COVER PAGE

Study title: Novel Pharmacotherapy Approaches in Smokers with Serious Mental Illness

ClinicalTrials.Gov (number NCT04011280)

October 28, 2021

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN – REVISED October 28, 2021

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.
Version date: 9/30/2013

1. PROJECT TITLE

Novel Pharmacotherapy Approaches in Smokers with Serious Mental Illness

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

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The Pacific Treatment and Research Center (Pac-TARC) is located at 3252 Holiday Court, La Jolla, CA 92037, across the street from the main UCSD campus. This 3000 sq. ft. office space includes 6 independent offices for use by laboratory staff; a medical examination room; psychophysiology suite; conference room; a locked, dedicated, temperature-controlled medication storage room that contains double-locked medication storage cabinets; laboratory space for preparing biological specimens; a waiting room; and a break room. The medical examination room is equipped with an examination table and ECG equipment, and the laboratory is equipped with a tabletop centrifuge and a sample storage refrigerator and freezer.

4. ESTIMATED DURATION OF THE STUDY

The estimated duration of the study, from HRPP approval to HRPP closure for recruitment and data analysis is up to four years. The investigators received an administrative extension to the protocol due to recruitment delays caused by the COVID-19 pandemic.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Sixty chronic smokers with bipolar disorder, schizophrenia or schizoaffective disorder who are motivated to try to quit smoking will be randomized to receive smoking cessation treatment with the FDA-approved medication, varenicline, delivered either a) at its standard dose and titration schedule (half of the participants) versus b) at a lower dose and slower titration schedule (the other half), for 12 weeks. All smokers will choose a target quit date sometime between 8 to 35 days after starting the medication. All participants will receive ten 30-minute sessions of a behavioral treatment called Acceptance and Commitment Therapy (ACT). Participants will be followed for an additional 12 weeks off study medication. The major endpoints are the percentage participants quitting smoking and the incidence of psychiatric side effects. We will also conduct a blood test that measures the breakdown of nicotine in the body to see if that measure influences treatment response and side effects.

6. SPECIFIC AIMS

Aim 1. To examine the feasibility of combining ACT with two different varenicline-assisted quitting strategies: a) slower titration of lower dose varenicline, versus b) standard titration of standard dose varenicline - - both

delivered using a flexible quit date paradigm that allows gradual preloading of varenicline prior to the target quit date (TQD).

Hypothesis 1A. There will be high demand from SMI smokers to participate in the trial as evidenced by achieving targeted accrual rates and budgeted recruitment costs.

Hypothesis 1B. Combining ACT with both dosing strategies will be practical as evidenced by high rates of study and ACT counseling session retention, and completion of study procedures.

Hypothesis 1C. Acceptability of the flexible quit date and varenicline dosing strategies will be high as demonstrated by good adherence to making a quit attempt within the quit window and taking at least 80% of prescribed study medication doses. Satisfaction with ACT either delivered in person or via telephone will be high consistent with our prior work in bipolar smokers.

Aim 2. To explore whether nicotine clearance rate as measured by the plasma 3'-hydroxycotinine / cotinine NMR influences the incidence of NPSAEs and medication tolerability in varenicline-treated SMI smokers.

Hypothesis 2. We hypothesize that slow nicotine metabolisers will exhibit trends for more neuropsychiatric adverse events (NPSAEs) of any severity to standard varenicline dosing compared with normal metabolisers treated with low dose varenicline.

7. BACKGROUND AND SIGNIFICANCE

People with SMI such as bipolar disorder (BD) and schizophrenia spectrum disorders (SSD) smoke tobacco cigarettes at a rate 3-4 times higher than the general population (1,2) and are disproportionately affected by tobacco-related diseases and premature death (3). SMI smokers also have a harder time quitting smoking than NMI tobacco users. Recent evidence from our group derived from the multinational Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES; 4) measures this reduction in quit rates as 35% lower in BD (5) smokers and 54% lower in SSD smokers (6), respectively, compared with NMI smokers using the 1st-line smoking cessation medications and standard counseling. However, EAGLES results likely reflect a best case scenario given that its participants were highly motivated to try to quit, were psychiatrically stable, and received rigorous smoking cessation treatment. That only 2 in 10 SMI smokers in EAGLES were able to stop smoking at 6 months speaks to the need to develop new strategies to help SMI smokers quit. That only ~5% of EAGLES SMI smokers administered placebo quit, despite all of them receiving standard counseling, highlights the importance of developing improved behavioral interventions as adjunctive treatment.

Although most studies in stably treated SMI smokers find that the 1st-line smoking cessation medications are generally well-tolerated and that smoking cessation does not exacerbate psychiatric symptoms (1,2), SMI smokers are 3- to 5-times more likely to develop moderate to severe NPSAEs when engaged in a medication-assisted quit attempt compared with NMI smokers (5,6). The risk appears highest among smokers with BD: in the EAGLES trial, ~15% of varenicline-treated BD smokers experienced moderate to severe NPSAEs when trying to quit compared with 2% of varenlicine-treated NMI smokers (5). While the incidence of moderate to severe NPSAEs as defined in EAGLES was not significantly different from placebo among BD smokers, the incidence of NPSAEs of any severity was significantly higher begging the question whether lower dosages of the medication can be used to lower side effects in some individuals without compromising efficacy.

Over the past two decades there have been improved efforts to address this neglected epidemic in harder-to-treat SMI smokers (1); however, in general, advancements in cessation treatment research among SMI smokers far lags that of NMI smokers. Additionally, exciting new research results such as 1) how genetically informed biomarkers of nicotine clearance moderate smoking cessation medication treatment outcomes (7), 2) varenicline preloading increases smoking cessation rates (8), and 3) novel behavioral interventions such as ACT therapy can boost quit rates (9,10), have not been adequately tested in SMI smokers. Thus, the purpose of this proposal is to test the feasibility of whether these treatment innovations can be applied in SMI smokers with high rates of demand, practicality and acceptability for subsequent use in a large randomized clinical trial (RCT).

How Does an SMI Smoker's NMR Affect Treatment Response and Adverse Event Propensity? The NMR as measured by the ratio of 3'-hydroxycotinine (the breakdown product of cotinine) divided by the

concentration of cotinine (the breakdown product of nicotine) in a smoker's blood or urine is a genetically-informed biomarker of nicotine clearance (7). It is a surrogate measure of CYP2A6 activity - - the liver enzyme that catabolizes nicotine and other drugs and which is under genetic control11. Studies in NMI smokers have found that classifying smokers into slow versus normal nicotine metabolisers based on a cutoff score for this ratio affects how that individual is likely to respond to the 1st-line smoking cessation medications both in terms of treatment efficacy and propensity to develop side effects (7,12). The NMR predicts treatment responses to varenicline delivered at standard doses: among slow metabolisers, which represents ~40% of the general population of NMI smokers, varenicline users had comparable quit rates to nicotine patch-treated smokers and were more vulnerable to side effects than normal metabolisers. However, varenicline standard dose treatment produced higher quit rates than patch in normal metabolisers (7). To our knowledge, the NMR ratio has not been examined in a RCT of varenicline in SMI smokers. This gap is important to fill given that varenicline is the most effective monotherapy treatment for SMI smokers and these individuals have a greater propensity to develop NPSAEs.

Would Lower Dosages of Varenicline Be Better Tolerated, Especially Among Slow Metabolisers? It is also important to determine whether a lower dose of varenicline can be used in some smokers to reduce medication side effects without significantly reducing efficacy. Our earliest work with the medication in a Phase II trial in NMI smokers found that 0.5 mg twice daily titrated varenicline - - one-half of what eventually became the FDA-approved titrated dose of 1 mg twice daily, produced similar quit rates to the approved dose (13), a result confirmed in a related Phase II varenicline trial (14) and a recent Phase IV trial (15). However, all of these studies also found lower rates of treatment emergent AEs in the lower dose varenicline group. While **none of the earlier studies focused on NPSAEs**, in the Oncken et al. trial (2006) discontinuation rates due to AEs and the incidence of nausea, insomnia, and abnormal dreams were markedly lower among low-dose treated participants compared with standard-dose treated smokers (13; see Table 2). Reducing NPSAEs in SMI smokers is particularly salient because, as we have shown in the EAGLES trial (see Figure 2), BD and SSD smokers are 3- to 5-times more likely than NMI smokers to experience moderate to severe NPSAEs when trying to quit using 1st-line medications or placebo. Moreover, although at times difficult to disentangle from negative affective symptoms associated with nicotine withdrawal, our more recent analysis of NPSAEs of any intensity level in BD smokers reveals a 61% increase among varenicline-treated participants compared with placebo (see Table 1), begging the question whether lower doses might help reduce the incidence of NPSAEs.

