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Study Protocol and Analysis Plan

2.1 Participants. Participants seeking treatment for CUD were enrolled between October 2014 to September 2016 at Dartmouth College and the University of Washington. The study was conducted in compliance with Internal Review Boards at Dartmouth College and the University of Washington and registered on clinicaltrials.gov (NCT02277665). Participants at both sites were recruited from advertisements posted online (Craigslist, Facebook), in newspapers, on radio, posters throughout the community, and notices to professionals and service agencies. Participants were included if they met the following criteria: 1) $\geq$ 18 years of age, 2) current diagnosis of cannabis abuse or dependence made using the Structured Clinical Interview for DSM-IV (SCID: First et al., 1995), 3) cannabis use on $\geq$45 of the past 90 days, 4) regular use of tobacco (i.e. $\geq$5 days per week) or report primary administration of cannabis via blunts/spliffs, and 5) self-reported at least minimal interest in quitting tobacco in the next six months during the pre-intake screening (i.e. rating of $\geq$ 2 on a 5-point scale). Exclusion criteria included: 1) current dependence (DSM-IV criteria) in the last 6 months on alcohol or any drug other than tobacco and cannabis with the exception of opiate dependence maintained with agonist replacement therapy, 2) use of non-tobacco nicotine (i.e. nicotine replacement therapy, NRT), or exclusive use of smokeless tobacco products, 3) currently in treatment for substance dependence, 4) severe psychological distress (e.g. active suicidal ideation, debilitating panic disorder), 5) medical condition that required physician approval before using NRT (e.g. pregnancy or myocardial infarction), 6) legal status that would interfere with participation, 7) living with someone enrolled in the study, 8) not fluent in English, or 9) living $\geq$45 miles from the study site.

Of the 146 participants screened for the study, 53 did not meet inclusion / exclusion criteria, 15 were eligible but declined treatment, and 11 did not enroll for other reasons (e.g. lost contact after intake) (see Figure 1). Sixty-seven adults (45 male), age 18-60 years signed a study consent and were enrolled. Participant characteristics by treatment condition are presented in Table 1.

2.2 Interventions

2.2.1 CUD Intervention. The CUD treatment approach has been described previously (Budney et al., 2011, 2015; Lee et al., 2014, 2015). Briefly, this treatment comprised a 9-session computer-assisted delivery of a motivational enhancement therapy (MET), cognitive behavioral therapy (CBT) and abstinence-based contingency management (CM) provided over 12 weeks. Participants attended the clinic twice weekly, where they received nine MET/CBT computer modules (weeks 1-8 and week 12), three 15 to 30-minute supportive counseling sessions (weeks 1, 4 and 12), and provided urine specimens. Computer modules were also available remotely with individualized passwords throughout the study. The CM program targeted cannabis abstinence by providing an escalating schedule of monetary incentives contingent on cannabis-negative urine toxicology derived from twice-weekly observed urine specimens. Participants could earn up to $435 for continuous abstinence throughout the intervention. Incentives were delivered after each visit via electronic deposits to a debit card.

2.2.2. Tobacco Intervention (TI). The TI included NRT and seven computer-delivered psychoeducational and behavioral counseling modules developed specifically for this project.

The first module was a translated and adapted version of a Swiss/French language, evidence-based, on-line assessment and feedback program (Stop Tabac: Etter, 2005, 2009; http://www.stop-tobacco.ch/en/), which focused on the pros and cons of smoking tobacco, encouraged motivated participants to set a tobacco quit date, and included a personalized tobacco use feedback report. The second module provided information about co-use of cannabis and tobacco, including potential additive health risks, difficulties with quitting one substance while continuing to smoke the other, planning to quit both substances, and roadblocks to quitting both. The third module provided NRT education and instruction. The fourth module focused on planning for change and setting a quit date. The fifth module provided reduction strategies for those interested in reducing rather than quitting. The sixth module included information and strategies for relapse prevention. The seventh module provided education on electronic cigarettes. The TI modules could be accessed remotely at any time with individualized passwords.

At each visit, participants were encouraged by staff, but not required, to complete at least one module and consider initiation of NRT. Participants were required to complete the NRT education module prior to receiving NRT. NRT was provided on a bi-weekly schedule free of charge and could be initiated anytime during the TI. NRT options included a combination of patch and gum or lozenges, following standard guidelines for dosing (Stead et al., 2012).

2.3 Trial Design, Treatment Conditions, Hypotheses

This two group, 24-week study randomized participants seeking treatment for CUD to either a simultaneous (SIM) or a sequential (SEQ) treatment condition (Figure 1). Urn randomization procedures balanced the conditions on the following baseline characteristics: cannabis abstinence prior to treatment initiation, tobacco dependence severity (low vs. high, based on the Fagerstrom), blunt/spliff smoker or not, ethnicity (African American or not), and gender. Assessments occurred at week 12 (end of Phase 1) and week 24 (end of Phase 2).

2.3.1. SIM Condition. During weeks 1-12 (Phase 1), participants in the SIM condition received immediate access to the previously described CUD and tobacco interventions. The first five CUD MET/CBT modules were completed in a fixed order starting at the first visit. The TI modules and NRT were also available starting at the first visit, but for most participants, this did not occur until the second visit due to time constraints. TI modules could be completed in any order selected by participants, but as per above, NRT was not available until the NRT education module was completed. Both the CUD and TI modules viewed during clinic visits could then be accessed remotely with an ID and password. During weeks 13-24 (Phase 2) SIM participants could continue to access the cannabis and tobacco intervention modules ad libitum remotely but did not attend clinic visits or receive additional NRT. SIM participants that expressed an interest in continuing NRT after Phase 1 were provided with a one-week supply and instructed on how to purchase additional NRT on their own. For those not interested in continuing use, NRT dose was tapered during weeks 10-12 to reduce the probability of nicotine withdrawal symptoms from discontinuation.

