

**SMOKING CESSATION TREATMENT WITH TRANSDERMAL
NICOTINE REPLACEMENT THERAPY IN SUBSTANCE ABUSE
REHABILITATION PROGRAMS**

**NATIONAL DRUG ABUSE TREATMENT
CLINICAL TRIALS NETWORK**

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PI:	Malcolm S. Reid (New York)
Co-PI:	John Rotrosen (New York)
Clinical Project Director:	Paul Casadonte (New York)
Project Manager:	Frank Flammino (New York)
Scientific Collaborators:	Kathleen Brady (South Carolina)
	Mitch Greenlick (Oregon)
	Sharon Hall (Ohio Valley)
	Laura Juliano (Mid Atlantic)
	Steve Shoptaw (Pacific)
CTP Collaborators:	Al Cohen (Pacific)
	Barbara Campbell (Oregon)
	Randy Seewald (New York)
	Dorsey Ward (North Carolina)
Biostatistician:	Sherryl Baker (New York)

Data Specialist:	James Robinson (New York) Constance Klein (New York)
Regulatory Specialist:	Shirley Irons (New York)
QA Specialist:	Sherryl Baker (New York)
Training Specialist:	Kathlene Tracy (New York)
NIDA Liaison:	Cynthia Kleppinger (NIDA)

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List of Abbreviations

AA	Alcoholics Anonymous
AE	Adverse Events
ASI	Addiction Severity Index
ASI Lite	Addiction Severity Index (Lite version)
BDI-II	Beck Depression Inventory-II (Beck, 1996)
BSCS	Brief Substance Craving Scale
CAB	Common Assessment Battery
CO	Carbon Monoxide
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Programs
CURRY	CURRY Reason for Quitting Questionnaire
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Version 4
GI	Gastro Intestinal
HMO	Health Maintenance Organization
IRB	Institutional Review Board
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
NIDA	National Institute on Drug Abuse
OHRP	Office for Human Research Protections
PDR	Physicians' Desk Reference
PI	Principal Investigator
QA	Quality Assurance
RBS	Risk Behavior Scale
SAE's	Serious Adverse Events
SF-36	SF-36 Health Status Questionnaire
SOP	Standard Operating Procedure
SUR	Substance Use Report
TQD	Target Quit Day
UCSF	University of California – San Francisco
URICA	University of Rhode Island Readiness to Change Assessment
USDHHS	United States Department of Human Health Services
VAS	Visual Analog Scale

STUDY SYNOPSIS

The prevalence of cigarette smoking among substance abusers is high, and substance abusers that smoke have increased health problems, mortality rates, and drug and alcohol addiction severity. In the past decade, clinical studies have demonstrated that smoking cessation treatment, and smoke-free policies, can be implemented in drug and alcohol rehabilitation clinics with a reasonable level of success. Briefly, treatment retention is moderately enhanced, a moderate level of smoking abstinence is achieved, and drug and alcohol abuse rates are not adversely impacted. The current study will investigate the feasibility of smoking cessation treatment in community substance abuse rehabilitation programs, and its impact on cigarette smoking and substance abuse treatment outcomes.

This is a randomized, open-label, multi-site study comparing smoking cessation treatment as an adjunct to standard substance abuse treatment to standard substance abuse treatment alone. The study is a 9-week study with three follow-up visits at 9, 13 and 26 weeks after the target smoking quit date. Subjects will be screened 1 to 30 days prior to randomization; and, will have baseline assessments measured 1 to 21 days prior to randomization.

The study population will include drug or alcohol dependent patients treated in an outpatient setting at methadone/LAAM maintenance treatment programs or drug-free rehabilitation clinics. Subjects must smoke ≥ 11 cigarettes/day, have an interest in quitting smoking, and have been enrolled in their respective drug treatment program for at least 1 month to participate in the study. A total of 864 male and female patients will be enrolled from approximately 12 participating CTP clinics. Each clinic will attempt to enroll 72 subjects. Subjects will be recruited by word of mouth, use of CTP communications, announcements and referral networks, and with the aid of a clinic wide survey on interest in quitting smoking.

Eligible subjects will be randomized in a 2:1 ratio to either *Group 1*) standard substance abuse treatment plus smoking cessation counseling with nicotine patches or *Group 2*) standard substance abuse treatment. Subjects randomized to the smoking cessation group will receive 1 week of smoking cessation counseling prior to the start of medication; and, will receive 6 weeks of concurrent counseling and medication, followed by two additional weeks of medication alone. Subjects in both groups will receive standard substance abuse treatment for all 9 weeks of the study. Subjects randomized to standard substance abuse treatment may be offered deferred (6 month) smoking cessation treatment if they comply with study procedures.