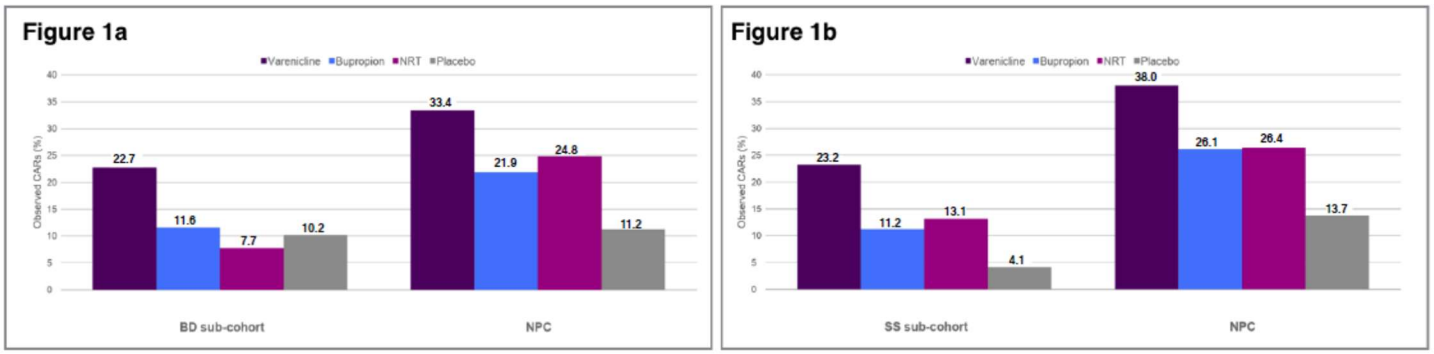
How Might Varenicline Preloading Affect Quit Rates in SMI Smokers? Another new finding that has not been adequately tested in SMI smokers is the potential beneficial effects of varenicline preloading to enhance quit rates. Extending pre-quit treatment with varenicline prior to TQD has been found to reduce smoking and urges to smoke among non-treatment seeking NMI smokers (16), and to enhance quit rates in treatment-seeking NMI smokers compared with individuals treated with standard varenicline dosing and TQD (8,17,18). A derivative of this strategy that employed a flexible quit date paradigm with standard varenicline dosing in NMI smokers produced significantly higher odds of quitting with varenicline compared to placebo with similar safety between groups (19). While **all of the aforementioned studies excluded individuals with psychiatric conditions from participating**, the mechanisms underlying enhanced quit rates with varenicline preloading may be particularly salient in SMI smokers. Since these individuals are more nicotine dependent than NMI smokers (20), the tempo with which partial agonism of α4β2 nicotinic acetycholine receptors (nAChRs) occurs in relation to the TQD likely influences neuroadaptive changes in nAChR density, activity and turnover (21,22). From the perspective of extinguishing learned smoking behaviors (17,18), SMI smokers might benefit more by cigarettes becoming less satisfying to help "unlearn" that cigarette smoking alleviates negative affect. There is also the possibility that such use of varenicline will increase an SMI smoker's self-efficacy since the number of cigarettes smoked should gradually reduce, rendering the smoker less nicotine dependent (19,23).

Can Varenicline Be Combined With Behavioral Treatment Targeting Quitting- and Illness-Related Distress Tolerance to Enhance Tolerability and Efficacy? While there is broad agreement that the best way to quit smoking is by combining evidence-based behavioral and pharmacological treatments (24,25), the

optimal combination of treatments is not known. This is important for SMI smokers who have a harder time quitting and experience more NPSAEs yet receive the same standard behavioral counseling as NMI smokers. ACT takes a different approach to smoking cessation counseling that might lend itself well to SMI smokers making a varenicline-assisted quit attempt. It focuses on increasing acceptance of aversive physical and emotional states that commonly occur during nicotine withdrawal as smoking triggers, and teaches the skills (e.g., mindfulness) for allowing these feelings to come and go without acting on them by smoking (9,10). In the context of varenicline preloading, ACT's mindfulness strategies, along with the drug's reduction in smoking satisfaction and urges to smoke (8,18) might synergize to help boost quit rates. Changes in affective states related to the smoker's illness itself, nicotine withdrawal, or, possibly, medication side effects, might be ameliorated and/or cause less distress through the combined effects of ACT and varenicline.

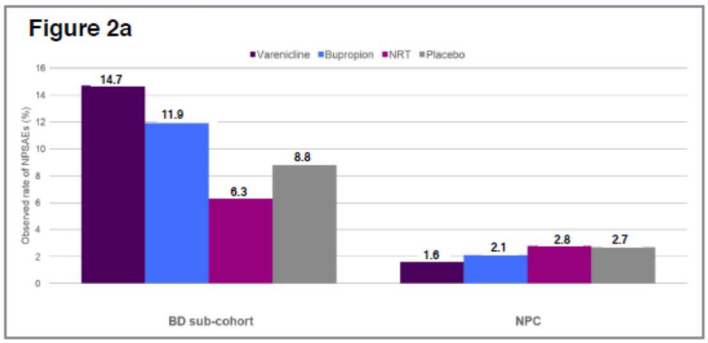
Preliminary Studies: Varenicline Is the Most Effective Monotherapy in SMI Smokers, Yet Still, < 25% of Smokers Are Able To Achieve 4-Week Continuous Abstinence: The EAGLES trial accrued the largest samples of smokers with BD (N = 285) and SSD (N = 390) ever assembled in a double-blind, placebo- and active- (nicotine patch [NRT]) RCT comparing varenicline 1 mg twice daily and bupropion 150 mg twice daily. The study was designed to be able to compare smokers having these and other psychiatric disorders with smokers without a history of mental illness (NMI smokers in the non-psychiatric cohort or NPC in the figures below). Our major efficacy findings were: a) Across all treatments, and in contrast to NMI smokers, BD smokers (OR = 0.65; 95% CI = 0.43 - 0.97) and SSD smokers (OR = 0.46; 95% CI = 0.32 – 0.66) were 35% and 54% less able to quit smoking, respectively; b) Among BD and country-matched NMI smokers, only varenicline had better efficacy than bupropion, NRT and placebo (**see Figure 1a, left panel**). c)Among SSD and all NMI smokers, all 3 active treatments had better efficacy than placebo, and varenicline was superior to bupropion and NRT (**see Figure 1b, right panel**).

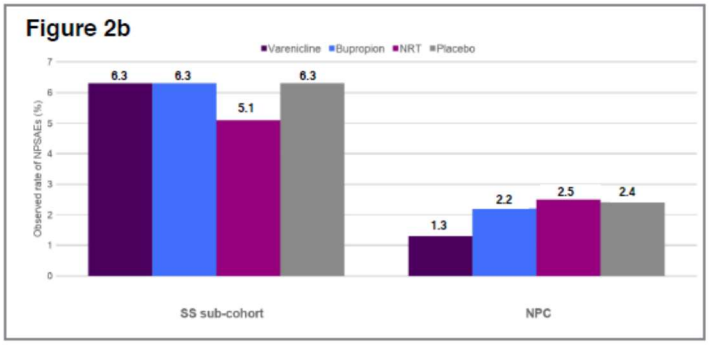
Figure 1. *4-Week Continuous Abstinence Quit* Rates in BD vs. NPC Smokers & SSD vs. NPC Smokers



Regardless of Treatment, SMI Smokers Were 3- to 5-Times More Likely to Experience Clinically Significant NPSAEs than NMI Smokers: Using a composite primary neuropsychiatric safety endpoint developed in consultation with the U.S. FDA4, we found the risk for moderate to severe NPSAEs was significantly higher in SSD smokers (Risk Difference [RD]% = 3.96; 95% CI = 1.63 – 6.29) and BD smokers (RD% = 7.73; 95% CI = 4.15 – 11.3) compared with NMI smokers. The observed incidence of the primary composite NPSAE endpoint for the two groups is depicted below (**see Figures 2a and 2b**). Although there was no evidence for a significant risk difference by treatment in the BD subcohort, the observed incidence of clinically significant NPSAEs was highest among varenicline-treated participants.

Figure 2. Incidence of *Moderate-to-Severe* NPSAEs in BD vs NPC Smokers & SSD vs. NPC Smokers





Rates of NPSAEs of Any Severity Were Higher Among Varenicline BD Smokers Compared with Placebo BD Smokers: In contrast to the pre-specified primary composite safety endpoint that was designed to capture clinically significant, moderate to severe NPSAEs, Table 1 below illustrates the rates of NPSAEs reported at ≥ 1% at any severity level (mild, moderate or severe) and coded according to the MedDRA category psychiatric disorders. Compared with placebo, varenicline-treated BD smokers had significantly higher rates of NPSAEs of any intensity, including sleep disorders.

Table 1. Neuropsychiatric Adverse Events *of Any Severity* in EAGLES Bipolar Participants

Mild, Moderate or Severe AEs* Coding to the MedDRA Category Psychiatric Disorders	All BD Subjects	Varenicline	Buproprion	NRT	Placebo
Any Psychiatric AEs	36.8%	45.3%	44.0%	25.0%	28.1%
Depressed mood disorders and disturbances	11.1%	16.0%	13.1%	4.7%	8.8%
Manic and bipolar mood disorders and disturbances	5.0%	6.7%	7.1%	0%	5.3%
Sleep Disorders & Disturbances	18.2%	26.7%	19.0%	14.1%	10.5%

AE = adverse event; BD = bipolar disorder; NRT = nicotine replacement therapy (transdermal nicotine patch)

Lower Dosage Varenicline is Associated with Fewer Adverse Events and Only Modestly Reduced Efficacy: The PI was a member of the "Varenicline Study Group" for an early Phase II trial that evaluated the safety, tolerability and efficacy of 4 varenicline dose regimens (13). Of relevance to this study was the contrast in that trial between the 0.5 mg twice daily titrated arm versus the 1 mg twice daily titrated dosing regimens. We found no significant difference in quit rates between the two groups: Low dose 44%; High dose 49% vs. Placebo 11.6% ($p < .0001$ vs. both doses). However, adverse events across the two groups were markedly lower in the low dose group as illustrated below (see Table 2) resulting in a 35% drop in treatment discontinuations due to AEs in the low dose arm.

Table 2. Reduced Adverse Events With Lower Dose Varenicline *in NMI Smokers*

Adverse Event	0.5 mg BID Titrated (Low/n=129)	1.0 mg BID Titrated (Standard/n=129)	% Reduction Low vs. Standard
Discontinuation due to adverse event	14.0	21.7	35%
Any nausea	16.3	34.9	53%
Insomnia	20.9	37.2	44%
Abnormal dreams	11.6	19.4	40%
Dyspepsia	6.2	14.7	58%
Constipation	4.7	10.9	57%

BID = twice daily

ACT Is Well-Tolerated and Facilitated Quitting in BD Smokers: In a study in bipolar smokers, ACT showed preliminary evidence of facilitating quitting: 40% of BD smokers receiving 10 sessions of in-person ACT in combination with NRT patch, and 33% of BD smokers receiving 6 telephone sessions, achieved short-term (7-day PP) abstinence at end of treatment (9). There was also evidence that ACT increased participants' ability to accept cravings to smoke (>50% increase), and it was highly acceptable to participants with 80% retention and 90% satisfaction with in-person treatment and 67% retention and 100% satisfaction with telephone treatment (9). Regarding its potential for dissemination, ACT has preliminarily demonstrated higher 30-day quit rates than standard quit line counseling at 6-month follow-up (31% in ACT vs. 22% in standard counseling; 10), and this effect was even more pronounced among depressed smokers (33% in ACT versus 13% in standard counseling).

