto Transit Commission*

CLINICAL TRIAL SUMMARY

Title	Accelerated deep transcranial magnetic stimulation for smoking cessation
Short Title	adTMS smoking
Phase	Phase II
Methodology	One-arm, open-label pilot study
Clinical trial Duration	24 months
Participating site(s)	2 sites: Waypoint Centre for Mental Health Care and Sunnybrook Research Institute
Objectives	To examine the efficacy of accelerated deep transcranial magnetic stimulation on smoking abstinence
Number of Participants	40, aiming 30 completers
Duration of Intervention	5 days
Statistical Methodology	Descriptive statistics, mixed effect logistic regression, and linear/generalized mixed models will analyze abstinence and secondary outcomes, adjusting for covariates and missing data under the MAR assumption

1.0 INTRODUCTION

Tobacco use disorder is a serious and growing public health issue. The Global Burden of Disease Project (GBDP) estimated that 1.14 billion people smoked worldwide in 2019[1]. Smoking tobacco accounts for 7.69 million deaths per year and is the leading risk factor for death among males[1]. Increasing therapeutic strategies effective for the treatment of tobacco use disorder is therefore of tremendous importance. While first-line pharmacotherapies for tobacco use disorder demonstrate efficacy for short-term smoking cessation, relapse remains a challenge for smokers[2,3]; more modalities to address smoking cessation are needed.

In recent years, non-invasive brain stimulation (NIBS) approaches, such as transcranial magnetic stimulation (TMS), have gained attention. In 2020, the U.S. Food and Drug Administration (FDA) approved a deep TMS system for use in smoking cessation in adults[4], which was also approved by Health Canada in 2022, marking the first approval in the addiction field. This system focuses on the insula, which has been recognized as being related to nicotine cues and the self-administration of nicotine[5,6] in our previous studies. Our group has also evaluated deep TMS's efficacy in smoking cessation as an add-on treatment strategy to varenicline[7]. Beyond addiction, TMS has been approved and utilized in many neuropsychiatric disorders, such as treatment-resistant depression and obsessive-compulsive disorder, and has gradually developed many different modalities within TMS. One of these promising modalities is the accelerated protocol for TMS (aTMS).

aTMS could reduce depressive symptoms with a large effect size[8], which is comparable to or even superior to the standard TMS protocol in some settings[9,10]. For depression, deep aTMS could reach response and remission in less than one week, with such effects persisting for up to 6 months[11]. Given the great potential of this TMS protocol and the current need to expand and improve the modality for smoking cessation, we aim to examine deep aTMS's efficacy in smoking cessation and relapse prevention. To our knowledge, this will be the first trial testing deep aTMS for tobacco use disorder.

1.1 Background

Disease burden of smoking: The Global Burden of Disease Project (GBDP) estimated that the number of smokers worldwide increased from under 1 billion in 1990 to 1.14 billion in 2019[1,12]. Smoking is more prevalent among individuals with mental health disorders and co-addictions, such as substance use disorder, anxiety, depression, phobias, psychosis, and antisocial personality or conduct disorders[13–16]. Smoking that begins in adolescence or young adulthood and continues throughout life has a more severe impact on health than smoking that starts later or is not persistent[17,18]. If current trends continue, at least 320 million smoking-related deaths will occur among those under 30 unless they quit[19]. The mortality rate among long-term smokers could

be greater than one in two, potentially reaching as high as two in three[17,18,20,21], with half of these deaths likely occurring in middle age (30-69 years), leading to a loss of two or more decades of life[17,18]. Smoking remains the leading cause of premature death before age 70 in much of Europe and North America[17,18]. However, smoking cessation significantly reduces the risks associated with smoking. Smokers who quit before age 40 can avoid nearly all the increased mortality risks[19,21], and those who quit by age 50 reduce their risk of death from lung cancer by about two-thirds[22]. Given the significant health risks and high mortality associated with smoking, particularly among vulnerable populations, investigating new modalities for smoking cessation is crucial to reducing these risks and improving public health outcomes.

Repeated Transcranial Magnetic Stimulation (rTMS) as an innovative approach: rTMS is a technique that has been found to be useful as a potential treatment for neuropsychiatric diseases. rTMS is non-invasive, does not require anesthesia, and is not associated with significant side effects. There is compelling evidence that rTMS works by affecting the function of neuronal circuits and inducing local changes in neural excitability. Transient inactivation of a specific brain structure can also be induced in humans through rTMS, through mechanisms that are likely associated with potentiation of GABAB receptor mediated inhibitory neurotransmission[23]. However, rTMS effects are complex and likely involve local modifications in the dynamic release patterns of various neurotransmitters, including dopamine[24–28]. The fact that there is in vivo evidence that rTMS of frontal brain regions has a modulatory effect on dopaminergic system, suggest that rTMS may be particularly useful in neuropsychiatric disorders associated with dopamine dysfunction, such as addiction[25,29]. Moreover, with the recent development of Deep rTMS H-coils, it has become feasible to perform rTMS on deeper brain structures such as the insula[30–32].

Insula as a target structure: Several lines of research implicate the insula as a critical substrate in nicotine dependence following evidence that insular lesions produce a loss of self-reported cravings for cigarettes and immediate cessation of smoking without relapse[33,34]. As observed and examined by Naqvi et al., smokers with brain damage involving the insula are more likely to experience a disruption in their smoking addiction, often resulting in the ability to quit smoking without relapse and persistent urges, compared to smokers with brain damage that does not involve the insula[34]. They further proposed that the insula plays a role in the recall of the interoceptive effects of drug taking, and through interactions with other brain regions, mediates conscious urges and decision-making precipitating relapse[35]. This hypothesis is supported by preclinical studies[5,6,36–38] conducted at our translational addiction research laboratory, where we demonstrated that electrical stimulation at insular cortex significantly reduced nicotine-taking and nicotine-seeking behaviors triggered by cues and priming. These effects appear to be specific to nicotine-related behaviors, as stimulation did not affect food-taking behavior[6]. Additionally, GABA agonist-induced inactivation of both the granular and agranular insular cortex reduced nicotine self-administration[5,36]. Our previous preclinical studies have also shown that the insula plays a pivotal role in other addictions, including alcohol intake behavior[37] and rodent gambling task[38]. Neuroimaging studies further evidence significant associations

between cue-induced activation of the insula and self-reported craving for a cigarette[39], with greater bilateral insular pre-quit activity also predicting relapse in smokers[40]. Alongside the approval of deep TMS for clinical use in smoking[41], our laboratory has also tested the utility of insula-targeting deep TMS as an adjunctive treatment to varenicline, a psychopharmacological agent used for smoking cessation[7].

1.2 Study Intervention

Accelerated Transcranial Magnetic Stimulation (aTMS) protocols are increasingly being explored to address the practical challenges of conventional repetitive TMS (rTMS) and to enhance overall efficacy. Conventional rTMS typically involves one session daily over several weeks. In contrast, aTMS intensifies this approach by delivering multiple sessions per day, ranging from 2 to 10 sessions. In this study, we will implement the H4 deep aTMS protocol, administering 20 sessions over one week—four sessions daily for five consecutive days—targeting the bilateral insular cortex and prefrontal cortex using the Health Canada-approved H4 coil. The parameters used in each session will adhere to those approved by Health Canada, and will be described later (see Section 5.1). This method aims to improve efficacy and accessibility for smoking cessation, building on a more condensed and intensive schedule.

1.3 Preclinical Data to Date

Our Translational Addiction Research Laboratory has collected significant pre-clinical evidence supporting this trial. Preclinical results from our studies reveal that temporary insular inactivation in rats leads to reduced nicotine self-administration and seeking after exposure to nicotine-associated cues or a priming dose (Figure 1)[5,6]. These findings have been replicated under several conditions in rodent models, demonstrating that silencing the granular or agranular subregions of the insular cortex via local infusions of GABA receptor agonists (baclofen and muscimol) decreases both the motivation to self-administer nicotine and the likelihood of relapse when nicotine cues or priming doses are reintroduced [5,6,37].

Mechanistically, these results suggest that the insula integrates the interoceptive and affective states that drive nicotine use—disrupting insular activity weakens the craving and “urge” signals that typically reinforce smoking behavior [5,37]. Notably, such insular manipulations have been shown to have minimal effects on other reinforcers, such as food, indicating a degree of specificity for nicotine dependence[5]. Overall, these insights underscore the critical role of the insula in the neurocircuitry of tobacco addiction and support targeting insular function as a promising approach for reducing nicotine use and preventing relapse in smokers.

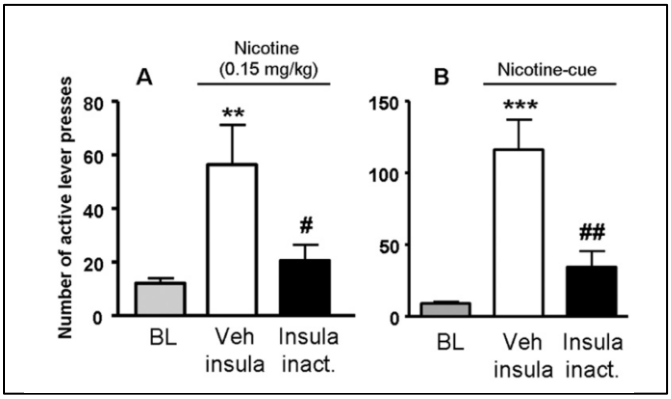

Figure 1. Effect of insula inactivation on (A) nicotine- (.15 mg/kg SC, 10 min before the session) or (B) cue-induced reinstatement of nicotine seeking tests after extinction (n = 8 and n = 6, respectively).; **p<0.01; ***p<0.001. Extracted from [5].

1.4 Clinical Data to Date

In a clinical trial, our group has suggested the efficacy of deep TMS in smoking cessation as an add-on treatment strategy to varenicline (Figure 2)[7].

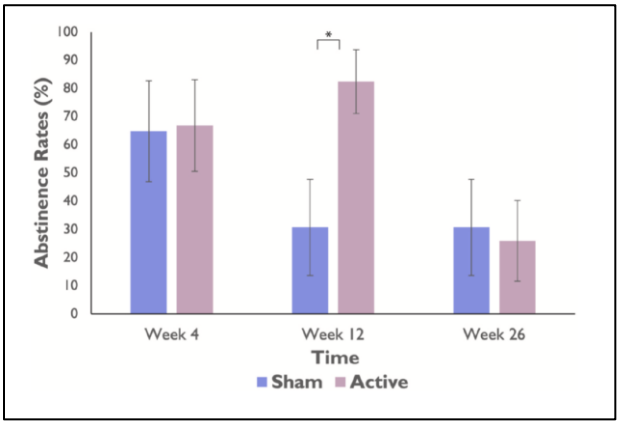

Figure 2. Abstinence rates at Week 4, 12, and 26. Abstinence was measured by 7- day point-prevalence abstinence. All measures were confirmed with plasma cotinine. Bars represent (±) standard error. Group sample sizes: Week 4 (n =18 active, n =16 sham), Week 12 (n =17 active, n =15 sham), and Week 26 (n = 16 active, n =15 sham).; *p<0.05.