The *primary outcome measure* is smoking abstinence rates. The *secondary outcome measures* include drug and alcohol abstinence rates, assessments of client retention, evaluations of subject interest, and feasibility of a smoking cessation program in this setting.

Efficacy assessments include weekly measures of urine drug screens, alcohol breathalyzer, carbon monoxide monitoring, self-reports of drug and nicotine use, tobacco withdrawal, craving for primary substance of abuse, depression, and compliance to smoking cessation counseling, drug rehabilitation treatment, and study medication. Safety assessments include weekly assessments of adverse experiences, vital signs, and concomitant medication usage. Additional assessments include the SF-36, Risk Behavior Scale and ASI.

1.0 Significance

The problem of cigarette smoking among drug and alcohol abusers has received increased attention in the past decade. Clinically important reasons for this include the high prevalence rate for smoking among substance abusers (60%-90%), markedly increased health risks and mortality rates, and evidence for greater drug or alcohol addiction severity/problems in substance abusers who smoke. Scientific reasons include numerous experimental findings that indicate a common pathway and/or mechanism mediating addictive processes with nicotine, alcohol, opiates, stimulants, and other drugs of abuse. Moreover, as social views towards smoking in the US have shifted towards viewing cigarette smoking as an addictive disease, substance abuse patients and their treatment providers have become far more receptive towards introducing smoking cessation programs in their clinics.

Substance abuse treatment in rehabilitation clinics throughout the U.S. encompasses multiple modes of treatment aimed at reducing and eliminating the use of illicit drugs and alcohol. The treatment programs usually focus on each client's primary drug or alcohol addiction problem, though the problems of polydrug abuse are invariably, and often necessarily, brought up to some degree. Despite this increasing awareness of polydrug addiction, and the need to treat addiction across multiple modalities, there are few current policies or programs for addressing the problems of the single most pervasive co-morbid addiction amongst all drug abusers and alcoholics, cigarette smoking.

To fully investigate the acceptance and effectiveness of smoking cessation in drug addiction rehabilitation programs, it will be necessary to examine this treatment across numerous clinical settings and with a large, diverse, substance abusing population. As such, this kind of investigation will greatly benefit from the research framework that is provided by the NIDA Clinical Trials Network (CTN). The objective of this proposal is to implement and evaluate in community treatment programs (CTP), smoking cessation treatment as an adjunct to outpatient, drug abuse rehabilitation.

2.0 Introduction

2.1 Background: Population surveys at treatment clinics through out the U.S. have demonstrated that a high proportion (60-90%) of substance abuse patients are cigarette smokers (Schnoll et al., 1985; Budney et al., 1993; Stark and Campbell, 1993). Such concurrent nicotine use may produce adverse behavioral and/or medical problems (Kreek, 1987; Hughes, 1993), and is associated with a longer history, and heavier abuse patterns, for cocaine (Budney et al., 1993), alcohol (Toneatto et al., 1995) and marijuana (Stark and Campbell, 1993). Nicotine itself has been shown to enhance cocaine craving in a laboratory setting (Reid et al., 1998) and, based on anecdotal reports, may potentiate the high derived from stimulants (Sees and Clark, 1993). Moreover, the frequency and amount of overall drug abuse have been correlated with the amount of cigarette smoking, and vice versa (Stark and Campbell, 1993; Burling and Ziff, 1988; Batel et al., 1995). However, though the problems of nicotine use and drug addiction have become better appreciated in the treatment community, there has been little progress in the way of establishing smoking cessation programs within substance abuse treatment programs. In addition, research on the impact of smoking cessation programs on drug and alcohol treatment outcome has been piecemeal at best.

Despite these shortcomings in treatment and research on smoking cessation in substance abuse treatment clinics there is evidence to suggest that such programs are feasible, and would be welcomed by treatment providers and their clients. Among treatment providers, a recent survey of 254 counselors in Kentucky revealed a majority was receptive to providing smoking cessation treatment (Hahn et al., 1999). Surveys of patients entering drug and alcohol treatment programs found that, among those who were cigarette smokers, 40-60% were interested in receiving smoking cessation treatment (Sees and Clark, 1993; Irving et al., 1994), only 10% believed that quitting smoking would adversely affect their drug and/or alcohol abuse treatment (Orleans and Hutchinson, 1993), and 25% enrolled in smoking cessation programs that were available (Saxon et al., 1997; Campbell et al., 1995). In a survey of methadone maintained outpatients, 58% of subjects (n=120) rated themselves as “somewhat” or “very interested” in a smoking cessation program (Frosch et al., 1998). Evidence suggests that smoking abstinence rates are somewhat lower in drug and alcohol dependent subjects enrolled in smoking cessation programs, nevertheless, a measurable level of success has been demonstrated. Thus, nicotine patch treatment results in smoking abstinence rates of approximately 25-35% in the general population (Hurt et al., 1997; Jorenby et al., Hughes et al., 1999; Levin et al., 1994), and 15-25% in drug and alcohol dependent subjects (Hurt et al., 1994; Campbell et al., 1995; Shoptaw et al., 2001) at the end of the medication treatment phase. Moreover, the addition of cognitive behavioral, relapse prevention, and mood management counseling has been shown to enhance the abstinence rates in smokers with a history of alcohol dependence (Patten et al., 1998), or concurrent drug dependence (Shoptaw et al., 2001). In a smoking cessation study that compared smoking abstinence (7-day point of prevalence) in current alcoholics and non-alcoholics, rates were 42% and 58%, respectively, at the end of an 8-week nicotine patch plus counseling treatment protocol (Hays et al., 1999).