8. PROGRESS REPORT

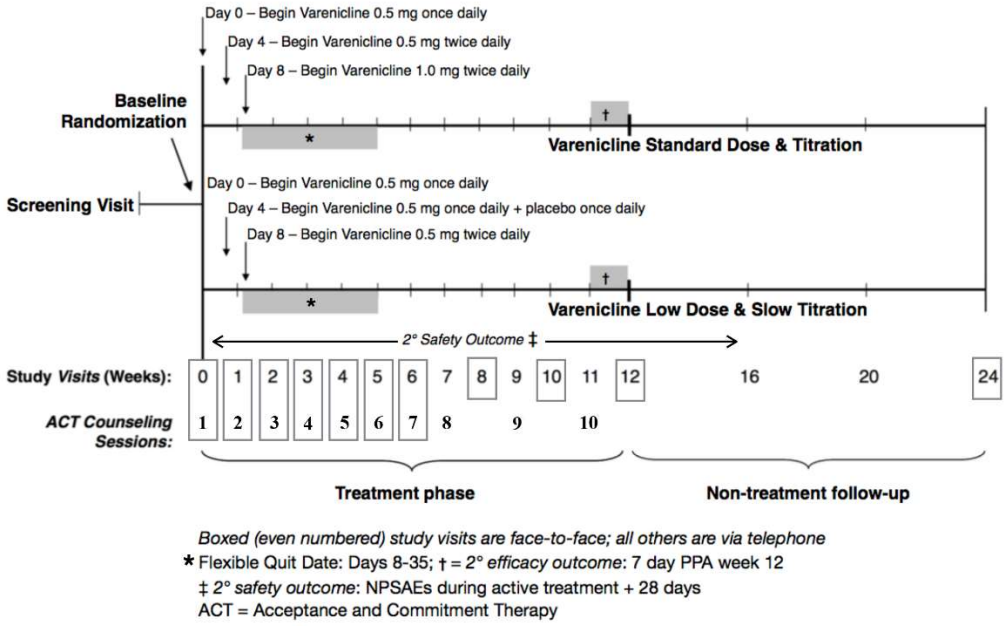
Progress reports to UCSD HRPP and TRDRP are submitted annually.

9. RESEARCH DESIGN AND METHODS

Overview: This pilot trial is a Phase IV, 12-week, single center, randomized, double blind, parallel group comparison of low (0.5 mg twice daily with slower titration over one full week) versus standard dose (1.0 mg twice daily with standard titration) varenicline in SMI individuals with DSM-V BD or SSD with a 12-week, post-treatment follow-up (see Figure 3 for study design). The 16 visits after screening (Weeks 0-24) will take place using the guidelines developed by the UCSD Office of the Vice Chancellor for Research. Participants will be screened, randomized and follow the protocol according to the Research Ramp-Up phase under which the university is operating at that time of (i.e., orange, yellow, or green).

Full participation includes 14 treatment visits and 3 follow up visits. All in-person visits will take place at Pac-TARC. In addition to testing low dose varenicline in SMI smokers for the first time, three other innovative design features are incorporated to try to improve medication tolerability and short-term quit rates. 1) Plasma will be obtained at baseline to measure participants' NMR and to identify slow versus normal nicotine metabolisers. 2) A flexible quit date (between days 8-35) will be employed allowing varenicline preloading to occur prior to the TQD. 3) Ten sessions of ACT for smoking cessation will be delivered by trained counselors first in 7 in-person sessions followed by 3 sessions delivered via telephone to all participants. Randomization of participants will occur in a 1 (low dose) to 1 (standard dose) ratio and participants will be balanced on diagnosis (BD vs SSD), gender, race (White vs. non-White) and whether or not they are taking antiepileptic medications (e.g., carbamazepine) as mood stabilizers (20) which, like the demographic/ethnic factors (11,26) can influence CYP2A6 activity and affect the NMR. Volunteered, observed and solicited NPSAEs will be assessed using standardized procedures developed in EAGLES and our other prior work (4,27). However, going beyond EAGLES, we will also assess participants' tobacco withdrawal symptoms, urges to smoke, sleep disturbances, self-efficacy & confidence to quit, and satisfaction with the protocol elements. To further extend EAGLES, we will include more "real world" participants who are somewhat less psychiatrically stable and who have comorbid substance use disorders (SUDs) in early remission.

Figure 3. Study Design – ACTSLOW Pilot Trial



Boxed (even numbered) study visits are face-to-face; all others are via telephone
* Flexible Quit Date: Days 8-35; † = *2° efficacy outcome*: 7 day PPA week 12
‡ *2° safety outcome*: NPSAEs during active treatment + 28 days
ACT = Acceptance and Commitment Therapy

All study procedures described below are considered investigational carried out solely for research purposes. varenicline is an FDA-approved medication (NDA# 21-928) for the treatment of smoking cessation in a wide range of individuals, including those with SMI that will be studied here. An IND exemption is attached to this proposal as this study 1) is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for varenicline; 2) is not intended to support a significant change in the advertising of varenicline; 3) does not involve a route of administration or dosage level change or use in a patient population or other factor that significantly increases risks associated with varenicline; 4) is conducted in compliance with requirements for instructional review with the requirements of informed consent; and 5) is not intended to promote or commercialize varenicline.

Participants: Approximately 90 participants will be screened and undergo written informed consent to arrive at 60 adult men and women (anticipated 33% screen failure rate) with DSM-V BD (Type I or Type II, N = 30) or SSD (schizophrenia or schizoaffective disorder, N = 30) and who are chronic smokers of ≥ 10 cigarettes per day will be recruited to participate in this pilot trial. Each group will include ~ 50% women. All data obtained from participants is used for research purposes described below will be de-identified and separate from identifiable information in concordance with UCSD regulations. No data will be collected from their existing medical record or outside sources unless participants sign a release of information form.

The schedule of study procedures and evaluations is illustrated in Table 3. Briefly, following a telephone screening visit that should take approximately 10 minutes to complete, eligible volunteers will be invited to participate in the informed consent process which varies in its delivery based on the Research Ramp-Up phase in place at the time of enrollment (see below). Once informed consent is obtained, a more elaborate, screening visit will determine their appropriateness for inclusion in the trial. Study assessment materials have been selected based on our prior work.

With the exception of red phase, participants who have been telephone screened and determined eligible for the screening process will be invited to participate in the study. Following UCSD's Research Ramp-Up phases of operation, participants will be screened and treated in accordance to the following protocols described

below. All telephone or tele-video visits will be completed on a HIPAA compliant app called Doximity (https://www.doximity.com/about/research)

Table 3. Schedule of Assessments

	Study Weeks																
Assessments	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**20**	**24**
Diagnostic Assessments																	
MINI[1]	X																
Nicotine Metabolite Ratio		X															
Medical History	X																
TLFB[2] for Drinking & Drug Use	X	X		X		X		X		X		X		X	X	X	X
Smoking-Related & Abstinence Verification Measures																	
FTCD[3]	X																
Smoking Diary/NUI[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QSU[5]-Brief		X		X		X		X		X		X		X			
MNWS[6]		X		X		X		X		X		X		X			
SEQ-12[7] & Confidence Scale[8]		*X*								*X*				*X*			*X*
Urine Cotinine	X													X			X
Expired CO Smokerlyzer	X	X		X		X		X		X		X		X			X
Mood, Sleep, & Suicidality-Related Measures																	
HADS[9]		X		X		X		X		X		X		X	X	X	X
Insomnia Severity Index		X		X		X		X		X		X		X			
ASRM[10]		X		X		X		X		X		X		X	X	X	X
C-SSRS[11]		X		X		X		X		X		X		X	X	X	X
Safety & Tolerability																	
General Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
NAEI[12]		X		X		X		X		X		X		X	X		
Concomitant Medications	X	X		X		X		X		X		X		X	X	X	X
Urine Pregnancy Test	X	X															
Urine Drug Screen	X																
Satisfaction & Protocol/Study Medication Adherence																	
ACT Treatment Satisfaction Questionairre						X				X		X					
CSQ-8[13]				X		X		X		X		X		X			X
Pill Counts				X		X		X		X		X		X			
ACT Mechanism of Change																	
Avoidance & Inflexibility Scale		X								X		X		X			X

[1]Mini International Neuropsychiatric Interview (MINI), Version 7.0.2 for DSM-V; [2] TimeLine Follow Back (TLFB); [3]Fagerstrom Test for Cigarette Dependence (FTCD); [4]Nicotine Use Inventory (NUI); [5]Questionnaire of Smoking Urges-Brief (QSU-Brief); [6]Minnesota Nicotine Withdrawal Scale (MNWS); [7]*Smoking Self-Efficacy Questionnaire (SEQ-12);* [8]*Confidence to Quit Scale;* [9]Hospital Anxiety and Depression Scale (HADS); [10]Altman Self-Rating Mania Scale (ASRM); [11]Columbia-Suicide Severity Rating Scale (C-SSRS); [12]Neuropsychiatric Adverse Events Interview (NAEI); [13]Client Satisfaction Questionnaire-8 (CSQ-8)

Phase 1 (Red Phase):
Screening Visit (Week -2). If the University reverts to the Red Phase again, potential participants will not be recruited, screened or enrolled. Participants who are currently enrolled in the study, however, will continue to be followed.