In previous aTMS depression studies, the effect of aTMS may be attributed to several factors, including optimized neurocircuit-based targeting, an accelerated treatment schedule, and a higher total pulse count[42–46]. Optimized neurocircuit-based targeting can be achieved through e-field modeling or personalized, connectivity-based biomarkers, such as DLPFC-subgenual anterior cingulate cortex connectivity[42]. The higher total pulse count may also contribute to positive treatment outcomes. For example[47], 90,000 pulses delivered with accelerated protocol (1,800 pulses per session, 10 sessions per day, 5 days per week, over one week) demonstrated better efficacy in treating depression compared to 18,000 pulses administered through a standard protocol (600 pulses per session, 1 session per day, 5 days per week, over 6 weeks). However, the individual components of aTMS still need to be isolated. Many

previous aTMS depression studies combine more than one of these factors. Therefore, even when considering aTMS beyond smoking cessation, isolating the effect of the accelerated treatment schedule is crucial to understand this technique.

1.5 Risks/Benefits

Risk: Several recent investigations have demonstrated that aTMS maintains a favorable safety profile similar to conventional once-daily protocols[47–49]. In a real-world study of accelerated deep TMS for major depression, no serious adverse events were observed among 111 patients receiving two to ten sessions per day[11]. Parallel evidence from a transdiagnostic review of 63 aTMS studies likewise concluded that aTMS appears to be safe and well-tolerated, with adverse event rates comparable to once-daily TMS[50].

The most serious potential adverse event with TMS is seizure. Among 1543 participants undergoing 43,873 aTMS sessions, only one seizure (0.0023%) was reported—a rate similar to or lower than that of conventional rTMS delivered once per day[50]. Notably, the patient who experienced this single event later resumed standard once-daily TMS safely and achieved remission.

Headaches are the most frequently reported side effect, and aTMS is no exception, though rates appear comparable to those in conventional once-daily rTMS. In the aTMS review, 28.4% of participants reported headaches, followed by mild, transient scalp pain or discomfort (8.3%)[50]. Similar to once-daily TMS, these effects often diminish over the first few sessions. Apart from headache and scalp discomfort, side effects such as fatigue and other adverse events remained below 10%, and dropout rates attributable to side effects were approximately 2%[50].

This underscores that intensifying the treatment schedule with multiple daily sessions does not substantially amplify risk. Overall, the safety and tolerability of aTMS are consistent with the well-established profiles observed in standard TMS protocols.

Benefit: The advantage of an accelerated approach is based on three theoretical reasons[9,51]. First, it presumes that equal or greater effects can be achieved by repeatedly applying stimulation within a short time interval. Second, it suggests that the effects induced within densely scheduled sessions have durable efficacy. Third, aTMS has the theoretical advantage of an accelerated response to treatment, given that it clusters the stimulation intervention within days. Regarding the theoretical equal or greater effect of aTMS, neurophysiologic evidence supports this by showing that a greater effect on cortical excitability is observed if a second rTMS session is administered within 24 hours of the first session[52]. Such equal or greater effects are also observed clinically in patients with depression treated with aTMS[9]. The durability

and rapid onset of the proposed effects have also been demonstrated in naturalistic studies applying aTMS for depression[11]. Supporting a more densely clustered protocol, other research has proposed a dose-response relationship for rTMS, indicating that the number of stimuli and total session number correlate with the response[53].

In addition to the possible benefits already mentioned, examining the efficacy of aTMS for smokers has practical significance. The daily administration of rTMS over several weeks can limit its accessibility, particularly for patients who are working or must travel long distances to reach a treatment site[54]. Furthermore, individuals with tobacco use disorder often struggle with treatment adherence, even with psychopharmacological approaches[55], while longer treatment courses are more difficult to adhere to. About 98% of adults with tobacco use disorder complete psychopharmacological treatment in randomized controlled trial[56], but only 25~30% of adults with tobacco use disorder complete nicotine replacement therapy or psychopharmacological treatment in real life settings[57,58]. By consolidating the full course of TMS treatments from weeks into days, aTMS offers advantages in addressing these challenges, making it particularly relevant for patients with addictive disorders. For example, in a conventional once-daily 20-session treatment course, patients need to visit the TMS clinic over 20 days. In contrast, this proposed accelerated protocol allows 20 sessions to be administered within 5 days, meaning patients only need to visit the clinic for 5 days. By further confirming the comparable effectiveness of accelerated TMS to the standard protocol, we expect this approach to greatly enhance the feasibility and acceptability of the treatment for patients.

2.0 CLINICAL TRIAL OBJECTIVES

We will test, for the first time, the overall feasibility of bilateral accelerated deep transcranial magnetic stimulation (deep aTMS) for smoking abstinence, including measures of tolerability, acceptability, retention, and adherence. Our secondary objectives are to assess the effects of deep aTMS on short-term point prevalence abstinence—measured by self-reported abstinence over the past 7 days and confirmed with urine cotinine—at the end of treatment (Week 1), and at Weeks 3, 5, 9, 13, and 26, as well as prolonged and continuous abstinence rates at Weeks 13 and 26. We also aim to explore the potential for rapid onset of effect, along with its impact on attenuating craving, reducing cigarette consumption, and decreasing dependence severity throughout the study.

2.1 Primary Objectives

To assess the overall feasibility of bilateral accelerated deep TMS (aTMS) for smoking abstinence, including measures of tolerability, acceptability, retention, and adherence.

2.2 Secondary Objectives

Secondary Aim 1: To examine the effect of bilateral deep aTMS on short-term abstinence at the end of TMS treatment, at post-treatment follow-ups (point prevalence abstinence at Week 3, Week 5, Week 9, Week 13, Week 26),

Secondary Aim 2: To examine the effect of bilateral deep aTMS on prolonged and continuous abstinence at 3-month and 6-month follow-up (Week 13 and Week 26).

Secondary Aim 3: To examine the effect of bilateral deep aTMS on other smoking outcomes throughout study duration including self-reported craving, cigarette smoking and dependence severity.

3.0 CLINICAL TRIAL DESIGN

3.1 Overall Design

This clinical trial is designed as a one-arm, open-label study to evaluate the efficacy and feasibility of the H4 deep accelerated transcranial magnetic stimulation (aTMS) protocol for smoking cessation. The absence of a control group is intentional, as this pilot study focuses on assessing the intervention's preliminary efficacy in a single arm of 40 participants with tobacco use disorder who are motivated to quit, aiming for 30 completers to guide a future controlled trial. Each participant's involvement will last 26 weeks, starting with a screening phase at Week 0, followed by a one-week treatment period in Week 1, and concluding with follow-up visits at Weeks 3, 5, 9, 13, and 26. The entire trial is expected to span approximately 2 years, covering recruitment, treatment, and follow-up for all participants.

During Week 1, participants will receive 20 rTMS sessions using the Health Canada-approved H4 deep TMS coil, administered at four sessions per day over five consecutive days, targeting the insular cortex, alongside brief counseling adapted from the Mayo Clinic's 'Smoke Free and Living It' manual. Daily assessments will monitor safety, Timeline Followback (TLFB), and nicotine craving and withdrawal symptoms. The primary outcome is overall feasibility, including measures of tolerability, acceptability, retention, and adherence. Secondary outcomes include 7-day point prevalence abstinence—verified by self-report and urine cotinine levels (<200 ng/mL)—at the end of treatment and at Weeks 3, 5, 9, 13, and 26. We will also assess 3-month abstinence at Week 13 and 6-month abstinence at Week 26, both verified by continuous self-reported abstinence during

the respective periods and corresponding urine cotinine levels. Factors such as comorbidities, pre-existing tobacco use disorder severity, or motivation level for abstinence may influence results; these are addressed through eligibility criteria and statistical adjustments.

It is anticipated that a proportion of enrolled participants may not proceed to the treatment phase (Week 1) due to scheduling, logistical, or personal factors. These individuals will be classified as early dropouts and excluded from the intent-to-treat analysis, which will include only participants who initiate at least one TMS session.

3.2 Primary Endpoints

The overall feasibility of accelerated deep TMS (aTMS) for smoking abstinence: assessed through tolerability (frequency of side effects reported at each visit during Week 1), acceptability (self-reported ratings collected at the end of treatment), retention rate (the proportion of participants who completed the full study), and adherence rate (the proportion of completed sessions among participants who initiated treatment).

3.3 Secondary Endpoints

1. Proportion of participants achieving 7-day point prevalence abstinence at end of treatment, Week 3, Week 5, Week 9, Week 13, and Week 26.

2. Proportion of participants achieving prolonged and continuous abstinence at Week 13 and Week 26.

3. Change in self-reported craving, average cigarettes smoked per day, and dependence severity (e.g., using standardized questionnaires) from baseline through study completion.

4.0 PARTICIPANT SELECTION, RECRUITMENT AND WITHDRAWAL

4.1 Target Population

This trial targets 40 adults (aged 18-65) with tobacco use disorder who smoke ≥10 cigarettes daily, have an FTND score ≥4, and a Contemplation Ladder score ≥7, aiming for 30 completers. Pregnant people, children, cognitively impaired individuals (MMSE <24), and those with rTMS safety concerns, such as underlying neurological diseases or a history of seizures or suicidal behavior, are excluded.

4.2 Participant Recruitment and Screening

Recruitment: Participants in the proposed study will be individuals with tobacco use disorder (n=40). The anticipated accrual rate is approximately 20 participants per year. With a target sample size of 40, we expect to complete enrollment over a period of 2 years. We will recruit through various sources: local newspaper ads, the community, Waypoint Centre for Mental Health Care, and Sunnybrook Health Sciences Centre clinics, word of mouth, and/or through posters/flyers distributed in and around the research sites. Approved study recruitment ads will be placed primarily around, but not limited to, the Midland-Penetanguishene and downtown Toronto areas to target participants who can feasibly travel to either study site. In Toronto, ads may also be placed in TTC streetcars, buses and subways. Ads and flyers will be approved by the REB. Participants may also be recruited from similar protocols approved at each research center provided they have agreed to being contacted about future studies.