Numerous studies have evaluated the impact of smoking cessation programs on concurrent substance abuse treatment. The introduction of smoking cessation programs in established substance abuse treatment programs did not impact overall patient enrollment and retention (Sterling et al., 1994) and in patients that significantly reduced their smoking habits an impressive (96%) decline in drug/alcohol abuse has been reported (Pletcher, 1993). In studies on drug and alcohol treatment outcomes, the addition of smoking cessation to standard drug/alcohol abuse treatment resulted in similar drug and alcohol abstinence rates at 3-month, 6-month, and 1 yr follow-up relative to control groups (Burling et al., 1991; Hurt et al., 1994; Joseph et al., 1993; Bobo et al., 1998). In one study there was actually a greater reduction in moderate to heavy drinking (Bobo et al., 1998) and in another there was higher treatment retention for the first 30 days (Burling et al., 1991). In a study on smoking cessation in methadone maintained patients, subjects in the relapse prevention group had higher rates of opiate abstinence (40%) versus the no counseling group (26%), and cocaine abstinence rates were approximately 45% across all counseling groups (Shoptaw et al., 2001). Moreover, subjects that were no longer smoking had significantly higher rates of opiate and cocaine negative urine samples (Shoptaw et al., 2001). In a study on drug and alcohol dependent patients at a therapeutic community setting, drug and alcohol abstinence rates (30-day point of prevalence) at the end of active treatment were 77% and 61% in the smoking cessation and no smoking cessation intervention groups, respectively (Burling et al., 2001).

These studies demonstrate that a moderate level of smoking abstinence can be achieved with drug dependent patients. Furthermore, the addition of smoking cessation treatment to an alcohol or drug addiction rehabilitation program does not jeopardize the recovery process.

On the contrary, there are indications that subjects receiving smoking cessation treatment will do better in their drug rehabilitation programs. Indeed, smoking cessation treatment may present an opportunity to treat addictive processes in a more global manner.

The impact of smoking cessation programs on substance abuse rehabilitation programs has been examined extensively in inpatient and residential settings (Joseph et al., 1993, Burling et al., 1991; 2001; Pletcher, 1993; Hurt et al., 1994; Saxon et al., 1997) or in studies on methadone maintained patients (Shoptaw et al., 2001; see Campbell et al., 1995). However, few studies have examined smoking cessation in a drug-free outpatient setting, free of the constraints (on participants) of methadone maintenance (Bobo et al., 1998; Hays et al., 1999). This study will examine the effects of smoking cessation treatment, transdermal nicotine patch therapy (NicoDerm CQ®) (Hurt et al., 1997; Hughes et al., 1999) combined with a mood management and cognitive behavioral smoking cessation counseling (Munoz et al., 1988; Hall et al., 1994; Patten et al., 1998), in drug or alcohol dependent smokers. Participants from both drug-free and methadone maintenance outpatient rehabilitation clinics will be included, and the feasibility of this treatment in such outpatient settings will be examined.

2.2 Hypotheses: It is hypothesized that smoking cessation treatment will be associated with a significant drop in smoking.

3.0 Objectives

This protocol will investigate a science based smoking cessation program that utilizes both medication (transdermal nicotine replacement therapy), and behavioral therapy (mood management and cognitive behavioral therapy for smoking cessation), as an adjunct to outpatient drug and alcohol abuse rehabilitation. The main goal of the study is to determine if this integrated medication/behavioral smoking cessation therapy, versus no smoking cessation therapy, is effective at reducing cigarette smoking when conducted in community based outpatient drug and alcohol abuse treatment programs. The *primary outcome measure* is smoking abstinence rates. The *secondary outcome measures* include drug and alcohol abstinence rates, assessments of client retention, evaluations of subject interest, and feasibility of a smoking cessation program in this setting. Gender differences for the primary and secondary outcome measures will also be examined.

4.0 Study Sites

The study will be conducted at methadone/LAAM maintenance treatment programs and outpatient drug and alcohol rehabilitation clinics. For the specific purposes of evaluating the smoking cessation treatment intervention, each participating treatment clinic (CTP) is required to **not** have an existing smoking cessation treatment service.