Baseline Visit (Week 0). We will randomize already screened and consented participants remotely during this phase. Eligible participants will continue participation for a baseline evaluation that will take approximately 2-3 hours by telephone (via HIPAA compliant Doximity). Although the method of administration varies by Research Ramp-Up phase (see below), the following standardized questionnaires will be collected for all phases of

operation, at baseline and throughout the study: **Minnesota Nicotine Withdrawal Scale** (MNWS; 31) to monitor symptoms of tobacco withdrawal; **Questionnaire of Smoking Urges-Brief** (QSU-Brief; 32) to measure cravings to smoke; the **TLFB for Alcohol and Drug Use** (33,24); the **Nicotine Use Inventory** (NUI; 4, 27) is a brief questionnaire that has been used throughout the varenicline Phase III-IV trials that monitors smoking rates and probes for other forms of nicotine use including e-cigarettes, hookah, cigars, etc; the **Hospital Anxiety and Depression Scale** (HADS; 35) is comprised of two separate 7-item self-report questions assessing anxiety and depressive symptoms, respectively; the **Altman Self-Rating Mania Scale** (ASRM; 36) is a 5-item self-rating mania scale with a scoring range from 0-20 that assesses symptoms of mania and hypomania; the **Columbia-Suicide Severity Rating Scale** (C-SSRS; 37) is a semi-structured interview conducted by trained raters to monitor suicide ideation and behaviors; the **Insomnia Severity Index** (ISI; 38) is a reliable and valid 7-item self-report measure to evaluate perceived sleep difficulties; the **Avoidance and Inflexibility Scale** (AIS; 41) is a 27-item questionnaire measuring changes in acceptance-based processes of smoking cessation based on this technique's hypothesized mechanism of action; the **Neuropsychiatric Adverse Events Interview** (NAEI) is a 25-item questionnaire that was used in EAGLES (4) and our prior work (27) to probe for neuropsychiatric complaints that might qualify as adverse events in a clinical trial; an **Assessment of General AEs** using standard operating procedures to record AEs according to the Medical Dictionary for Regulatory Activities version 18.0 (MedDRA; 44) – derived preferred terms; and the **Self Efficacy Questionnaire** (SEQ-12; 42) **and Confidence to Quit Scale** (43) measuring participants' self-efficacy and confidence to quit smoking. Study medication will be dispensed to participants by mail per VMRF pharmacy's shipping protocol with instructions on its use. Participants will also have their first session of ACT session (see below) at their week 0 baseline visit. All assessments will be performed by telephone (on HIPAA compliant Doximity) as scheduled with the exception of vitals, urine or blood collection, and exhaled CO which will not be collected during this Red phase.

Treatment & Follow-up Visits (Weeks 1-12). Table 3 illustrates the schedule of assessments for all follow-up visits, which will be done by telephone via Doximity during this phase. On Day 8 (week 1) participants will pick a day between 8 and 35 to be their target quit date considering that one goal of the study is to have participants take varenicline for several weeks before trying to quit to maximize effectiveness. Study weeks 1, 3, and 5 will take approximately 30 minutes to complete as participants will have 30-minute ACT sessions, as described below. Study weeks 2, 4, and 6 will take approximately 1 hour as participants will have ACT sessions and questionnaires to complete (see table 3). Study weeks 8, 10, and 12 will take 30-45 minutes to complete as participants will not have ACT on these visits but will complete questionnaires. Telephone visits for study weeks 7, 9, and 11 will take ~35 minutes, as the last ACT sessions will be completed during these visits. In addition to the questionnaires given at baseline described above the following questionnaires will be given during the treatment phase: the **Client Satisfaction Questionnaire – 8** (CSQ-8; 39) is a standardized measure of treatment satisfaction that has been used widely across mental health services (40) and in smoking cessation research with varenicline preloading (18) and the **ACT Treatment Satisfaction Questionnaire** (ACT-TSQ) measures treatment satisfaction with ACT counseling using two force-choice response items and a Likert scale (9).

Non-Treatment Follow-up Visits (weeks 13-24): Following discontinuation of the medication participants will be followed every 4 weeks until conclusion of the study assessing mood, any suicidal thinking, and nicotine or other drug use. Visits for study weeks 16, 20 and 24 will be done via Doximity and take approximately 30-45 minutes.

Phase 2 (Orange Phase):
Screening Visit (Week -2). Prior to the screening visit, participants will be mailed or emailed a blank copy of the informed consent form. Potential participants will be consented by phone/video conferencing using Doximity to orient them to the study procedures and requirements. Participant's decisional capacity will be assessed during consent by a trained research staff member to ensure they fully understand the study. After obtaining informed consent, participants will undergo a semi-structured clinical interview, the Mini-International Neuropsychiatric Inventory Version 7.0.2 for DSM-V (MINI; 28) administered by a trained research assistant. A standardized health assessment and mental status examination, including motivation to quit (29), will be

performed by a medical staff by using Doximity. The only in-person procedures conducted during this phase will be for medical procedures. Specifically, a urine sample will be obtained for on-site urine toxicology, baseline cotinine level, and pregnancy screening. Expired breath CO will be measured and blood pressure and heart rate will be obtained along with height and body weight. Lastly, the **Fagerström Test for Cigarette Dependence** (FTCD; 30), a standardized self-report questionnaire will be used to measure nicotine dependence severity and the **TimeLine Follow-Back (TLFB) for Alcohol and Drug Use** (33,24) which obtains estimates of daily drinking and drug use using a calendar technique will be used. The screening visit will take approximately 2-3 hours to complete in both its virtual and face-to-face forms and the latter will follow follow all guidelines to mitigate COVID-19 risk to participants and staff (see below).

Baseline Visit (Week 0). Eligible participants will continue participation for a baseline evaluation that will take approximately 2-3 hours by Doximity. Separately, they will come to Pac-TARC in order to have two 4mL tubes of blood will be collected via venipuncture for use in determining the NMR outcome variable and as a backup sample stored at Pac-TARC and baseline blood pressure and heart rate will be measured. Similar to Phase 1, the following standardized questionnaires will be collected for all phases of operation, at baseline and throughout the study: **Minnesota Nicotine Withdrawal Scale** (MNWS; 31); **Questionnaire of Smoking Urges-Brief** (QSU-Brief; 32); the **TLFB for Alcohol and Drug Use** (33,24); the **Nicotine Use Inventory** (NUI; 4, 27); the **Hospital Anxiety and Depression Scale** (HADS; 35); the **Altman Self-Rating Mania Scale** (ASRM; 36); the **Columbia-Suicide Severity Rating Scale** (C-SSRS; 37); the **Insomnia Severity Index** (ISI; 38); the **Avoidance and Inflexibility Scale** (AIS; 41); the **Neuropsychiatric Adverse Events Interview** (NAEI); an **Assessment of General AEs**; and the **Self Efficacy Questionnaire** (SEQ-12; 42) **and Confidence to Quit Scale** (43). Study medication will be dispensed to participants by mail per VMRF pharmacy's shipping protocol with instructions on its use. Participants will also have their first session of ACT session (see below) at their week 0 baseline visit. All assessments will be performed by telephone (on HIPAA compliant Doximity) as scheduled with the exception of vitals, urine or blood collection, and exhaled CO.

Treatment & Follow-up Visits (Weeks 1-12). Table 3 illustrates the schedule of assessments for all follow-up visits by telephone via Doximity. On Day 8 (week 1) participants will pick a day between 8 and 35 to be their target quit date considering that one goal of the study is to have participants take varenicline for several weeks before trying to quit to maximize effectiveness. Study weeks 1, 3, and 5 will take approximately 30 minutes to complete as participants will have 30-minute ACT sessions, as described below. Study weeks 2, 4, and 6 will take approximately 1 hour as participants will have ACT sessions and questionnaires to complete (see table 3). Study weeks 8, 10, and 12 will take 30-45 minutes to complete as participants will not have ACT on these visits but will complete questionnaires. Telephone visits for study weeks 7, 9, and 11 will take ~35 minutes, as the last ACT sessions will be completed during these visits. In addition to the questionnaires given at baseline described above the following questionnaires will be given during the treatment phase: the **Client Satisfaction Questionnaire – 8** (CSQ-8; 39) is a standardized measure of treatment satisfaction that has been used widely across mental health services (40) and in smoking cessation research with varenicline preloading (18) and the **ACT Treatment Satisfaction Questionnaire** (ACT-TSQ) measures treatment satisfaction with ACT counseling using two force-choice response items and a Likert scale (9).

Non-Treatment Follow-up Visits (weeks 13-24): Following discontinuation of the medication participants will be followed every 4 weeks until conclusion of the study assessing mood, any suicidal thinking, and nicotine or other drug use. Visits for study weeks 16, 20 and 24 will be done via Doximity and take approximately 30-45 minutes.

Phase 3 and 4 (Yellow and Green Phases). These phases will use our prior HRPP-approved methodologies involving both in-person and telephone appointments. The only difference will be that during the Yellow Phase the density of laboratory staff, PPE requirements, and social distancing will be strictly enforced as per the Research Ramp-Up guidelines.

Screening Visit (Week -2). At screening, participants will arrive at Pac-TARC and be consented to study procedures. Participant's decisional capacity will be assessed during consent by a trained research staff

member to ensure they fully understand the study. After consenting, participants will undergo a semi-structured clinical interview, the Mini-International Neuropsychiatric Inventory Version 7.0.2 for DSM-V (MINI; 28) administered by a trained research assistant. A standardized health assessment and mental status examination, including motivation to quit (29), will be performed by a medical staff member and a urine sample will be obtained for on-site urine toxicology, baseline cotinine level, and pregnancy screening. Expired breath CO will be measured and blood pressure and heart rate will be obtained along with height and body weight. Lastly, the **Fagerström Test for Cigarette Dependence** (FTCD; 30), a standardized self-report questionnaire will be used to measure nicotine dependence severity and the **TimeLine Follow-Back (TLFB) for Alcohol and Drug Use** (33,24) which obtains estimates of daily drinking and drug use using a calendar technique will be used. The screening visit will take approximately 2-3 hours to complete.