Eligibility Screening: Potential participants will undergo Waypoint or Sunnybrook REDCap pre-screening to determine initial eligibility. They will subsequently be invited to an in-person or remote Screening Assessment to confirm final eligibility to participate. Following the review and signing of the Informed Consent Form, the following measures and assessments will be administered at the screening visit:

1) Fagerstrom Test of Nicotine Dependence (FTND). The FTND is a measure of physical dependence severity.

2) Mini International Neuropsychiatric Interview (MINI). MINI will be used to diagnose tobacco use disorder in participants and/or any other psychiatric issues.

3) Smoking Contemplation Ladder. This questionnaire allows for the measure of readiness to quit smoking in individuals. A cutoff score of 7 is commonly used to determine individuals who are motivated to quit.

4) Medical and/or psychiatric assessment by study physician (or delegate).

5) Demographic and contact forms.

6) TASS form (TMS Adult Safety Screening Questionnaire).

7) Concomitant medication log.

Compensation: Participants who complete the full study will receive a total compensation of $550, provided either in cash (in CAD) or as an electronic gift card (e.g., EverythingCard). This amount comprises $25 for the screening and baseline visit each, $250 for the series of accelerated rTMS visits ($50 per visit for five visits), and $50 for each of the five follow-up visits.

4.3 Equity, Diversity and Inclusion Considerations

This study aims to recruit a diverse sample that reflects Ontario's population, ensuring the inclusion of historically underserved groups from various socioeconomic backgrounds. Given that we will also be recruiting participants at Sunnybrook Health Sciences Centre in Toronto, the most multicultural city in Canada, we anticipate strong minority group inclusion and will implement recruitment strategies that promote participation without restrictions based on race or ethnicity. Additionally, in alignment with Waypoint Centre for Mental Health Care's Equity, Diversity, and Inclusion strategy, we will integrate training on Indigenous Cultural Safety, Anti-Black Racism, and EDI principles to foster an inclusive research environment. Recruitment and retention strategies will also be designed to ensure that our research team and staffing reflect the diverse patient populations we serve.

Recognizing that sex and gender differences influence addiction and treatment outcomes, our study will integrate sex- and gender-based analysis to ensure a comprehensive approach to data interpretation. We will collect and analyze self-reported biological sex and gender identity to assess potential differences in treatment efficacy and interpret findings through a sex- and gender-based lens, ensuring that our recommendations remain relevant across diverse populations. Given established sex-related differences in smoking behaviors and nicotine metabolism, we will make every effort to recruit an equal number of male and female participants for robust sex-based analyses. Additionally, studies have shown that hormonal fluctuations can influence rTMS effects, with women exhibiting greater sensitivity to stimulation during periods of high estrogen. To ensure safety, pregnant or breastfeeding individuals will be excluded, as the safety of deep TMS in these populations has not been established.

4.4 Eligibility Criteria

4.4.1 Inclusion Criteria

The participant must meet all of the inclusion criteria to be eligible for this clinical trial:

1. Aged 18 years or older;
2. Tobacco use disorder as assessed by DSM-5;
3. Fagerstrom Test of Nicotine Dependence (FTND) ≥ 4;
4. Reported motivation to quit within 30 days as assessed using the Contemplation Ladder score of ≥ 7;
5. Must sign and date the informed consent form;
6. Stated willingness to comply with all study procedures.
7. Able to communicate in English.

4.4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this clinical trial:

1. Reported smoking abstinence in the 3 months preceding screening visit;
2. Current use of other smoking cessation aids;
3. Contraindication to rTMS;
4. Pregnancy, trying to become pregnant or breastfeeding;
5. Current or recent history of cerebrovascular disease;
6. Unstable major psychiatric disorder(s) (i.e. Axis I Disorders) that would prevent participation in the study at PI (or its delegate) discretion;
7. Serious current or personal history of medical condition/disease (neurological disorders, brain lesions, multiple sclerosis, head trauma, loss of consciousness, hearing loss, etc.) preventing same inclusion as per PI (or its delegate) discretion;
8. Current, personal history or family history of seizures;
9. Concomitant use of medication that lowers seizure threshold, such as clozapine;
10. Concomitant use of more than 2 mg lorazepam (or an equivalent) or any anticonvulsants.

4.5 Lifestyle Considerations

- Refrain from use of unregulated or illicit substance use during the rTMS treatment course. If there is use of any of these substances they will be assessed by a study physician to ensure that they are safe to continue with treatment.
- Refrain from problematic alcohol use that includes frequent and recent binge drinking (5 or more drinks on an occasion for men or 4 or more drinks on an occasion for women), the presence of significant alcohol withdrawal symptoms, unpredictable pattern of use with varying amounts of drinking, and in the high-risk category according to low-risk drinking guidelines. Any of these signs will require assessment by a study physician.
- Cannabis use will be assessed prior to treatment start. In general, they will be advised not to make any abrupt changes to their cannabis use without informing the study team. Those that show up visibly intoxicated or in withdrawal from any substance, including cannabis, will need to be seen by a study physician to ensure safety and whether they are appropriate to continue in the trial. Recreational cannabis use is not prohibited as long as they are not exhibiting signs of problematic cannabis use that would destabilize them medically or psychiatrically.
- If problematic substance use as above should arise during the trial, to notify the principal investigator to manage with any other clinical care providers connected to the participant. Emergency medical services will be accessed as needed. Withdrawal from the trial will be determined based on inclusion/exclusion/withdrawal criteria and safety considerations at the discretion of the PI and study team.
- Cigarette smoking induces the liver enzyme CYP1A2, and thus increases metabolism by certain medications that are metabolized by CYP1A2[59]. Participants that are on

these medications will be reviewed to determine whether dose reductions may be needed if patients reduce their cigarette smoking during the treatment course.
- As well, patients with diabetes will also be instructed to monitor their blood sugars more regularly due to the variable effects of smoking cessation on blood sugar control and insulin sensitivity[60].

4.6 Screen Failures

For all screen failures, information including demography, screen failure details, and eligibility criteria will be collected. Re-screening generally will be considered after ≥1 month and/or at the discretion of the Lead PI, Site-PI, and study team depending on reason for screen failure.

4.7 Participant Withdrawal Criteria

4.7.1 When and How to Withdraw Participants

Patient participants are free to withdraw from participation in the clinical trial at any time. Completion of the study visits involving doing self-report surveys or semi-structured interviews do not have any withdrawal criteria except clinical instability precluding them from safely engaging in the assessment, as determined by the Lead PI/Site-PI.

For the Week1, accelerated deep TMS treatment period: An investigator will discontinue or withdraw a participant for the following reasons:
- Requires in-patient psychiatric hospitalization.
- Develops clinically significant hypomanic or manic symptoms. Possible hypomanic or manic syndromes may be identified by study staff and a study physician will be immediately notified to conduct an assessment.
- Cannot tolerate stimulation at 90% RMT on ≥5 treatment sessions overall.
- Develops any medical illness that may be unstable or experience a seizure.
- If a participant must miss rTMS treatments because of COVID-19 symptom screening/exposure restrictions and are not allowed to be on-site, those sessions will not count towards having to discontinue from study treatment per withdrawal criteria. It will be at the discretion of the investigators on a case-by-case basis if a participant needs to discontinue treatment during the trial should the absence secondary to COVID-19 symptom restrictions be prolonged.

For the entire study period: An investigator may discontinue or withdraw a participant for the following reasons:
- Pregnancy
- Withdraws consent.

- Meets an exclusion criterion (either newly developed or not previously recognized) related to safety that precludes further treatment.
- Demonstrates clinical instability to the point where further participation in the study would not be in the best interests of the participant, at the discretion of the PI and the study investigator team.

The reason for participant discontinuation or withdrawal from the study will be recorded within the participant's research record, and/or legal health record. Data up to the point of their last visit may be included in the analysis.

4.7.2 Follow-up for Withdrawn Participants

If a participant withdraws consent, they can also request the withdrawal of their data subject to any research-specific restrictions, unless the data has already been de-identified and shared. Once withdrawn from the clinical trial, no further research procedures or evaluations will be performed, or additional research-specific data collected on the participant. Reasonable effort will be made to obtain permission to document the reason for withdrawal.

4.7.3 Early Termination Visit

If a patient participant withdraws from the clinical trial, they will be asked to attend an Early Termination Visit. This includes all assessments included in the post rTMS treatment visit as well as:

- Assessment of new and ongoing AEs.
- Assessment of any complications following the study intervention.
- Documentation of all concomitant medications.

The PI will ensure the participant is appropriately followed for any additional care as required. Data collected until the time of withdrawal may be used in analyses.

4.7.4 Participants who are Lost to Follow-up

A patient participant will be considered lost to follow-up if they fail to return for >3 scheduled visits that cannot be rescheduled and are unable to be contacted by the research team.

The following actions will be taken if a participant fails to attend a required study visit:

- The research team will attempt to contact the participant and reschedule the missed visit within the next 4 weeks and reconfirm whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the research team will make every effort to regain contact with the participant (where possible, at least five contact attempts including both telephone calls and emails, unless specific contact preferences were specified by the participant). These contact attempts will be documented in the participant's research record and/or legal health record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the clinical trial with a primary reason of lost to follow-up. Data up to the point of their last visit will be included in the analysis.

5.0 STUDY INTERVENTION

5.1 Description

Treatment will be delivered through the H4 coil (Brainsway, Israel) and Brainsway stimulator system, generally following previously established reports[41]. Week 1, the treatment period, will begin on the participant's Target Quit Date (TQD), which will be standardized to coincide with the first day of TMS, as smokers are believed to be most susceptible to relapse during the early abstinence phase[61]. However, this may vary due to scheduling constraints. Resting motor threshold (RMT) will be established to determine stimulation intensity at the beginning of the treatment course. This is obtained by finding the optimal position of the helmet that elicits reliable activation of the right abductor pollicis brevis muscle, before then aligning the helmet symmetrically and moving it 6 cm anteriorly. Titration of stimulus intensity may occur to enhance tolerability. Stimulation intensity will be set at 120% RMT, with a minimum of 90% RMT if there are issues with tolerability. Initial sessions may start at a lower intensity (approximately 70% RMT) and increase accordingly. Sixty trains of 30 pulses each (total 1,800 pulses) will be applied at 10 Hz, for 3 second trains, with a 15 second inter-train interval, for approximately 18 minutes of treatment time. For each day within Week 1, four sessions will be administered, with an intersession interval of 30 minutes. TMS could be reschedule the next week in case of holidays, hospital closure or other factors that prevent booking the subjects.