2.3.2 SEQ Condition. During Phase 1, SEQ participants received only the CUD MET/CBT/CM intervention. They could not access the TI modules, NRT was not provided by the clinic, and no counseling for tobacco cessation was offered. During their first visit, they were given a booklet on tobacco cessation, *Clearing the Air*

(https://www.cancer.gov/publications/patient-education/clearing-the-air) that provided education and guidelines for quitting and a Quitline telephone number (SIM participants also received the booklet). This reflected "treatment as usual" for tobacco cessation in the context of outpatient treatment for CUD. SEQ participants interested in tobacco cessation during Phase 1 could make cessation attempts but had to obtain tobacco medications on their own. During Weeks 13-24, (Phase 2), SEQ participants were offered the TI as described above, and encouraged to attend weekly clinic visits to help facilitate engagement and adherence. Note that during Phase 2 clinic staff were highly flexible and encouraging of any attendance schedule with the primary goal of accommodating participants so that they could complete TI modules and obtain NRT.

2.3.3 Primary Hypotheses. Based on prior pilot study and the literature on targeting tobacco use in the context of treatment for other SUDs, we hypothesized that: (1) the TI would be acceptable to participants in the SIM condition (i.e., Phase 1 retention and CUD engagement would not differ between conditions, and that the majority of SIM participants would engage with the TI components; (2) during Phase 1, the SIM condition would engender greater use of NRT, more tobacco quit attempts, greater sustained tobacco abstinence than SEQ, and cannabis abstinence would not differ between conditions; (3) at the end of Phase 2, after participants in both conditions were exposed to the TI, a greater percentage of SIM than SEQ participants would have initiated NRT and made a tobacco quit attempt.

2.4 Measures

2.4.1 Substance Use. At intake, the Substance Use Disorders section of the SCID (First et al., 1995) was administered to determine SUD diagnoses. The timeline follow-back (TLFB) procedure (Sobell and Sobell, 1992) was used to obtain self-reported substance use information for the 90 days preceding intake, and then again at each clinic visit to assess substance use since the last clinic visit. TLFB assessments included cannabis, cigarettes, other tobacco and nicotine products (including smokeless tobacco and electronic cigarettes), alcohol, other drug use, and NRT use. Nicotine dependence was assessed at baseline using the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991).

Cannabis abstinence was verified via twice-weekly observed collection of urine specimens which were then tested immediately thereafter. Cannabis and adulterant testing were performed using dipstick tests with a minimum THC detection cutoff of 50 ng/ml (http://www.americanscreeningcorp.com). Failure to submit a specimen without an excused absence was treated as a cannabis-positive result.

Self-reported tobacco abstinence was verified using expired carbon monoxide (CO; coVita Micro + Smokerlyzer: http://covita.net/micro+.html). Participants with a CO level ≤ 5 were considered tobacco abstinent. In the event of self-reported tobacco abstinence, a breath CO >5, and self-reported cannabis use (which could increase CO level), tobacco abstinence was verified using urine cotinine (ONESCREEN Cotinine Test; http://www.americanscreeningcorp.com).

2.5 Outcomes. Primary engagement outcomes included Phase 1 treatment retention defined as clinic attendance, and treatment engagement defined by completion of cannabis and tobacco computer modules, and initiation and duration of NRT. The primary cannabis outcome was the duration of continuous abstinence achieved during Phase 1, assessed using the twice-weekly observed urine specimens. Primary tobacco outcomes included the percent of participants who

made at least one self-reported tobacco quit attempt during Phase 1, and percent of participants who achieved sustained tobacco abstinence over the final eight weeks of Phase 1. Secondary outcomes included: percent of participants who achieved any biologically-verified cannabis or tobacco abstinence ($\geq$1 negative urine THC/cotinine specimen or expired carbon monoxide <5 ppm), percent of participants who achieved cannabis abstinence throughout the final four weeks of treatment, reduction in percent days of cannabis and tobacco use during treatment relative to baseline, and point-prevalence cannabis and tobacco abstinence at the 12-week follow-up assessment.

2.6 Data Analysis. Sociodemographic and baseline drug use characteristics between treatment conditions were compared using t-tests for continuous measures and chi-square tests for nominal measures (Table 1). The primary cannabis and tobacco abstinence outcomes were analyzed using an intent-to-treat approach with missing biological verification data and dropouts treated as a positive indicator of cannabis or tobacco use. Longest duration of continuous abstinence from cannabis (primary), number of days abstinent from tobacco, and number of tobacco quit attempts (primary) were all zero-inflated and therefore could not be analyzed with models that assume continuous, normally distributed outcomes. We therefore analyzed each of these outcomes using a zero-inflated Poisson model which provides an odds ratio describing the relative likelihood of achieving a zero-response to the outcome in the two treatment arms and a ratio of means describing the relative mean of the outcome in the two treatment groups. Additionally, several binary outcomes were analyzed via chi-square tests: cannabis abstinence in the final 4 weeks, point prevalence abstinence at the end of treatment, achievement of at least 50% reduction in days of using cannabis from intake to the final 4 weeks, and achievement of continuous tobacco abstinence for $\geq$ 2 consecutive weeks. Phase 2 outcomes were analyzed using descriptive statistics. Statistical comparisons were not made between SEQ Phase 2 and SIM Phase 1 outcomes because of the lack of Phase 2 data due to only a 30% participation rate for SEQ during Phase 2. All analyses were performed using SAS version 9.4.