Baseline Visit (Week 0). Eligible participants will return to Pac-TARC following screening for a baseline evaluation that will take approximately 2-3 hours. First, two 4mL tubes of blood will be collected via venipuncture for use in determining the NMR outcome variable and as a backup sample stored at Pac-TARC and baseline blood pressure and heart rate will be measured. Next, the following standardized questionnaires will be collected at baseline and throughout the study: **Minnesota Nicotine Withdrawal Scale** (MNWS; 31) to monitor symptoms of tobacco withdrawal; **Questionnaire of Smoking Urges-Brief** (QSU-Brief; 32) to measure cravings to smoke; the **TLFB for Alcohol and Drug Use** (33,24); the **Nicotine Use Inventory** (NUI; 4, 27) is a brief questionnaire that has been used throughout the varenicline Phase III-IV trials that monitors smoking rates and probes for other forms of nicotine use including e-cigarettes, hookah, cigars, etc; the **Hospital Anxiety and Depression Scale** (HADS; 35) is comprised of two separate 7-item self-report questions assessing anxiety and depressive symptoms, respectively; the **Altman Self-Rating Mania Scale** (ASRM; 36) is a 5-item self-rating mania scale with a scoring range from 0-20 that assesses symptoms of mania and hypomania; the **Columbia-Suicide Severity Rating Scale** (C-SSRS; 37) is a semi-structured interview conducted by trained raters to monitor suicide ideation and behaviors; the **Insomnia Severity Index** (ISI; 38) is a reliable and valid 7-item self-report measure to evaluate perceived sleep difficulties; the **Avoidance and Inflexibility Scale** (AIS; 41) is a 27-item questionnaire measuring changes in acceptance-based processes of smoking cessation based on this technique's hypothesized mechanism of action; the **Neuropsychiatric Adverse Events Interview** (NAEI) is a 25-item questionnaire that was used in EAGLES (4) and our prior work (27) to probe for neuropsychiatric complaints that might qualify as adverse events in a clinical trial; an **Assessment of General AEs** using standard operating procedures to record AEs according to the Medical Dictionary for Regulatory Activities version 18.0 (MedDRA; 44) – derived preferred terms; and the **Self Efficacy Questionnaire** (SEQ-12; 42) **and Confidence to Quit Scale** (43) measuring participants' self-efficacy and confidence to quit smoking. Participants will also have their first session of ACT session (see below) at their week 0 baseline visit.

Treatment Follow-up Visits (Weeks 1-12). Table 3 illustrates the schedule of assessments for treatment follow-up visits. On Day 8 (week 1) participants will pick a day between 8 and 35 to be their target quit date considering that one goal of the study is to have participants take varenicline for several weeks before trying to quit to maximize effectiveness. In-person visits for study weeks 1, 3, and 5 will take approximately 30 minutes to complete as participants will have 30-minute ACT sessions, as described below. In-person visits for study weeks 2, 4, and 6 will take approximately 1 hour as participants will have ACT sessions, assessment of blood pressure and heart rate, and questionnaires to complete (see table 3). In-person visits for study weeks 8, 10, and 12 will take 30 minutes to complete as participants will not have ACT on these visits but will fill out questionnaires and have blood pressure/heart rate assessed. Telephone visits for study weeks 7, 9, and 11 will take ~35 minutes, as the last ACT sessions will be completed at these visits. Figure 3 illustrates the study design. In addition to the questionnaires given at baseline described above the following questionnaires will be given during the treatment phase: the **Client Satisfaction Questionnaire – 8** (CSQ-8; 39) is a standardized measure of treatment satisfaction that has been used widely across mental health services (40) and in smoking cessation research with varenicline preloading (18) and the **ACT Treatment Satisfaction Questionnaire** (ACT-TSQ) measures treatment satisfaction with ACT counseling using two force-choice response items and a Likert scale (9).

Brief description of ACT intervention: Previous work has demonstrated that ACT, delivered as either 10 in-person or 6 telephone-delivered sessions, was feasible as evidenced by very high rates of participant retention and satisfaction (9). Others have also found preliminary evidence for ACT facilitating abstinence when combined with NRT patches: 40% of bipolar smokers receiving face-to-face ACT therapy, and 33% of those receiving ACT telephone therapy, achieved 7-day PP abstinence. Notably, higher quit rates were observed in ACT-treated bipolar smokers compared with another cohort treated with mood management cognitive behavioral therapy (46). Further, there was face validity to the proposed mechanism of action of ACT with >50% of participants reporting increasing acceptance of cravings to smoke. When one considers that 7-day PPA rates at end of treatment in EAGLES bipolar smokers treated with NRT patch was 10.8%, and for SSD smokers was 15.2% (unpublished data), the potential 2 to 4-fold booster effects with ACT deserve further testing. The ACT treatment manual to be used in this pilot trial was developed by Dr. Heffner and colleagues and was pilot tested in smokers with BD (9). The ten 30-minute sessions will target the six core processes in ACT: acceptance, cognitive diffusion, being present, self as context, defining valued directions, and committed action. The intervention relies heavily on experiential in-session exercises and metaphors as a means of helping smokers learn to apply ACT principles to the task of quitting smoking as well as managing negative affect. ACT counselors will have at least three years of counseling experience, established therapeutic skills (e.g., empathy), and a master's degree in clinical psychology. Counselors will receive 40 hours of didactic and role-play training in the ACT intervention provided by Dr. Heffner prior to the study commencing. Counselors will be certified as study therapists prior to delivering ACT, defined as passing scores on fidelity measures as outlined in the ACT Adherence Raters' Manual (47). ACT treatment fidelity will be evaluated by Dr. Afari assessing a twenty percent random sample of each therapist's audiotaped calls. ACT sessions will be rated using the ACT Adherence Raters' Manual (47,48). Dr. McKenna and the counselors will also meet biweekly to review implementation quality data and coordinate intervention delivery based on fidelity feedback he receives from Dr. Afari.

Non-Treatment Follow-up Visits (weeks 13-24): Following discontinuation of the medication participants will be followed every 4 weeks until conclusion of the study assessing mood, any suicidal thinking, and nicotine or other drug use. Visits for study weeks 16 and 20 will be done via telephone and take approximately 30-45 minutes. The final visit at week 24 will take place at Pac-TAC and take approximately 1 hour to complete.

Medication Adherence: Although aware of their limitations, due to budgetary constraints we will use participant self-report and pill counts of capsules returned at the biweekly visits as the measure of study medication adherence. Compliance will be defined as having any (partial or full) daily dose of study drug for 80% of the planned treatment period of 84 days.

Medication Tolerability Outcome Measure - - We will also assess: 1) % participants in each dosing arm who tolerate twice daily dosing with no dosage reductions; 2) % participants in each arm who continue on treatment but with a dosage reduction to once daily dosing; 3) % participants who discontinue medication treatment, but continue in study (off treatment/in study; treatment discontinuation rate); and 4) % participants who discontinue treatment and study enrollment (e.g., study discontinuation rate).

Assessment of NPSAEs & 2° NPS safety outcome: We will use the identical procedures we helped develop and used in the EAGLES trial to monitor neuropsychiatric safety (7). Briefly, all NPS complaints that are volunteered, observed or solicited with the NAEI; any elevated scores on the mood-, sleep- and suicidality-related measures described above, and any proxy reports from collateral informants will be evaluated as potential NPSAEs by the study team. Each AE will be rated by one of the study clinicians as to its intensity using the standardized EAGLES procedure: Mild = no or minimal interference in functioning; Moderate = some interference in functioning; Severe = significant interference with functioning. Based on this scoring, we will determine the composite safety endpoint used in EAGLES (i.e., NPSAEs that were rated as moderate to severe across the 16 pre-specified domains). We will also examine the observed incidence of participants experiencing NPSAEs of any intensity (i.e., mild, moderate or severe) as our 2° NPS safety outcome during the 12-week active treatment phase plus 28 day as also done in EAGLES.

2° Efficacy Outcome: In keeping with the pilot nature of this trial, we will use 7-day point prevalence abstinence (PPA) at week 12 confirmed by expired CO levels ≥ 4 ppm and urine cotinine levels < 200 mg/ml as the secondary efficacy endpoint. We will continue to track smoking outcomes through week 24 using these same biochemical verification measures to assess 7-day PPA at week 24 as a tertiary outcome.
Other Secondary Outcome Measures: Our gathering of data on the MNWS, QSU-Brief, ISI, SEQ-12, Confidence to Quit Scale is exploratory in nature and is intended to provide preliminary information on the mechanism of action of combined varenicline and ACT in SMI smokers and their relation to NPSAEs. We will also explore ACT's effects on avoidance and inflexibility with the AIS at weeks 12 and 24.

Determination of the NMR: The ratio of trans-3'-hydroxycotinine (3HC) and cotinine (COT) will be measured in plasma using electrospray ionization liquid chromatography tandem mass spectrometry (ESI LC-MS/MS) technology adapted from the protocols described by Tanner et al. (45) and Lerman et al. (7). COT and 3HC in plasma will be determined by quantifying with standard deuterium labeled COT and 3HC, known as COT-d3 and 3HC-d3 (commercially available from Sigma-Aldrich). Plasma samples will be spiked with a known amount of COT-d3 and 3HC-d3, and samples will be subjected to MS to quantitate the endogenous levels of COT and 3HC by parallel reaction monitoring. LC-MS/MS will be performed on the high-resolution Orbitrap Q-Exactive LC -MS system located in the Hook lab in the Skaggs School of Pharmacy and Pharmaceutical Sciences. Standard plots of different amounts of deuterated and non-deuterated COT and 3HC standards into control plasma, followed by LC-MS/MS, will define the linear range of quantitative measurements, lower limit of detection, and reproducibility of replicate samples. Ratios of 3HC/COT will be calculated from quantitative MS data analyzed by the Skyline software. Reliability of these procedures in plasma is high with NMR measurements robust even to differences in analytic methods used by different laboratories (45). The NMR data will be compiled with the phenotypic data of this study to examine the relationship of NMR to NPSAEs and smoking cessation.

Data Storage: Data from assessments will be collected solely for research purposes by self-report, interview, urinalysis, and venipuncture and de-identified with an alpha-numeric code. The link between Urine will be immediately processed upon collection and then disposed of in accordance with UCSD policies. Blood data collected at baseline will be de-identified and stored in a -80^0 C freezer within Pac-TARC until transferred and processed by Dr. Hook in her laboratory to calculate the nicotine metabolite ratio.

Data Analytic Plan -- Aim 1: Examine the feasibility of combining ACT with two different varenicline-assisted quitting strategies using a flexible quit date in SMI smokers. Three feasibility domains will be examined across hypotheses assessing demand, practicality, and acceptability (18).

Hypothesis 1a posits that there will be demand for such a combined pharmacological-behavioral trial among SMI smokers as evidenced by achieving a) targeted accrual rates (average of 6 participants screened & 4 randomized per month), and b) recruitment costs not exceeding the advertising budget (~$200 per screened subject).

Hypothesis 1b assessing practicality posits that the piloted elements of the study will be successfully carried out as defined by ≥ 80% retention of participants and completion of study procedures during a) the 12-week active treatment phase, and b) 12-week follow-up period. We also predict that ≥ 80% of ACT sessions will be completed with no drop-off across in-person and telephone counseling sessions.