Participants will be asked to abstain from smoking for ≥2 hours before each visit in Week 1. Before the first session of each day in Week 1, it will be preceded by a brief provocation procedure that involves participants being asked to imagine one of their biggest triggers for smoking cravings, viewing pictures of smoking and handling a cigarette and lighter (with no lighter fluid) guided by a scripted recorded voice. In their baseline clinical assessment, participants will identify a list of their top 5 triggers for smoking. For the first session of each day in Week 1, prior to stimulation, first the participant will be asked to close their eyes and imagine one of the identified triggers for 30 seconds. Next they will be presented with real cigarettes and a lighter, and then be asked to listen to a recording for how to handle a cigarette and a lighter for 2 minutes. The recording will tell the participant to hold both items; they will not be asked to light the cigarette or smoke the cigarette. The cigarette and lighter will be as similar as

possible to what each individual participant usually uses. If possible, the lighter fluid will be removed from the lighter to reduce fire risk. Following this, they will watch a PowerPoint presentation of smoking pictures for 2 minutes and 30 seconds. Thus, the entire procedure will be 4 minutes prior to stimulation start administered by trained research staff.

5.2 Treatment Regimen

The treatment course consists of daily treatment with four sessions per day, over five days in Week 1 (one week), for a total of 20 treatment sessions.

5.3 Method for Assigning Participants to Treatment Groups

Since this is a one-arm trial, all participants will receive accelerated deep TMS, with no randomization or allocation to different groups.

5.4 Administration of Study Intervention

Deep TMS with accelerated protocol: Each treatment will be administered by an rTMS technician, RPN, or other trained individual. The individual responsible for administering all treatments will be adequately trained through the Sunnybrook Research Institute and Waypoint Centre for Mental Health Care, in collaboration with the University of Toronto, which offers a successful rTMS technician course covering all the technical and hands-on training required for the safe and effective delivery of rTMS.

Each day in Week 1 will last approximately 3 hours including 4 minutes for general setup, 3 minutes for the cue-induced craving protocol, and four 18-minute rTMS sessions interleaved with three 30-minute intervals approximately (4-3-18-30-18-30-18-30-18). Scheduling may vary slightly based on equipment availability.

5.5 Participant Compliance Monitoring

Attendance to rTMS treatment sessions will be tracked and missed sessions will be counted. Any withdrawal from the study due to non-compliance will be addressed as per section 4.7.

5.6 Concomitant Therapy

All prescribed medications, over-the-counter medications, and supplements will be recorded and reviewed by the Lead PI/Site-PI at screening/baseline. Concomitant

medications and therapies will be verified with research participants at each study visit. All participants will have the opportunity to discuss their concomitant medications, and the risks and benefits of the study intervention will be reviewed with the study doctor (see Section 4.4.2: Patient Participant Exclusion Criteria).

Currently, no pharmacological agents have been shown to have any clear interactions (whether beneficial or harmful) with rTMS. Participants will be informed that the pilot and pivotal RCTs supporting the use of deep TMS for smoking cessation also excluded individuals already using other smoking cessation treatments. Therefore, participants will be asked not to initiate any new medications intended to aid smoking cessation during the 13-week study course, as outlined in Section 4.4.2.

As mentioned in Section 4.5: Lifestyle Considerations, reducing cigarette smoking may alter the levels of certain medications due to its effects on CYP1A2 metabolism. Additionally, smoking reduction may impact insulin resistance and glycemic control in individuals with diabetes. In such cases, medications metabolized by CYP1A2 or those used for diabetes management may require dose adjustments at the discretion of the study physician and the prescribing physician.

5.7 Packaging

N/A

5.8 Blinding of Study Intervention

This is an open-label trial, so there will be no blinding for participants and study assessors.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Study Intervention Supplies

N/A

5.9.2 Storage

Details of rTMS device storage will be maintained and overseen by the Harquail Centre for Neuromodulation at Sunnybrook Research Institute and Neuromodulation Program at Waypoint Centre for Mental Health. Existing devices are stored at the two sites. Maintenance and calibration will be according to manufacturer guidance from Brainsway and will be performed according to their standards.

5.9.3 Dispensing of Study Intervention

N/A

5.9.4 Return or Destruction of Study Intervention

N/A

6.0 RESEARCH PROCEDURES

6.1 Research Visits

Prescreening during initial contact through phone, email or REDcap: A delegated research staff will conduct prescreening with the participants during their initial contact call to determine their initial eligibility to be screened in the study. This consists of a set of questions regarding inclusion and exclusion criteria. During pre-screening, we will ask participants to indicate their preferred site (Waypoint or Sunnybrook).

Screening visit (SC): A delegated research staff will conduct the informed consent discussion with the patients at the beginning of the screening visit before the assessments to determine their eligibility to participate in the study (Section 6.2. Table). The informed consent process will include a short quiz of five questions to ensure that the participant understands the key information provided. This quiz will be completed after the ICF is explained and before the participant signs it. The screening visit will confirm eligibility through the eligibility checklist that also relies on administration of the TASS and FTND, and the Mini International Neuropsychiatric Interview (MINI) to screen for psychiatric diagnoses according to the DSM-5. We will also collect demographic information, medical history and current medications. The informed consent and assessments may be performed virtually, depending on the scheduling availability of study staff and the participant (refer to Sections 8.5 and 12.2).

- Informed consent (including informed consent quiz)
- Medical history for underlying diseases
- Basic demographics, such as age, sex at birth
- Mini International Neuropsychiatric Interview (MINI)
- TMS Adult Safety Screening Questionnaire (TASS)
- Smoking Contemplation Ladder
- Target Quit Day, for scheduling the week for TMS treatment[61]
- Concomitant medication log, recorded by its generic name, dosage, and dosing frequency
- Fagerstrom Test of Nicotine Dependence (FTND). The FTND is a measure of physical dependence severity.

Baseline visit (BL):

The baseline visit will consist of urine testing using point-of-care dip testing, a concomitant medication survey, and self-report questionnaires. All components of the baseline visit must be completed within 30 days prior to W1D1; otherwise, they should be reassessed.

For the urine drug panel test at the baseline visit (BL) and at the fifth day of Week1 (W1D5), which includes opioids, stimulants, and alcohol, the rationale is that intoxication or withdrawal from stimulants or alcohol may affect the safety of receiving TMS. While the use of non-nicotine substances does not determine eligibility, participants will be advised to refrain from using these substances during treatment in Week 1. However, if the use of a non-nicotine substance demonstrates clinical instability to the extent that continued participation would not be in the best interest of the participant, PI and the study investigator team may decide to discontinue their involvement at PI and Site-PI's discretion (refer to Section 4.7.1). The final eligibility will be determined by the site PIs based on information collected at the screening and baseline visits.

The screening and baseline visits may be completed on site in a single day, depending on research staff availability and participant preference.

Urine testing:

- Urine drug panel, to test recent substance use, including opioids, stimulants, and alcohol, as intoxication or withdrawal from stimulants or alcohol may affect the safety of receiving TMS
- Urine pregnancy test, if required. To confirm pregnancy status, as pregnancy is an exclusion criterion.
- Urine cotinine test (threshold: 200 ng/ml) to confirm recent cotinine use.

Self-report questionnaires:

- Timeline Follow-Back (TLFB) – Amount of cigarette used every day since the last follow-up
- Fagerstrom Test of Nicotine Dependence (FTND). The FTND is a measure of physical dependence severity.
- Tobacco Craving Questionnaire-Short-Form (TCQ-SF), to measure smoking craving.
- Minnesota Nicotine Withdrawal Scale (MNWS), to measure the nicotine withdrawal symptoms.
- Patient Health Questionnaire (PHQ-9), to track the possible effects of TMS on depression symptoms.
- General Anxiety Disorder-7 (GAD-7), to track the possible effects of TMS on anxiety symptoms.
- Altman Self-Rating Mania Scale (ASRM), to track the possible effects of TMS on developing manic/hypomanic symptoms.

Treatment period (Week 1)

Accelerated deep TMS will be administered daily, with four sessions per day, lasting approximately 3 hours (refer to Section 5.4), along with assessments for safety/adverse effects and scales for nicotine dependence, craving, and withdrawal symptoms. Participants' activities were not systematically controlled during treatment sessions or during the intersession intervals; participants were allowed to do light cognitive activities such as reading or using their computer or smartphone.

On each day of Week 1, the TCQ-SF will be administered twice to measure nicotine craving—once before and once after the aTMS treatment.

Brief counseling for smoking cessation, adapted from the Mayo Clinic's 'Smoke Free and Living It' manual, will be administered at W1D1 and W1D5. The brief counseling sessions may also be offered remotely, based on participant preference and logistical feasibility.

<u>The first day of Week 1 (W1D1)</u>

- Concomitant medication log, recorded by its generic name, dosage, and dosing frequency
- Timeline Follow-Back (TLFB) – Amount of cigarette used every day since the last follow-up
- Tobacco Craving Questionnaire-Short-Form (TCQ-SF), to measure smoking craving. TCQ-SF will be administered twice—once before and once after the aTMS treatment.
- Minnesota Nicotine Withdrawal Scale (MNWS), to measure the nicotine withdrawal symptoms.
- Urine drug panel
- Urine pregnancy test, if required
- Brief counseling for smoking cessation, adapted from the Mayo Clinic's 'Smoke Free and Living It' manual.
- Resting motor threshold measurement
- Accelerated deep TMS treatment
- Adverse event log

<u>The second, third, and fourth days of Week 1 (W1D2, W1D3, W1D4)</u>

- Concomitant medication log, recorded by its generic name, dosage, and dosing frequency
- Timeline Follow-Back (TLFB) – Amount of cigarette used every day since the last follow-up
- Tobacco Craving Questionnaire-Short-Form (TCQ-SF), to measure smoking craving. TCQ-SF will be administered twice—once before and once after the aTMS treatment.
- Minnesota Nicotine Withdrawal Scale (MNWS), to measure the nicotine withdrawal symptoms.

- Accelerated deep TMS treatment
- Adverse event log

The fifth day of Week 1 (W1D5)

At the end of Week 1 (W1D5), a urine cotinine test will be performed, alongside TLFB to determine 7-day point-prevalence abstinence.

At W1D5, for acceptability assessment, a TMS Experience Questionnaire will be administered. Participants will be asked to retrospectively rate (from 1=not at all to 5=very much so) 15 items querying their perceptions of the treatment, its side effects, and its benefits as well as their preferences regarding treatment format and logistics.