Hypothesis 1c predicts that acceptability of the flexible quit date and varenicline dosing procedures will be high as demonstrated by ≥ 80% adherence to a) making a quit attempt within the 27-day quit window, and b) taking at least 80% of the prescribed study medication doses. Furthermore, we posit that satisfaction with the trial overall will be high with scores on the CSQ-8 registering in the 24-32 range, as will satisfaction with ACT counseling as demonstrated by ≥ 80% of participants endorsing scores in the satisfactory to highly satisfactory range on the 2-item ACT-Treatment Satisfaction Questionnaire used in our prior work (9).

For each feasibility measure we will compare study values to the targeted benchmarks which are based on our prior work in SMI smokers (4,49) and the relevant literature (13,19). While formal hypothesis testing is not planned given the pilot nature of this proposal (50,51), we will calculate effect sizes (i.e., Cohen's d or odds ratios [ORs]) and standard deviations, as well as confidence intervals (CI), for our feasibility variables and use

them as preliminary data for the subsequent larger RCTs. We will also calculate and examine Cohen's kappa coefficients for our clinician-obtained measures including the MINI, TLFB, C-SSRS, and assessments of NPSAEs and general AEs. These values will be used to assess the inter-rater reliability of relevant measures in SMI smokers and to refine our rater training procedures if necessary.
Aim 2: Explore whether nicotine clearance rate as measured by the NMR influences the incidence of NPSAEs in varenicline-treated SMI smokers. This exploratory aim will begin to test the **hypothesis** that incidence of NPSAEs of any severity will be higher in slow nicotine metabolisers assigned to standard dose varenicline compared with normal metabolisers treated with low dose varenicline.

To gather preliminary data on the NMR, the frequency distributions of the NMR values in this SMI sample will be compared with the published data from Lerman et al. (2015) in a large sample of NMI smokers that found a cutoff score of 0.31 as the demarcating point between slow (<0.31) and normal (including rapid) metabolisers. Based on this analysis, we will calculate Cohen's d effect sizes comparing slow metabolisers on standard dose vs. normal metabolisers on low dose, as well as standard deviations and CIs, for incidence of NPSAEs of any severity to examine the direction and magnitude of the effect. Secondary outcome measures will also be examined using the same methodologies including 7-day PPA at weeks 12 and 24, to guide future studies. Regarding the secondary efficacy outcomes, and anticipating possible quit-boosting effects from ACT and varenicline preloading, we predict 7-day PPA rates at week 12 will be at least comparable to those observed in varenicline-treated EAGLES SMI participants which was 28.2%, and that 7-day PPA rates at week 24 will be at least comparable to the 20.0% observed in EAGLES (unpublished data). To examine the possible confounding effect of variable lengths of abstinence depending on when participants first attempt to quit smoking within the quit window, we will examine the effect of a time factor (i.e., the number of days from the first dose of medication to the date of the first quit attempt) with the methodologies described above.

Sample Size Determination: The aims of this pilot trial are to gather preliminary data or demonstrate proof of principle with potential for high impact within one or more stated research priorities of the funding agency. Thus, Aim 1 of the proposal addresses feasibility while Aim 2 is exploratory and begins to test the principle as to whether NMR influences NPSAE propensity and medication tolerability in SMI smokers by estimating effect sizes. The study is designed to provide preliminary data on the feasibility of a larger RCT that would further develop these novel pharmacotherapy approaches in SMI smokers. It is not powered to test clinical outcomes, thus, safety (incidence of NPSAEs) and efficacy (7-day PPA at week 12 and at week 24) outcome measures are considered secondary endpoints. In our group's previous work with varenicline in EAGLES (4) and another trial done in SMI smokers (49), we randomized ~80% of those screened and retained >80% of study participants. Similar retention rates were found in another pilot trial of varenicline in bipolar smokers (52) and in Dr. Heffner's preliminary study. Therefore, we expect that with N=60 we will be able to adequately determine the feasibility of the proposed study procedures.

Consistent with recommendations on the proper sizing for pilot studies literature (50,51,53), we chose a sample size of 60 participants based on maximal accrual expectations over a 15-month recruitment period and practical cost constraints to conduct a pilot trial in this special population of smokers. Previous studies examining target sample sizes for pilot studies have argued that as few as 12 participants per group is adequate to estimate standard deviations for a two-group study (54,55), while others have suggested that a total sample of 30 is an acceptable size for a pilot study (56). With a sample of 60 (n=30 per dosing group), we will have the ability to estimate effect sizes, standard deviations, and their CIs with adequate precision to evaluate the feasibility of study procedures and to subsequently conduct formal power analyses for future RCTs (57). As such, it is amply sized as a pilot trial. For example, given a small-to-medium estimated effect of d=0.40, we would have 80% confidence that the true effect fell between 0.064 and 0.733 with a pilot sample of N=60. For a smaller effect of d=0.30, this 80% CI becomes 0.005-0.672 providing adequate precision in detecting an effect (i.e., zero not in the CI) for use in power analyses for a larger RCT. Furthermore, applying Sims' and Lewis' (2012) calculations, the sample size of N=60 will allow us to estimate standard deviations around our feasibility estimates with a minimal inflation factor (e.g., 1.09 for one-sided 80% CIs) for use in future RCT power analyses.

10. HUMAN SUBJECTS

Sixty men and women with DSM-V BD (Type I or Type II, N = 30) or SSD (schizophrenia or schizoaffective disorder, N = 30) and who are chronic smokers will be recruited to participate in this pilot trial at Pac-TARC, which is a research center housed within the UCSD Department of Psychiatry. With an anticipated 33% screen failure rate, we anticipate screening up to 90 participants to accrue the sample. Each group will include ~ 50% women and individuals of any ethnic background are eligible to participate. Based on our prior work recruiting for EAGLES in San Diego where 35% (182/523) of those phone-screened self-identified as BD or SSD smokers, we expect that the SMI smokers who call to inquire about the study will have demographic and clinical characteristics similar to those SMI smokers enrolled in EAGLES (e.g., ~47% female, 65% White). Also, like EAGLES, we expect BD and SSD smokers to have similar baseline smoking characteristics.

Inclusion Criteria

- 18-70 years of age
- Outpatients with a DSM-V diagnosis of BD or SSD
- Smoke at least 10 cigarettes per day and have an expired carbon monoxide (CO) breathalyzer of ≥ 10 ppm at screening and baseline visits
- Are motivated to quit smoking by scoring 5 or higher on the Contemplation Ladder (28)
- Have access to a mental health provider should their condition worsen during study enrollment

Exclusion Criteria

- Females who are pregnant, planning to become pregnant, or lactating
- Test positive for any non-prescribed medications (e.g., opiates, benzodiazepines, psychostimulants) or illicit drugs excluding cannabis during screening
- Have made a suicide attempt or engaged in self-mutilatory behavior in the past year
- Meet criteria for another SUD in the past month
- In the investigators' judgement, are either psychiatrically (e.g., presently manic, hypomanic, acutely psychotic, depressed or suicidal) or medically (e.g., uncontrolled hypertension, angina) unstable to safely participate
- Are currently using any other form of treatment for smoking cessation

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Outpatients who are interested in treatment for smoking cessation will be recruited from the UCSD Outpatient Psychiatry Clinics in La Jolla and Hillcrest, the VA San Diego Mental Health Care Line including its Mood Clinic (where Dr. McKenna is a Staff Psychologist), and the general San Diego community with help from local mental illness support groups including the National Alliance on Mental Illness and Depression and Bipolar Support Alliance. We will also utilize print, on-line, and radio ads for recruitment. We will **not** review potential participant's private health information in recruitment and/or identifying participants to contact. As an example of our capabilities to recruit such smokers, 231 SMI patients have been screened in previous smoking cessation studies at Pac-TARC.

When interested candidates call study staff in response to recruitment materials, confidentiality will be reviewed briefly and verbal consent will be requested and documented by the staff member prior to asking screening questions. Protected Health Information will be collected during this screening process, which includes name, address, date of birth and some psychiatric and medical history. This information is collected to assess for study eligibility and will be accessed by only the study staff members with appropriate training. This prescreening stage of research presents no more than minimal risk of harm to the subjects and involves no procedures for which written consent is normally required outside of the research context. All participants will be provided ample information verbally to allow them to make an informed decision regarding whether to participate in the telephone screen, and eligible participants interested in the study will review a thorough written informed consent form with study staff at their first face-to-face clinic visit. To protect identifiers from improper use and disclosure, all telephone pre-screen forms will be filed in a locked cabinet in a secured file room. The reason these pre-screening forms will be retained is so they can be cross-referenced across our

studies to prevent duplicate screenings or concurrent enrollment. In addition, these forms are kept on file for those who have expressed interest in future studies.

12. INFORMED CONSENT

At the screening visit at the Pac-TARC facility a study staff member designated to obtain informed consent will provide an explanation of the study purpose and requirements (in English). This staff member will have completed appropriate training in Human Subjects Protection and Good Clinical Practice, have specific training regarding recruitment, screening and assessment for the current study, and will be supervised by Drs. Anthenelli and McKenna. The investigators ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The informed consent form will be in compliance with UCSD HRPP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, will be prospectively approved by the UCSD HRPP before use. Written informed consent will be obtained from each subject or the subject's legally acceptable representative before any study-specific activity is performed. We will retain the original of each subject's signed consent form and authorization. Staff will also review the approved HIPAA Research Authorization form and answer any questions subjects may have regarding HIPAA and use of their data in this study. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the UCSD's HRPP, and the HIPAA Research Authorization form "University of California Permission to Use Personal Health Information for Research" and given the "SUBJECT'S BILL OF RIGHTS" as required by California State law.

Subjects will be given a copy of the signed informed consent, HIPAA Research Authorization form, UCSD's Experimental Subjects Bill of Rights and the Registry Authorization Informed Consent for their own records and study staff will retain the originals. These documents will be filed in a locked cabinet, in a locked office that only authorized study staff can access. This location will be separate from all de-identified data collected to reduce risks to participant confidentiality.