- Concomitant medication log, recorded by its generic name, dosage, and dosing frequency
- Timeline Follow-Back (TLFB) – Amount of cigarette used every day since the last follow-up
- Fagerstrom Test of Nicotine Dependence (FTND). The FTND is a measure of physical dependence severity.
- Tobacco Craving Questionnaire-Short-Form (TCQ-SF), to measure smoking craving. TCQ-SF will be administered twice—once before and once after the aTMS treatment.
- Minnesota Nicotine Withdrawal Scale (MNWS), to measure the nicotine withdrawal symptoms.
- Patient Health Questionnaire (PHQ-9), to track the possible effects of TMS on depression symptoms.
- General Anxiety Disorder-7 (GAD-7), to track the possible effects of TMS on anxiety symptoms.
- Altman Self-Rating Mania Scale (ASRM), to track the possible effects of TMS on developing manic/hypomanic symptoms
- Accelerated deep TMS treatment
- Adverse event log
- Urine drug panel
- Urine pregnancy test, if required
- Urine cotinine test (threshold: 200 ng/ml)
- TMS Experience Questionnaire
- Brief counseling for smoking cessation, adapted from the Mayo Clinic's 'Smoke Free and Living It' manual.

Follow-up period (Week 3, 5, 9)

During the Week 3, Week 5, and Week 9 visits, a urine cotinine test and TLFB will be administered to determine 7-day point-prevalence abstinence. Side effect evaluation and brief smoking counseling will also be provided at these three visits, along with

assessments for nicotine dependence, withdrawal, craving, and symptoms of depression, anxiety, and mania.

- Concomitant medication log, recorded by its generic name, dosage, and dosing frequency
- Timeline Follow-Back (TLFB) – Amount of cigarette used every day since the last follow-up
- Fagerstrom Test of Nicotine Dependence (FTND). The FTND is a measure of physical dependence severity.
- Tobacco Craving Questionnaire-Short-Form (TCQ-SF), to measure smoking craving.
- Minnesota Nicotine Withdrawal Scale (MNWS), to measure the nicotine withdrawal symptoms.
- Patient Health Questionnaire (PHQ-9), to track the possible effects of TMS on depression symptoms.
- General Anxiety Disorder-7 (GAD-7), to track the possible effects of TMS on anxiety symptoms.
- Altman Self-Rating Mania Scale (ASRM), to track the possible effects of TMS on developing manic/hypomanic symptoms
- Adverse event log
- Urine cotinine test (threshold: 200 ng/ml)
- Brief counseling for smoking cessation, adapted from the Mayo Clinic's 'Smoke Free and Living It' manual.

Follow-up period (Week 13 and 26)

During the Week 13 and 26 visit, a urine cotinine test and TLFB will be administered to determine prolonged abstinence and continuous abstinence. Three-month or six-month prolonged abstinence is defined as abstinence from the end of treatment (W1D5) to the end of follow-up (Week 13 or 26), while three-month or six-month continuous abstinence is defined as abstinence from the target quit day (in Week 1) to the end of follow-up (Week 13 or 26). Assessments for nicotine dependence, withdrawal, craving, and symptoms of depression, anxiety, and mania will also be performed.

- Concomitant medication log, recorded by its generic name, dosage, and dosing frequency
- Timeline Follow-Back (TLFB) – Amount of cigarette used every day since the last follow-up
- Fagerstrom Test of Nicotine Dependence (FTND). The FTND is a measure of physical dependence severity.
- Tobacco Craving Questionnaire-Short-Form (TCQ-SF), to measure smoking craving.
- Minnesota Nicotine Withdrawal Scale (MNWS), to measure the nicotine withdrawal symptoms.
- Patient Health Questionnaire (PHQ-9), to track the possible effects of TMS on depression symptoms.

- General Anxiety Disorder-7 (GAD-7), to track the possible effects of TMS on anxiety symptoms.
- Altman Self-Rating Mania Scale (ASRM), to track the possible effects of TMS on developing manic/hypomanic symptoms
- Adverse event log
- Urine cotinine test (threshold: 200 ng/ml)
- Brief counseling for smoking cessation, adapted from the Mayo Clinic's 'Smoke Free and Living It' manual.

All assessments and surveys during research visits can be completed in one of two ways, based on participant preferences or each site's standard data collection practices:

1. **Paper option:** Assessments and surveys printed from REDCap will be completed by hand. A study delegate will review the paper source for completeness and accuracy and enter the data into REDCap.
2. **Electronic:** A study delegate will log into REDCap and will remain present while the participant enters their responses to assessments on an electronic device (e.g., computer, iPad). The study delegate will review the assessment for completeness before saving and help the participant navigate to the next assessment or survey, as necessary.

Procedures for addressing active suicidal ideation during research visits can be found in Section 8.5 (Safety Management Plan).

6.2 Schedule of Events

Below is the table outlining the assessments, measures, and treatments done at each visit.

		Screening	Baseline	Treatment					Follow-ups				
	Week			**W1**					**W3**	**W5**	**W9**	**W13**	**W26**
	Visit Code/Number	**SC**	**BL**	**W1D 1**	**W1D 2**	**W1D 3**	**W1D 4**	**W1D 5**	**W3**	**W5**	**W9**	**W13**	**W26**
Assessments & Measures	**In-person visit**		X	X	X	X	X	X	X	X	X	X	X
	ICF	X											
	Contact & Demographic Form	X											
	Medical history	X											
	MINI	X											
	TASS	X											
	Smoking Contemplation Ladder	X											
	Quit day plan	X											
	Concomitant Medication Log	X	X					X	X	X	X	X	X
	Urine Drug Panel		X	X				X					
	Urine Pregnancy Test (if required)		X	X				X					
	TLFB(Cigarettes)		X	X	X	X	X	X	X	X	X	X	X
	FTND	X	X					X	X	X	X	X	X
	TCQ-SF (regular or pre-TMS)		X	X	X	X	X	X	X	X	X	X	X
	TCQ-SF (post-TMS)			X	X	X	X	X					
	MNSW		X	X	X	X	X	X	X	X	X	X	X
	PHQ-9		X					X	X	X	X	X	X
	GAD-7		X					X	X	X	X	X	X
	ASRM		X					X	X	X	X	X	X
	AE Log			X	X	X	X	X	X	X	X	X	X
	Counseling			X				X	X	X	X	X	
	Urine cotinine test		X					X	X	X	X	X	X
	Confirm eligibility		X										
	TMS Experience Questionnaire							X					
	Point Prevalence Abstinence							X	X	X	X	X	X
	Prolonged Abstinence											X	X
	Continuous Abstinence											X	X
	RMT for TMS			X									
Treat	**TMS**			X	X	X	X	X					

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

We aim to assess the abstinence rate at different time points and the feasibility of the accelerated deep TMS protocol for smoking cessation. Based on our previous trial[7], which tested the efficacy of deep TMS as an add-on to varenicline treatment, the point prevalence abstinence rate at Week 12 (8 weeks after the treatment ends) was 82.4% in the varenicline + deep TMS group and 30.7% in the varenicline + sham stimulation group. For this feasibility study, we plan to recruit 30 completers, targeting a sufficient number of completers to allow for meaningful estimates of the abstinence rate across multiple time points. This sample size is consistent with the exploratory nature of a pilot study and will provide valuable preliminary data for planning a larger, fully powered clinical trial in the future.

7.2 Statistical Methods

Descriptive statistics will be used to summarize the baseline clinical and demographic variables for the study population. Subjects with missing values will be compared with completers on baseline characteristics, to help in the understanding of the reasons for missing values, if at least 10 subjects (25%) are found to be missing.

For the abstinence measure, an intent-to-treat (ITT) approach will be used, including all participants who received at least one TMS session, regardless of treatment completion.

Mixed effect logistic regression, using abstinence at the end of treatment, Week 3, Week 5, Week 9, Week 13, and Week 26 as dependent variables will be adjusted to the data. Categorical time points (end of treatment and Week 3, Week 5, Week 9, Week 13 and Week 26) will be specified as fixed effect, and subject intercepts as random effects. Baseline variables correlated with missingness and/or known to be associated with the outcome will be added as covariates, with focus on model parsimony (not to include many covariates) due to small sample size. Abstinence will be analyzed at the end of treatment, Week 3, Week 5, Week 13, and Week 26 as part of our secondary objectives.

Mixed effect models using maximum likelihood estimation accounts for missingness in the dependent variable by using all available information in the estimation, under the MAR assumption (Missing At Random – the values of a data points are not associated with the missing status of the data point after accounting for relevant covariates)[1]. Other measures related to our secondary objectives (e.g., FTND, TLFB, etc.) will also be analyzed using linear mixed or generalized mixed models, depending on the nature of the outcome of interest. Graphs will be used to explore the data, the models assumptions (for example, residual plots), as well as model results (for example, estimated means plot).

Due to small sample, effect sizes with 95% confidence intervals as well as standardized effect sizes will be reported.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

An **adverse event** (AE) is any untoward medical occurrence in a research participant administered an investigational product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational product.

In this trial, symptoms commonly associated with smoking withdrawal (e.g., irritability, anxiety, increased appetite, restlessness, and difficulty concentrating) will not be classified as adverse events unless they exceed the expected severity or duration. These withdrawal-related symptoms will still be systematically documented and monitored using standardized measures, such as the Minnesota Nicotine Withdrawal Scale (MNWS), and assessed during study visits for safety monitoring purposes.

Serious Adverse Event

A **serious adverse event** (SAE) is any AE that is:

- Fatal.
- Life-threatening.
- Requires or prolongs hospital stay.
- Results in persistent or significant disability or incapacity.
- A congenital anomaly or birth defect; or
- An important medical event (events that may not be life threatening but are of major clinical significance, such as a drug overdose or seizure that did not result in in-patient hospitalization).

Adverse Event Collection Period

The period during which adverse events must be collected is normally defined as the period from the initiation of any research procedures to the end of the study treatment follow-up. For this clinical trial, the study treatment follow-up is defined as 30 days following the last administration of the study intervention.

Preexisting Condition

A preexisting condition is one that is present at the start of the clinical trial. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. Throughout the clinical trial, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
At the last scheduled visit, each participant will be asked of any subsequent event(s) that the participant believes might reasonably be related to participation in this clinical trial. The Sponsor should be notified of any death or reportable adverse event occurring at any time after a participant has discontinued or terminated participation that may reasonably be related to this clinical trial. The Ssponsor should also be notified if the study team should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a participant that was involved in this clinical trial.

8.2 Recording of Adverse Events

Safety monitoring will be implemented through the documentation and monitoring of AEs and SAEs through the use of incidence tables by severity, relationship to treatment and baseline parameters. Thorough causality analyses will be undertaken, and the necessary corrective and preventive actions will be implemented as applicable. All clearly related signs, symptoms, and abnormal diagnostic procedure results will be recorded in the research record and clinical chart and assessed by the Site-PI or other study physician in a timely manner allowing sufficient time to meet required reporting timelines for SAEs if needed.