13. ALTERNATIVES TO STUDY PARTICIPATION

Participants do not have to be in this study to receive treatment for their smoking habit. Instead of taking part in this study, they may choose to receive treatment with medications that have been approved for use in this country or they may choose non-drug therapies. If a participant would like referrals or does not want to continue in the study, the following is a list of alternative treatments that would be recommended after talking with one of the study doctors. The study doctor will discuss the risks and benefits of the alternative treatments including: Nicotine gum, Nicotine patch, Nicotine inhaler, Nicotine spray, Nicotine lozenge, Bupropion, Hypnosis, "Cold turkey", and Counseling/Self-help other than ACT.

14. POTENTIAL RISKS

The inherent risks in randomization by chance to low (0.5 mg twice daily with slower titration over one full week) versus standard dose (1.0 mg twice daily with standard titration) varenicline will be explained to participants during the consenting process. The risk of the lower 0.5 mg dose twice daily is minimal given the previous studies described in the Background section; in fact, fewer side effects have been associated with the lower dose. Specifically, our earliest work with varenicline in a Phase II trial in NMI smokers found that 0.5 mg twice daily titrated varenicline - - one-half of what eventually became the FDA-approved titrated dose of 1 mg twice daily, produced similar quit rates to the approved dose (13), a result confirmed in a related Phase II varenicline trial (14) and a recent Phase IV trial (15). Furthermore, all participants will receive ACT in helping them quit smoking.

<u>Potential risks for varenicline tartrate:</u>
The negative events that are the most likely to happen when receiving varenicline in this study are nausea, headaches, sleep disturbances (insomnia, abnormal dreams), dizziness, constipation, flatulence (gas) and

vomiting. Even though these side effects are expected to occur in some people, most have not had to discontinue varenicline treatment because of side effects. Varenicline is an FDA-approved medication or the treatment of smoking cessation. To date, over 24 million people worldwide have been exposed to varenicline.

The following adverse events have been reported after varenicline came on the market. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or know whether the drug actually causes these events.

Less Common
Changes in mood (depression and mania), agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, and suicidal ideation.

Rare (but serious)
Hypersensitivity reactions (swelling of face, mouth, extremities, and neck that can make breathing difficult) and skin reactions (rash, swelling, redness, and peeling of the skin which can sometimes be life-threatening)

Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients reporting these events had prior psychiatric illnesses and not all had stopped smoking. The role of varenicline in these reports is not known.

Other Study Risks and Discomforts:

In September 2021, Pfizer – the maker of varenicline (Chantix), began a voluntary recall of this medication. This was done because some lots or batches of the medication contained too high of a level of a substance called “N-nitroso-varenicline.”

According to the drug maker, “long-term ingestion of N-nitroso-varenicline may be associated with a theoretical potential increased cancer risk in humans, but there is no immediate risk to patients taking this medication.” According to both the drug maker and the US Food and Drug Administration (FDA): “The health benefits of stopping smoking outweigh the cancer risk from the nitrosamine impurity in varenicline.”

As a result of the Pfizer drug recall, in this amended study protocol, participants will be informed as part of the consent process that they will receive a generic version of the medication that the U.S. Food and Drug Administration (FDA) has allowed to be temporarily imported into the U.S. That generic medication, named Apo-Varenicline, contains n-nitroso-varenicline amounts at a level deemed acceptable by the FDA. Apo-varenicline is approved for use as a generic medication for smoking cessation in Canada.

The researchers are in communication with Pfizer about this development and are tracking the FDA guidance on n-nitroso varenicline. They will not knowingly dispense any medications that contain levels of this impurity that are above the FDA’s acceptable levels. However, if potential participants still have concerns about this newly identified potential safety risk, they will be told to speak with Dr. Anthenelli and/or their own healthcare provider about alternate approaches to quitting smoking.

Additional Study Risks and Discomforts include:
1. Pain, bleeding, bruising or swelling at the site of needle sticks (where the needle is inserted to draw blood) which is sometimes likely and not serious in our experience.
2. Lightheadedness and fainting during needle sticks which is not likely nor serious in our experience.
3. Distress due to the personal nature of questions asked in the context of completing the diagnostic interview and clinical rating scales which is not likely nor serious in our experience.
4. Distress due to the Acceptance and Commitment Therapy (ACT) which is not likely nor serious in our experience.
5. As always in research settings, there is the remote possibility of a breach of confidentiality due to disclosure of personal information which might embarrass or negatively impact the participant’s mental illness.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

The basic protection against risk in this study is the standardization of assessment that will be provided by the study. The study investigators, study coordinator, study staff, and data manager will meet weekly to review accrued data, data confidentiality, recruitment, and subject complaints. Assessment of changes to the risk/benefit ratio, and subject complaints will be reviewed by the principal investigators and reported to the HRPP in accordance with HRPP reporting guidelines. Minutes derived from these meetings will be submitted to the IRB annually. Strict confidentiality will be maintained. Code numbers will identify all subjects, and their research records will be kept in a locked file. No participant will be identified by any published report. Data will be entered by staff who are authorized by the principal investigator to do this, and they will abide by confidentiality regulations of the HRPP. These data will be secured for minimal access to authorized personnel associated with the study. Subject anonymity will be preserved by the use of a code number on all questionnaires and reports. A list of subject names will be kept in a locked file cabinet with minimal access to the study personnel authorized by the principal investigator. We do not expect any breach of confidentiality; however, if one occurs, it will be reviewed and reported to the HRPP. In the event of a breach of confidential information, attempts will be made to limit the spread of the information, identify the nature of the information and any specific risks its propagation may convey, and to contact the HRPP for further guidance in determining whether the affected individual should be contacted regarding the breach.

During the course of the study, safety data will be collected for all subjects who have enrolled into the study. Participants will receive an Emergency Contact Information card in case they need to reach study doctors outside the working day. The incidence and severity of treatment-emergent Adverse Events (AEs) will be assessed at each in-person and telephone visit by trained study staff members. Further, the Neuropsychiatric Adverse Event Interview (NAEI) will be conducted at each in-person visit by a trained interviewer, which will also assess changes in psychiatric symptoms. The professional, experienced staff members conducting the clinical assessments and venipuncture will be sensitive to any patient discomfort and will make every effort to minimize aggravation by taking breaks or discontinuing the assessment if necessary. Similarly, trained therapists delivering ACT will discuss any study issues as they arise with participants as part of the therapy. Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigators for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort will be made to contact the participant. In any circumstance, every effort will be made to document the outcome, if possible. The principal investigator will inquire about the reason for withdrawal, request that the participant return for a final visit, if applicable, and follow-up with the participant regarding any unresolved AEs. On the day of randomization, participants are given an emergency notification card. The emergency notification card has a 24-hour emergency number by which to contact a clinical study staff member in case of an after-hours emergency. Participants who discontinue treatment will be encouraged to continue participation in the study and all planned assessments/evaluations. Specifically, they will maintain the visit schedule and should continue participation through the non-treatment follow-up phase of the study. All participants who permanently discontinue study drugs for any reason will remain in the study as Off Treatment and In Study (OTIS). Every effort will be made to keep the subject in the study until the final visit and all planned assessments/evaluations should be performed. Specifically, the subject will maintain the visit schedule and continue participation through the non-treatment follow-up phase of the study.

If a participant is identified as suicidal or at risk of harming themselves via self-report or on the C-SSRS one of the study's licensed clinicians (M.D. or Ph.D.) will evaluate the participant in more detail for assessment of suicidal ideation, plans, and intent. As part of this evaluation, a safety plan will be established and documented, and the necessary referrals will be made for mental health care including contacting the participant's usual mental health provider or family member and, if necessary, referring for emergency psychiatric evaluation at a hospital emergency department. If the participant is an imminent threat to themselves as determined by a licensed provider, confidentiality will be broken to ensure the safety of the participant in compliance with California State Laws. Pac-TARC is located approximately 2 miles from three major hospitals.

A Data Safety and Monitoring Board (DSMB) has also been established for this study. They will receive aggregated safety reports on a semi-annual basis that includes unblinding codes from the research

pharmacist. This board will be co-chaired by two independent individuals who are not part of the treatment providing team: Arthur Brody, M.D. (a professor and addiction psychiatrist working at the Veterans Affairs San Diego Healthcare System) and Timothy Chen, Pharm.D., BCACP, BCGP, APh (Director, Tobacco Cessation Clinical Resource Center, VHA Office of Mental Health and Suicide Prevention).

COVID-19 Risk Management Plans: For all on-site, in-person visits we will be follow UCSD guidelines and health and safety protocols as outlined in the UC San Diego Research Ramp Up Guidelines (https://blink.ucsd.edu/research/covid-19/research-ramp-up.html) including the use of personalized protective equipment (PPE), social distancing, and sanitization. Standard operating procedures in place at Pac-TARC are outlined below:

1. SAFETY
   - 1.1. PPE including masks must be worn by all staff, visitors, and participants.
   - 1.2. Staff members are limited to only those who are required to be present for the visit.
   - 1.3. Only one visit will be scheduled at any one time allowing 15 minutes between participants or visitors to allow for proper sanitization.
   - 1.4. Hand washing for 20 seconds or longer will be required prior and following visits.
   - 1.5. If gloves are worn, they are to be changed between tasks.
   - 1.6. Each participant will be assigned a clinic room at scheduling and documented.
   - 1.7. Participants are asked to arrive at the clinic unaccompanied unless absolutely necessary (e.g., disabled and requires assistance).
   - 1.8. Clinic room(s) used for participant visits will be thoroughly wiped down with University provided disinfectant prior to and between all visits.
   - 1.9. Staff, visitors and participants will be instructed to utilize hand sanitizer prior to entering clinic rooms.
   - 1.10. Staff will self-monitor on a daily basis, per University guidelines, for COVID-19 symptoms including using the online tool https://blinkucsd.edu/go/screening.
   - 1.11. All personnel will be instructed not to come to work if sick.
   - 1.12. Participants will be questioned the day prior to scheduled visits by phone and on the day of scheduled visits utilizing the University's Patient and Visitor Screening Questions form.
   - 1.13. Signage indicating max occupancy limits, social distancing requirements, safety procedures and disinfection protocols will be visible in all offices, clinic rooms, waiting areas and laboratory spaces.
   - 1.14. Tape and placards will be placed to encourage physical distancing.
   - 1.15. All personnel capable of working remotely will be directed to do so.
   - 1.16. Personnel shifts will be staggered to reduce in-person contact.
   - 1.17. Laboratory supplies will be accessible in each clinic room and be cleaned following every visit.
   - 1.18. Personnel are prevented from sharing items when applicable (e.g., pens, phones, desks, workstations) or disinfected between each use.
   - 1.19. Hand sanitizers will be kept at workstations and high-touch areas.
   - 1.20. All personnel will be responsible for their workstations and must clean their workstation following a shift.
   - 1.21. Assigned personnel will disinfect common areas (including doorknobs, light switches, pens, waiting area), high-touch areas (doorknobs, light switches), between visitors and participants or at the beginning and end of each day.
   - 1.22. A two-week supply of PPE and disinfectants will be kept on hand in the facility.

2. RISK
   - 2.1. Using UCSD's Important Information about COVID-19 and Research Participation form, participants will be informed as part of the informed consent process of their risk of exposure to the COVID-19 virus may be higher by participating in any in-person clinic visit.
   - 2.2. Participants will be questioned a day prior to scheduled visit by phone and on the day of scheduled visit utilizing the University's Patient and Visitor Screening Questions form.
   - 2.3. Documentation will be filed with the participant's source records.

3. SANITIZATION
   3.1. Signage indicating disinfection protocols will be visible in all offices, clinic rooms, waiting areas and laboratory spaces.
   3.2. Sanitizing must occur after each participant visit
   3.3. Hand washing for 20 seconds or longer will be required prior, following visits and after sanitizing.
   3.4. If gloves are worn, they are to be changed between tasks.
   3.5. Disinfectant and cleaners used will be approved by the EPA.
   3.6. When disinfecting, cleanser will be kept on the surface to be sanitized for the directed amount of time by the manufacturer.
   3.7. PPE will be worn while sanitizing.
   3.8. Gloves must be discarded after cleaning to prevent cross contamination.
   3.9. Disposing of biohazards will be in accordance with the EH & S guidelines.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

The following steps have been taken to ensure the protection of confidential patient information: 1) All data collected from subjects (i.e., biological and behavioral) will be numerically coded using a system that will not be decipherable based on personal information, including date of assessment, birthday etc., 2) No mechanism for deciphering the coded participant information will be readily accessible in the context of the proposed work, 3) All requests for access to participant information are subject to review according to HRPP-approved written policies, 4) All researchers involved with handling of samples from participants will be required to receive training in ethical principles, information security and appropriate handling of human subject information, 5) Hard copies of data will be stored exclusively in a secure records room within Pac-TARC, in a locked room. Electronic data will be stored on a secure computer with password access required for viewing in accordance with UCSD regulations on data security, 6) No identifiable participant data will be included on any shared data, and the release of all data for sharing will be authorized by local officials in accordance with UCSD policies prior to release, 7) Consent and other forms containing identifying data will be kept separate from other research data, and 8) One key hard document connecting the names with the codes will be maintained and kept by the applicant in a separate location than the data under lock and key.

Efforts will be made to protect Participant's privacy. Recruitment will happen via potential participants receiving HRPP-approved recruitment materials from their clinic providers or seeing the materials on their own and calling Pac-TARC. All in-person procedures, including consent, assessments, and ACT will be done in private rooms within Pac-TARC. During telephone calls participants will first be asked if they are in a place where they feel comfortable speaking privately. If not, the call will be rescheduled to a time the participant will have privacy.

17. POTENTIAL BENEFITS

Participants may be able to quit smoking. It is possible that their condition or health may improve because of quitting smoking or because of their visits to the research clinic. However, there is no guarantee that they will benefit in any way. Information from this study may help other people who would like to quit smoking in the future.

18. RISK/BENEFIT RATIO

There may or may not be any direct benefit to from the study procedures. Participants may or may not decrease smoking cigarettes from the treatment and counseling provided in this study. Participation in the study will help determine the feasibility of combining ACT with two different varenicline-assisted quitting strategies: a) slower titration of lower dose varenicline monotherapy, versus b) standard titration of standard dose varenicline - - both delivered using a flexible quit date paradigm that allows gradual preloading of varenicline prior to the target quit date. There will be no charge to participation in this study. These potential benefits outweigh the minimal risks involved.

19. EXPENSE TO PARTICIPANT

The study drugs, study-related procedures, and study visits will be provided at no charge to the subject.

20. COMPENSATION FOR PARTICIPATION

Participants will be compensated up to $390 for their participation assuming they complete all study visits and phone calls. Participants will be compensated at the following rates:
Screening visit, $20; Face-to-face visits on study weeks 0, 2, 4, 6, 8, 10, 12, and 24 ($25 each); 5 phone visits on weeks 7, 9, 11, 16, 20 ($15 each); and 3 face-to-face visits on study weeks 1, 3, and 5 ($15 each); weeks 12 & 24 completion ($25 each) and bonus payments ($25 each) for consistent attendance.
If requested, participants will also be provided with transportation to/from the research site in accordance with UCSD-contracted Lyft rideshare services paid by Pac-TARC.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Investigators and research personnel are trained in ethical standards for human research and are current with IRB requirements for training and certification and adhere to ICH guidelines. To ensure that all research activities are in full compliance with HRPP standards, Dr. Anthenelli chairs a weekly meeting with the research team to provide oversight regarding recruitment, research procedures and the clinical status of all active subjects.

Robert M. Anthenelli, M.D. is Professor and Executive Vice Chair in the Department of Psychiatry and the Director of Pac-TARC. He has over 20 years of experience conducting clinical research in tobacco and other drug dependent individuals with comorbid psychiatric disorders including smoking cessation studies in persons with mental health conditions. He will oversee all aspects of the trial Dr. Anthenelli's responsibilities for this project include: 1) supervising all staff; manage overall study design and coordination; assist staff with clinical management of the trial; data analyses; preparation of abstracts, manuscripts, and other publications.

Benjamin McKenna, Ph.D. is a Project Scientist in the Department of Psychiatry and Staff Psychologist in the San Diego VA Healthcare System. He is a co-investigator on the study aiding in the oversight of the study with Dr. Anthenelli including: 1) supervising the ACT therapy; manage overall study design and coordination; assist staff with clinical management of the trial; data analyses; preparation of abstracts, manuscripts, and other publications.

Vivian Hook, Ph.D. is a Professor of Pharmacology in the UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences. She is a co-investigator on the study responsible for the oversight of the mass spectrometry processing and analyses to determine the nicotine metabolite ratio.

Niloo Afari, Ph.D. is a Professor of Psychiatry in the Department of Psychiatry. She is a co-investigator responsible for the dissemination of and training therapists to deliver the ACT therapy. She will work with Dr. McKenna to supervise therapists delivering ACT.

Jamiee Heffner, Ph.D. is an Assistant Member at the Fred Hutchinson Cancer Research Center in Seattle, Washington. She is a long-time collaborator of Dr. Anthenelli, and on this project she will train study staff on the delivery of ACT therapy in SMI patients. Her research program is in this area with studies examining the effectiveness of ACT for smoking cessation in SMI. She will work with the study team to implement ACT in this clinical sample including logistics, therapy manuals, and answering questions as they arise during the course of the study. She will be involved with data analyses; preparation of abstracts, manuscripts, and other publications.

Jillian Giannini,, B.A. is a Lab Assistant I. She will assist the study team with day-to-day laboratory activities and recruitment and screening of study participants. She is trained to administer all of the rating scales to be used in the trial.

Xia Li, M.D., Ph.D. is an Assistant Clinical Professor in the Department of Psychiatry and Pac-TARC. She will assist Dr. Anthenelli in the medical and psychiatric assessment of study participants and aid the study team in delivering ACT to study participants; screening participants; and recruitment.

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23. FUNDING SUPPORT FOR THIS STUDY

University of California Tobacco-Related Disease Research Program High Impact Pilot Research Award-Submitted

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

BMTA not required

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

All study participants will receive Apo-Varenicline which is a generic form of the FDA-approved medication, varenicline, delivered in two different dose strengths. The U.S. Food and Drug Administration (FDA) has allowed this generic formulation to be temporarily imported into the U.S.. Apo-Varenicline, contains n-nitroso-varenicline amounts at a level deemed acceptable by the FDA. Apo-varenicline is approved for use as a generic medication for smoking cessation in Canada.

The "Important Prescribing Information" for Apo-Varenicline is attached.

Varenicline is approved for use in 100 countries and more than 24 million individuals have been exposed to the drug worldwide. Notably, following the EAGLES trial results, the FDA removed the box around the neuropsychiatric safety warning for this medication. However, that safety warning remains in the package insert and we have captured that in this application.

26. IMPACT ON STAFF

Not applicable

27. CONFLICT OF INTEREST

Dr. Anthenelli provides consulting and/or advisory board services to Pfizer via an institutional agreement between the sponsor and The Regents of the University of California San Diego. Payment for Dr. Anthenelli's consulting services is received by UC San Diego. The terms of this arrangement have been reviewed and approved by UC San Diego in accordance with its conflict of interest policies. Dr. Anthenelli has also applied for and been awarded an investigator-initiated award from the sponsor to supply study medication for this trial. That investigator-initiated supply of varenicline has been suspended, however, because of the voluntary recall of Pfizer-made varenicline tablets. The sponsor has no other involvement, Both of these relationships will be disclosed to study participants as part of the informed consent process.

Dr. Niloo Afari, a researcher on the study team, receives royalties from New Harbinger, Inc. publishers from the sale of a book she co-authored related to ACT. The book Dr. Afari co-authored is not being used in this study. The terms of this arrangement have been reviewed and approved by UC San Diego in accordance with its conflict of interest policies. The publishing company has no role in this trial.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Participant's decisional capacity will be assessed during consent by a trained research staff member to ensure they fully understand the study. This will be done by a trained staff member asking them questions about the details of the study after consenting to ensure that participants understand the study procedures and have the capacity to make a decision to enroll in the study. In our experience working with adult participants with severe mental illness the vast majority of participants have the capacity to make informed decisions. Are exclusion criteria involve acute mood episodes and thus we will exclude participants whose judgment may be altered due to their mental illness.