In the event of a disagreement between the Lead PI and the site-PI over the assessment of a serious adverse event, the Lead PI will defer to the judgement of the Site-PI. If there is direct documented evidence that contradicts the Site-PI, the Lead PI will ask the Site-PI to provide the details of the event for sponsor assessment within 24 hours of the request, as per CAMH institutional procedures.

8.3 Reporting of Serious Adverse Events

8.3.1 Investigator Reporting: Notifying the Sponsor

This is an investigator-initiated study; the Lead PI is the Sponsor (Dr. Le Foll, Waypoint). Delegated study personnel will report SAEs to the Lead PI as soon as possible (within 24 hours of becoming aware of the event).

8.3.2 Investigator Reporting: Notifying the REB

The process for notification to the REB, designated by Clinical Trial Ontario, for applicable serious adverse events (SAEs) must be completed as per REB reporting requirements. SAEs and unanticipated events must be recorded and reported to the REB in accordance with the REB's reporting requirements and timelines. Copies of each report and documentation of REB notification and REB receipt/acknowledgement must be kept in the Investigator Study Binder.

8.3.3 Sponsor Reporting of Adverse Events: Notifying Health Canada

In accordance to Health Canada incident reporting for medical devices guidance, all reportable incidents are completed by the manufacturer and importer. Thus, as the study team, we will report all reportable incidences to the manufacturer and importer (Brainsway). This includes incidences where we become aware of an event that occurred with the device that is assessed to be linked to the device based on all available information and medical assessment, *and* it leads to death, serious deterioration in the state of health of the person, or potential for death or serious deterioration in health of the person.

8.3.4 Sponsor Reporting of Adverse Events: Notifying Sites

Adverse events that meet Health Canada reporting criteria must be submitted to Health Canada by the Sponsor within the required timelines. Serious adverse events that occur at external sites must be reported to the Sponsor within 24 hours of the site's awareness of the SAE. Updates to SAEs must be provided to the Sponsor as soon as possible and within 24 hours of site awareness of the update.

Adverse events which have been assessed and determined to meet the criteria for a serious unexpected adverse event will be reported on a monthly basis to all participating study sites via a monthly line listing. The line listing will include all serious unexpected adverse events that have occurred at all participating study sites. The line listing will be sent by the Sponsor to the participating study site(s) no later than 10 business days after the end of the month for which the serious unexpected adverse events are being reported. The site-PI must review and document their acknowledgement of the serious unexpected adverse events via their dated signature within a review timeline of 10 business days. The signed line listings must be filed in the site's records, and copies of signed line listings received from the participating study site(s) must be retained in the Trial Master File of the Sponsor.

8.4 Reporting of Device Deficiencies

Device deficiencies and malfunctions will be reported directly to the Manufacturer within 48 business hours. Device deficiencies will also be recorded in the Device Recall and Deficiencies Log maintained in the Investigator Binder. No information about participants will be included.

8.5 Safety Management Plan

Participant safety will be monitored as outlined in section 1.5 Risks/Benefits. Patient participants will receive full information regarding the treatment that includes known side effects of rTMS. Best practice guidelines for rTMS are now available and will be followed accordingly during this trial[62].

Criteria by which participants will be removed for safety reasons is outlined in 4.7 Participant Withdrawal Criteria.

The reporting procedure to ensure any information relevant to participant welfare is detailed in 8.2 Reporting of Adverse Events and 8.3 Reporting of Serious Adverse Events. Adverse events are monitored according to TCPS2 and Sunnybrook Health Science Centre's "Guidelines for Reporting an Internal Serious Adverse Event". Adverse events will be assessed for at each study visit after treatment start.

In the event of a suspected or confirmed breach of privacy, we will follow protocols according to the TCPS2, Ontario's Personal Health Information Protection Act (PHIPA), and Sunnybrook Health Science Centre's guideline "Privacy and security of personal health information".

In the event that the participant presents for an rTMS treatment visit and is visibly intoxicated or in withdrawal from substance use, the rTMS technician/RPN or other study staff will notify the study physician or delegate, and treatment will not be delivered on that day. Resuming treatment or withdrawal from rTMS will be at the discretion of the Lead PI and study team based on clinical assessment of risks.

In the event that the participant expresses active suicidal ideation during a study visit, such as indicated by the PHQ-9, the trained study personnel will follow existing safety escalation policies by contacting the Site-PI or delegate immediately. The Site-PI or delegate will then contact the participant for follow-up. If a participant reports feeling unsafe due to suicidal thoughts or requires medical attention, study personnel will advise to contact 911 or go to the nearest Emergency Room. All adverse events will be assessed and reported accordingly.

Depending on the current situation of the COVID-19 pandemic, or participant preference, some study procedures might be conducted virtually. Virtual assessments will include clinical rating scale assessments and self-report questionnaires and will be done via a secure video conferencing platform (Webex or Zoom)with a physician backup.

For virtual assessments, videoconferencing (e.g. Webex, Zoom) is preferred, as some of our assessments require scoring based on behavioral observation. If the participant has no access to videoconferencing, the procedures will be completed via telephone. Both videoconferencing and telephone calls will not be recorded.

Virtual Assessment Safety Plan:
Some participants may report worsening of symptoms or suicidal ideation that may pose a safety risk during virtual assessments. In addition, some participants may report adverse events that may require further investigation due to safety reasons. In such cases, the trained study personnel will follow existing safety escalation policies by contacting the Site-PI or delegate immediately. The Site-PI or delegate will then contact the participant for follow-up. If a participant reports feeling unsafe due to suicidal thoughts or requires medical attention, study personnel will advise to contact 911 or go to the nearest Emergency Room. All adverse events will be assessed and reported accordingly.

The following safety measures will be implemented for all virtual assessments over Webex or phone:

- Confirmation of an emergency contact number for the participant, and an alternate phone number to contact them if there is an emergency, or if the call/virtual session ends inadvertently
- Confirm the participant's address, and that they are in a fixed location for the duration of the call
- Confirm there is immediate access to necessary communications technology (i.e., landline or mobile device) in order to communicate with relevant research supports or emergency services in case of an emergent research situation
- Check in on participants who leave/drop off a virtual session (i.e., if there is a safety concern) by phone or separate videoconference.
- A physician backup to the study staff is available at all times

8.6 Unblinding Procedures

This is an open-label study and there will be no blinding procedures.

8.7 Data and Safety Monitoring Board

A Data and Safety Monitoring Board is not needed as this is not a regulated trial. Deep TMS (H4 coil) is already authorized for clinical use in smoking cessation, and its risk profile—primarily transient headaches or mild scalp discomfort, with rare seizures—is well characterized. Participants will undergo daily monitoring for adverse effects during Week 1, and repeated assessments at follow-up visits (Weeks 3, 5, 9, 13, and 26). The Lead PI will assume the overall responsibility for the management of the data and ensure proper protections against risk are in place with all study staff handling the data. The Lead PI will meet regularly with study staff to review collected data, confidentiality of data, and adherence to the study protocol and all relevant SOPs and research standards.

9.0 CLINICAL TRIAL DISCONTINUATION AND CLOSURE

9.1 Clinical Trial Discontinuation

This clinical trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (i.e. closure based on Lead PI decision, sponsor/funder decision, REB or other oversight bodies' decision; review of serious, unexpected and related AEs; noncompliance; futility). Notification, which includes the reason for study suspension or termination, will be provided by the suspending or terminating party to research participants, the Site-PI, funding agency, Waypoint, and Sunnybrook. If the clinical trial is prematurely terminated or suspended, the Site-PI will promptly inform research participants, the REB, and the sponsor, and will provide the reason(s) for the termination or suspension. All communication with participants for this purpose will go

through REB review and approval. Research participants will then be contacted, as applicable, and be informed of changes to the study visit schedule.

10.0 DATA HANDLING AND RECORD KEEPING

10.1 Source Documents & Case Report Forms

Data for this clinical trial will be managed using REDCap electronic case report forms. This system is maintained on Waypoint and Sunnybrook servers, with data backed up periodically. Please reference this study's Data Management Plan (DMP).

10.2 Protocol Deviations

No deviations from or changes to the protocol will be implemented without prior approval from the REB, unless to eliminate an immediate hazard to a participant. Any recorded protocol deviations will be reviewed by the PI in a timely manner. Any protocol deviations meeting the criteria of an Unanticipated Problem will be reported to REB.

10.3 Record Retention

In accordance to policy Health Canada's notice "Period reduced for keeping clinical trial records for drugs and natural health products" and Sunnybrook Research Institute's guideline "Guidance for Participants, Sponsors, and Researchers: Information about the changes to Clinical Trial Record Retention Periods", the research records of this clinical trial will be retained for 10 years after trial completion.

10.4 Clinical Trial Registration

In accordance with TCPS 2, a description of the clinical trial will be registered in a publicly accessible database, such as www.clinicaltrials.gov or equivalent, before the start of recruitment activities. The content will be updated throughout the duration of the clinical trial. All results, including negative results must be entered at the completion of the clinical trial.

11.0 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 Study Monitoring Plan

Quality assurance and quality control will be provided by the study Sponsor (Dr. Le Foll, Waypoint). The Sponsor will have primary responsibility for ensuring the well-being of research participants during their enrollment in the study, and that the conduct of the trial follows the currently approved protocol, ICH GCP and other applicable requirements. There will be meetings weekly with study personnel to review collected data, data confidentiality, and adherence to protocol design, recruitment, and participant complaints. During meetings the study Sponsor will also review the enrollment data, the collection and integrity of survey, qualitative, and clinical data, and any adverse event associated with the various components of the study, in collaboration with study co-investigators.

Data will be verified in a targeted review during weekly meetings depending on data collected. The Sponsor will ensure there are periodic, focused reviews of specific key indices of data (such as endpoint outcomes, safety data, recruitment/screening data, etc.) within the study team throughout the duration of the trial. Lastly, all REDCap data values undergo automated consistency and validity checks as detailed in the Data Management Plan. A CAMH-appointed monitor will conduct centralized (remote) monitoring in accordance with the Sponsor's study monitoring plan. This will involve reviewing consent and protocol adherence, source data verification, AE/SAE capture and reporting, and assessing participant safety and protection of rights. Centralized monitoring visits will be scheduled in coordination with each participating site, with findings reported to both the Sponsor and the site PIs.

11.2 Training and Qualifications of Study Personnel

All study personnel will complete Good Clinical Practice (GCP), protocol, and REDCap training. The following study-specific trainings (e.g., Standard Operating Procedures) (SOPs) will be completed according to role and assigned tasks: Brief Counselling SOP, Urine Collection SOP, Smoking Craving Provocation Procedure SOP, and course on Good Data Collection Practices. Personnel who interact directly with participants must also complete TCPS-2 training. All required training will be completed prior to the Site Initiation Visit and updated as required (e.g., protocol amendments, newly-appointed staff). Completion will be documented via training logs and/or certificates. The Sponsor (or designated study coordinator) will maintain a master training log across sites. Each site will maintain their training log and delegation of duties log in the site's Study Master File binder.

11.3 Auditing and Inspecting

The Lead PI, Site-PI and site will permit study-related audits, and inspections by the REB, Waypoint, Sunnybrook, and applicable granting agencies or regulatory bodies, including access to all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The Lead PI will ensure the capability for audits/inspections of applicable study-related facilities (e.g., research pharmacy, clinical laboratory, imaging facility, etc.).

12.0 ETHICAL CONSIDERATIONS

12.1 Research Ethics Board (REB) Approval

Research Ethics Board (REB) approval will be obtained prior to beginning any research-specific procedures. Following initial ethics approval, ongoing ethical approval will be maintained and the clinical trial will undergo REB review at least annually, in accordance with regulatory and REB requirements. The clinical trial will be conducted in accordance with the REB-approved study documents and the determinations (including any limitations) of the REB, and in compliance with REB requirements.

Whenever new information becomes available that may be relevant to participant consent, a consent form and/or consent for addendum will be presented to the REB for review and approval prior to its use. Any revised written information will receive REB approval prior to use.

12.2 Informed Consent Process & Documentation

The informed consent process will be obtained either remotely or in-person.

In-person consent

Informed consent is a process that is initiated prior to the individual agreeing to take part in the clinical trial and continues throughout their participation.

Informed consent will be obtained from each participant prior to their participation in the clinical trial. Informed consent will be obtained by appropriately trained and qualified CAMH research personnel who do not have an existing clinical relationship with the participant. The Lead PI and Site-PI will not obtain participant consent.

Each participant will be provided with a current copy of the REB approved ICF prior to the consent discussion. Research personnel will explain the clinical trial to the participant and answer any questions that may arise. This discussion will include an explanation of the clinical trial purpose, procedures, potential risks and benefits, confidentiality considerations and participant rights (e.g., participants will not be penalized or lose any benefits regardless of what they decide, and they have the right to withdraw from the clinical trial at any time). Participants may take as much time as they need to make their decision, and may consult with others (e.g. family members, other health care providers, etc.) if they like. Following the consent discussion, and once the participant has decided to take part, the participant and the person conducting the consent discussion will personally sign and date the ICF. Each participant will be provided with a complete (fully signed) copy of the ICF. The original ICF(s) and the informed consent process will be documented in the source documents.

Remote Consent Procedures

Prior to the consent discussion, research personnel will contact participants using a verbal consent script. Research personnel will obtain consent to send a copy of the ICF to the participant prior to the consent discussion, which may occur via REDCap, email, mail, or secure file transfer according to participant preference.

The consent discussion will occur by telephone or a secure video conferencing platform, at the participant's preference. The consent discussion will be conducted by research personnel who are not the PI and do not have a clinical relationship with participants.

Participants will be provided with a read-only copy of the ICF via REDCAP prior to conducting the consent discussion. The link may be used by participants as many times as they wish (it is not single use). Upon clicking the link, participants will review the landing page, and continue on to the ICF text. The entire contents of the ICF will be displayed

according to the current REB approved consent form, minus the signature/attestation page(s).

Informed consent will be documented using the REDCap e-Consent Framework. Following the consent discussion, the prospective participant will be sent a link to the e-consent via email, text, or chat feature in the secure video conferencing platformThe participant will complete the e-consent and be provided with the option to download and/or email themselves the signed ICF. If email is chosen, the email will only be used for this purpose (it is not retained by REDCap).

Following the participant signature, the person conducting the consent discussion will complete the Person Conducting Consent Discussion Attestation Page. PDF copies of the signed ICFs and Attestation pages will be retained in the REDCap File Repository. The research team will provide the participant with a copy of the fully signed ICF via mail and/or email, in accordance with the participant's wishes.

13.0 PRIVACY AND CONFIDENTIALITY

All clinical trial-related documents and data will be held in strict confidence and stored at Waypoint or on Waypoint servers and will follow institutional policies and procedures to ensure participant privacy and confidentiality.

REDCap software will be used for data collection and overall study data management over the course of this project. REDCap is an open-source, web-based clinical data management and electronic data capture system and database. The system is developed and managed in compliance with HIPAA, PIPEDA, and FDA 21 CFR Part 11 regulations, providing functions such as defined user roles and privileges, user authentication and encryption, electronic signatures, de-identification of protected health information, comprehensive auditing features to record and monitor access and changes to data, and a validated software development lifecycle. This system will be used to design electronic case report forms (eCRFs), data entry, data monitoring and cleaning, and for the query and export of datasets for statistical analysis.

Data is accessible by the research team only. No information concerning the clinical trial or the data will be released to any unauthorized third party without prior written approval of the sponsor, and the consent of the participant (where applicable).

All research activities will be conducted in as private a setting as possible. The authorized representatives of the sponsor, representatives of the REB, regulatory agencies may inspect all documents and records required to be maintained by the PI, including but not limited to, medical records and pharmacy records for the participants in this clinical trial. The participant's contact information will be securely stored at Waypoint for internal use during the clinical trial. At the end of the clinical trial, all records will continue to be kept in a secure location in accordance to applicable institutional and regulatory requirements.

14.0 CLINICAL TRIAL FINANCES

14.1 Funding Source

This trial has been submitted for funding consideration through the PSI Foundation (Application ID 2025-3725). However, recognizing the importance of this research, we will proceed with the REB submission concurrently, regardless of the outcome of the funding application. In the event that the initial funding application is unsuccessful or does not fully cover the trial's financial needs, alternative funding sources will be pursued. These may include internal funding or in-kind support from Waypoint, Sunnybrook, and other potential internal and external funding opportunities. The Lead PI and research team remain committed to securing the necessary resources to ensure the successful execution of the trial without compromising its scientific integrity or ethical standards.

14.2 Conflict of Interest

The investigators declare that no conflict of interest (COI) with this clinical trial (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) exist.

15.0 PUBLICATION POLICY/DATA SHARING

Publication

The Lead PI will be responsible for publication of the results of the clinical trial in a peer-reviewed journal publication. There are no publication policies for the participating funding agencies.

15.1 Future Secondary Use of Data

De-identified data from this trial may be used for future research by internal and/or external project collaborators. This data, having been stripped of direct identifiers, may be shared with researchers within the institution or external collaborators for secondary analyses, meta-analyses, or validation of findings. Any secondary use of the data will align with the original scope of research and comply with data sharing agreements, Waypoint and Sunnybrook policies, and relevant regulations, such as the Tri-Council Policy Statement (TCPS 2) and PHIPA. Data will be stored securely for 15 years. Researchers seeking access to the data for secondary analysis will be required to obtain appropriate approvals and adhere to applicable data use agreements.

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16.0 REFERENCES

[1] Reitsma MB, Kendrick PJ, Ababneh E, Abbafati C, Abbasi-Kangevari M, Abdoli A, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet 2021;397:2337–60. https://doi.org/10.1016/S0140-6736(21)01169-7.

[2] Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, Hajek P. Relapse prevention interventions for smoking cessation. Cochrane Database Syst Rev 2019;2. https://doi.org/10.1002/14651858.CD003999.PUB5.

[3] Hajek P, Tønnesen P, Arteaga C, Russ C, Tonstad S. Varenicline in prevention of relapse to smoking: effect of quit pattern on response to extended treatment. Addiction (Abingdon, England) 2009;104:1597–602. https://doi.org/10.1111/J.1360-0443.2009.02646.X.

[4] Zangen A, Moshe H, Martinez D, Barnea-Ygael N, Vapnik T, Bystritsky A, et al. Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial. World Psychiatry 2021;20:397–404. https://doi.org/10.1002/WPS.20905.

[5] Forget B, Pushparaj A, Le Foll B. Granular insular cortex inactivation as a novel therapeutic strategy for nicotine addiction. Biol Psychiatry 2010;68:265–71. https://doi.org/10.1016/J.BIOPSYCH.2010.01.029.

[6] Pushparaj A, Hamani C, Yu W, Shin DS, Kang B, Nobrega JN, et al. Electrical Stimulation of the Insular Region Attenuates Nicotine-Taking and Nicotine-Seeking Behaviors. Neuropsychopharmacology 2013;38:690. https://doi.org/10.1038/NPP.2012.235.

[7] Ibrahim C, Tang VM, Blumberger DM, Malik S, Tyndale RF, Trevizol AP, et al. Efficacy of insula deep repetitive transcranial magnetic stimulation combined with varenicline for smoking cessation: A randomized, double-blind, sham controlled trial. Brain Stimul 2023;16:1501–9. https://doi.org/10.1016/J.BRS.2023.10.002.

[8] Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, et al. Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry Res 2019;273:770–81. https://doi.org/10.1016/J.PSYCHRES.2018.12.041.

[9] Shi R, Wang Z, Yang D, Hu Y, Zhang Z, Lan D, et al. Short-term and long-term efficacy of accelerated transcranial magnetic stimulation for depression: a systematic review and meta-analysis. BMC Psychiatry 2024;24:1–13. https://doi.org/10.1186/S12888-024-05545-1/FIGURES/7.

[10] Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. American Journal of Psychiatry 2020;177:716–26. https://doi.org/10.1176/APPI.AJP.2019.19070720/ASSET/IMAGES/LARGE/APPI.AJP.2019.19070720F3.JPEG.

[11] Roth Y, Hanlon CA, Pell G, Zibman S, Harmelech T, Muir OS, et al. Real world efficacy and safety of various accelerated deep TMS protocols for major depression. Psychiatry Res 2023;328. https://doi.org/10.1016/J.PSYCHRES.2023.115482.

[12] Le Foll B, Piper ME, Fowler CD, Tonstad S, Bierut L, Lu L, et al. Tobacco and nicotine use. Nature Reviews Disease Primers 2022 8:1 2022;8:1–16. https://doi.org/10.1038/s41572-022-00346-w.
[13] Goodwin RD, Pagura J, Spiwak R, Lemeshow AR, Sareen J. Predictors of persistent nicotine dependence among adults in the United States. Drug Alcohol Depend 2011;118:127. https://doi.org/10.1016/J.DRUGALCDEP.2011.03.010.
[14] Weinberger AH, Gbedemah M, Wall MM, Hasin DS, Zvolensky MJ, Goodwin RD. Cigarette use is increasing among people with illicit substance use disorders in the United States, 2002-14: emerging disparities in vulnerable populations. Addiction (Abingdon, England) 2018;113:719–28. https://doi.org/10.1111/ADD.14082.
[15] Hassan AN, Le Foll B. Survival Probabilities and Predictors of Major Depressive Episode Incidence Among Individuals With Various Types of Substance Use Disorders. J Clin Psychiatry 2021;82. https://doi.org/10.4088/JCP.20M13637.
[16] Smith PH, Mazure CM, McKee SA. Smoking and mental illness in the U.S. population. Tob Control 2014;23:e147–53. https://doi.org/10.1136/TOBACCOCONTROL-2013-051466.
[17] Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. N Engl J Med 2014;370:60–8. https://doi.org/10.1056/NEJMRA1308383.
[18] Jha P. The hazards of smoking and the benefits of cessation: a critical summation of the epidemiological evidence in high-income countries. Elife 2020;9. https://doi.org/10.7554/ELIFE.49979.
[19] Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368:341–50. https://doi.org/10.1056/NEJMSA1211128.
[20] Banks E, Joshy G, Weber MF, Liu B, Grenfell R, Egger S, et al. Tobacco smoking and all-cause mortality in a large Australian cohort study: Findings from a mature epidemic with current low smoking prevalence. BMC Med 2015;13:1–10. https://doi.org/10.1186/S12916-015-0281-Z/FIGURES/5.
[21] Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. Lancet 2013;381:133. https://doi.org/10.1016/S0140-6736(12)61720-6.
[22] Jha P. Avoidable global cancer deaths and total deaths from smoking. Nat Rev Cancer 2009;9:655–64. https://doi.org/10.1038/NRC2703.
[23] Daskalakis ZJ, Möller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. Exp Brain Res 2006;174:403–12. https://doi.org/10.1007/S00221-006-0472-0.
[24] Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 2003;126:2609–15. https://doi.org/10.1093/BRAIN/AWG268.
[25] Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 2001;21. https://doi.org/10.1523/JNEUROSCI.21-15-J0003.2001.
[26] Keck ME, Welt T, Post A, Müller MB, Toschi N, Wigger A, et al. Neuroendocrine and behavioral effects of repetitive transcranial magnetic stimulation in a psychopathological animal model are suggestive of antidepressant-like effects. Neuropsychopharmacology 2001;24:337–49. https://doi.org/10.1016/S0893-133X(00)00191-3.

[27] Keck ME, Welt T, Müller MB, Erhardt A, Ohl F, Toschi N, et al. Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. Neuropharmacology 2002;43:101–9. https://doi.org/10.1016/S0028-3908(02)00069-2.
[28] Keck ME, Sillaber I, Ebner K, Welt T, Toschi N, Kaehler ST, et al. Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. Eur J Neurosci 2000;12:3713–20. https://doi.org/10.1046/J.1460-9568.2000.00243.X.
[29] Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 2009;56 Suppl 1:3–8. https://doi.org/10.1016/J.NEUROPHARM.2008.05.022.
[30] Zangen A, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. Clin Neurophysiol 2005;116:775–9. https://doi.org/10.1016/J.CLINPH.2004.11.008.
[31] Roth Y, Amir A, Levkovitz Y, Zangen A. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. J Clin Neurophysiol 2007;24:31–8. https://doi.org/10.1097/WNP.0B013E31802FA393.
[32] Roth Y, Zangen A, Hallett M. A coil design for transcranial magnetic stimulation of deep brain regions. J Clin Neurophysiol 2002;19:361–70. https://doi.org/10.1097/00004691-200208000-00008.
[33] Le Foll B, Pushparaj A, Pryslawsky Y, Forget B, Vemuri K, Makriyannis A, et al. Translational strategies for therapeutic development in nicotine addiction: rethinking the conventional bench to bedside approach. Prog Neuropsychopharmacol Biol Psychiatry 2014;52:86–93. https://doi.org/10.1016/J.PNPBP.2013.10.009.
[34] Naqvi NH, Rudrauf D, Damasio H, Bechara A. Damage to the insula disrupts addiction to cigarette smoking. Science 2007;315:531–4. https://doi.org/10.1126/SCIENCE.1135926.
[35] Naqvi NH, Bechara A. The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. Brain Struct Funct 2010;214:435–50. https://doi.org/10.1007/S00429-010-0268-7.
[36] Pushparaj A, Kim AS, Musiol M, Trigo JM, Le Foll B. Involvement of the rostral agranular insular cortex in nicotine self-administration in rats. Behavioural Brain Research 2015;290:77–83. https://doi.org/10.1016/J.BBR.2015.04.039.
[37] Pushparaj A, Le Foll B. Involvement of the caudal granular insular cortex in alcohol self-administration in rats. Behavioural Brain Research 2015;293:203–7. https://doi.org/10.1016/J.BBR.2015.07.044.
[38] Pushparaj A, Kim AS, Musiol M, Zangen A, Daskalakis ZJ, Zack M, et al. Differential Involvement of the Agranular vs Granular Insular Cortex in the Acquisition and Performance of Choice Behavior in a Rodent Gambling Task. Neuropsychopharmacology 2015;40:2832–42. https://doi.org/10.1038/NPP.2015.133.
[39] Brody AL, Mandelkern MA, London ED, Childress AR, Lee GS, Bota RG, et al. Brain metabolic changes during cigarette craving. Arch Gen Psychiatry 2002;59:1162–72. https://doi.org/10.1001/ARCHPSYC.59.12.1162.
[40] Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y. Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci Biobehav Rev 2014;38:1–16. https://doi.org/10.1016/J.NEUBIOREV.2013.10.013.

[41] Zangen A, Moshe H, Martinez D, Barnea-Ygael N, Vapnik T, Bystritsky A, et al. Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial. World Psychiatry 2021;20:397. https://doi.org/10.1002/WPS.20905.
[42] Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, et al. Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. Biol Psychiatry 2018;84:28–37. https://doi.org/10.1016/J.BIOPSYCH.2017.10.028.
[43] Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SB, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci 2014;34:6849–59. https://doi.org/10.1523/JNEUROSCI.4993-13.2014.
[44] Fitzgerald PB, Hoy KE, Anderson RJ, Daskalakis ZJ. A STUDY OF THE PATTERN OF RESPONSE TO rTMS TREATMENT IN DEPRESSION. Depress Anxiety 2016;33:746–53. https://doi.org/10.1002/DA.22503.
[45] Cash RFH, Cocchi L, Lv J, Wu Y, Fitzgerald PB, Zalesky A. Personalized connectivity-guided DLPFC-TMS for depression: Advancing computational feasibility, precision and reproducibility. Hum Brain Mapp 2021;42:4155–72. https://doi.org/10.1002/HBM.25330.
[46] Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad BSR, Barmak F, et al. Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. Am J Psychiatry 2022;179:132–41. https://doi.org/10.1176/APPI.AJP.2021.20101429.
[47] Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. American Journal of Psychiatry 2020;177:716–26. https://doi.org/10.1176/APPI.AJP.2019.19070720/SUPPL_FILE/APPI.AJP.2019.19070720.DS001.PDF.
[48] Cole E, O'Sullivan SJ, Tik M, Williams NR. Accelerated theta burst stimulation: safety, efficacy, and future advancements. Biol Psychiatry 2024;95:523–35. https://doi.org/10.1016/j.biopsych.2023.12.004.
[49] Fitzgerald PB, Hoy KE, Elliot D, Susan McQueen RN, Wambeek LE, Daskalakis ZJ. Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology 2018;43:1565–72. https://doi.org/10.1038/s41386-018-0009-9.
[50] Caulfield KA, Fleischmann HH, George MS, McTeague LM. A transdiagnostic review of safety, efficacy, and parameter space in accelerated transcranial magnetic stimulation. J Psychiatr Res 2022;152:384–96. https://doi.org/10.1016/j.jpsychires.2022.06.038.
[51] Fitzgerald PB. An update on the clinical use of repetitive transcranial magnetic stimulation in the treatment of depression. J Affect Disord 2020;276:90–103. https://doi.org/10.1016/J.JAD.2020.06.067.
[52] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000;111:800–5. https://doi.org/10.1016/S1388-2457(99)00323-5.
[53] George MS. Transcranial magnetic stimulation for the treatment of depression. Expert Rev Neurother 2010;10:1761–72. https://doi.org/10.1586/ERN.10.95.

[54] Holtzheimer PE, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, et al. Accelerated repetitive transcranial magnetic stimulation (aTMS) for treatment-resistant depression. Depress Anxiety 2010;27:960. https://doi.org/10.1002/DA.20731.
[55] Karadoğan D, Önal Ö, Şahin DS, Kanbay Y, Alp S, Şahin Ü. Treatment adherence and short-term outcomes of smoking cessation outpatient clinic patients. Tob Induc Dis 2018;16. https://doi.org/10.18332/TID/94212.
[56] Hays JT, Leischow SJ, Lawrence D, Lee TC. Adherence to treatment for tobacco dependence: Association with smoking abstinence and predictors of adherence. Nicotine and Tobacco Research 2010;12:574–81. https://doi.org/10.1093/ntr/ntq047.
[57] Liberman JN, Lichtenfeld MJ, Galaznik A, Mastey V, Harnett J, Zou KH, et al. Adherence to Varenicline and Associated Smoking Cessation in a Community-Based Patient Setting. vol. 19. 2013.
[58] Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stop-smoking medications: Data from the ITC four-country survey. Nicotine and Tobacco Research 2011;13:94–102. https://doi.org/10.1093/ntr/ntq215.
[59] Conney AH, Reidenberg MM. Cigarette smoking, coffee drinking, and ingestion of charcoal-broiled beef as potential modifiers of drug therapy and confounders of clinical trials. Journal of Pharmacology and Experimental Therapeutics 2012;342:9–14. https://doi.org/10.1124/jpet.112.193193.
[60] I ARA, Beigel Y, Schre R, Bman !, Shafer Z. Weight Gain and Insulin Resistance during Nicotine Replacement Therapy. vol. 22. n.d.
[61] Cobb CO, Niaura RS, Donaldson EA, Graham AL. Quit now? Quit soon? Quit when you're ready? Insights about target quit dates for smoking cessation from an online quit date tool. J Med Internet Res 2014;16. https://doi.org/10.2196/jmir.3086.
[62] McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. Journal of Clinical Psychiatry 2018;79:35–48. https://doi.org/10.4088/JCP.16cs10905.