5.0 Study Design

This is a randomized, open-label, multi-site study comparing standard substance abuse treatment to smoking cessation counseling with nicotine patches as an adjunct to standard substance abuse treatment. The study is a 9-week study with three follow-up visits at 9, 13 and 26 weeks after the initial target smoking quit date. Subjects will be screened for eligibility and will have baseline assessments measured 1 to 21 days prior to randomization.

Eligible subjects will be randomized in a 2:1 ratio to either *Group 1*) standard substance abuse treatment plus smoking cessation counseling with nicotine patches or *Group 2*) standard substance abuse treatment. Subjects randomized to the smoking cessation group will receive 1 week of smoking cessation counseling prior to the start of medication; and, will receive 6 weeks of concurrent counseling and medication, followed by two additional weeks of medication alone. Subjects in both groups will receive standard substance abuse treatment for all 9 weeks of the study. Subjects randomized to standard substance abuse treatment may be offered deferred (6 month) smoking cessation treatment if they comply with study procedures.

Smoking cessation medication will be provided for 8 weeks, beginning after subjects have quit smoking. Subjects will receive 21 mg/day transdermal nicotine patches for weeks 1-6, and 14 mg/day transdermal nicotine patches on weeks 7-8. This medication will be provided to study compliant participants: *Group 1* during the study, and *Group 2* after they have completed the study.

Counselors and counselor supervisors will meet specified qualifications and receive standardized training in the smoking cessation counseling program. All study counselors will conduct practice counseling sessions, rated by counselor supervisors using a standardized counselor fidelity monitoring checklist, and must demonstrate a standard rate of adherence to the checklist items in order to be certified and begin treating study patients. In the conduct of the study, the counselor supervisor will review and rate the counseling sessions on a monthly basis, using the standardized counselor fidelity monitoring checklist, and counselors will be given refresher training when adherence levels are not met. Counselor supervisors will complete inter rater reliability testing on a regular basis. All practice sessions, fidelity monitoring ratings, and inter rater reliability ratings will be maintained on a centralized database.

In this design the natural differences that might occur in the implementation of the behavioral therapy from site to site are limited by standardized training, the fidelity monitoring plan, and counselor supervisor inter rater reliability testing. Nevertheless, by testing this program across a variety of community treatment settings the potential for site by site differences in the behavioral therapy is recognized.

6.0 Subject Recruitment

Male and female subjects diagnosed with primary drug or alcohol dependence will be enrolled in the study. Subjects will be recruited from outpatient methadone/LAAM maintenance treatment programs and outpatient drug and alcohol rehabilitation clinics. Approximately 12 CTP clinics will participate in the study; and, each participating CTP clinic will enroll approximately 72 subjects for a total of 864 randomized subjects. **All subjects in each set of 72 randomized subjects will receive the same form of substance**

abuse treatment (outpatient methadone/LAAM maintenance treatment or outpatient drug and alcohol rehabilitation) and will be recruited from the same CTP. There is, however, no limitation on the number of clinics in a CTP that may participate in the study (i.e., one drug-free program and one methadone maintenance program, both at the same treatment facility, could run two parallel studies).

Subjects may be recruited by word of mouth, referrals from local narcotic treatment and outreach programs, outpatient drug and alcohol abuse clinics, local mental health centers and crisis clinics, public service announcements, newspaper advertisement, study brochures, and/or fliers posted at participating CTP sites.

NIDA-CTN-0009 study brochures will be available as recruitment tools to all participating sites, though their use of them is not mandatory.

Each site's Institutional Review Board (IRB) will approve all recruitment advertisements, brochures and fliers used to recruit study volunteers.

7.0 Subjects

In order to be eligible for the study, study subjects must meet all of the inclusion criteria and none of the exclusion criteria listed below.

7.1 Inclusion criteria:

1. Males or females, at least 18 yr old.
2. Meet both of the following enrollment criteria:
 - a. Enrollment and participation in a methadone or LAAM maintenance treatment program, or drug-free rehabilitation program, for the preceding 30 days or more prior to randomization.
AND
 - b. Scheduled to remain in treatment at the methadone or LAAM maintenance treatment program, or drug-free rehabilitation program, for 30 days or more after randomization.
3. Meet one of the following substance dependence criteria:
 - a. Drug or alcohol dependence (other than nicotine) according to DSM-IV checklist criteria within the last 12 months.
OR
 - b. Methadone or LAAM maintenance treatment, in treatment for the preceding 12 or more months, and on a stable maintenance dose.
4. Have smoked cigarettes for at least 3 months, and currently smoking ≥ 10 cigarettes/day, and has a measured exhaled CO level > 10 ppm.
5. Interest in quitting smoking and willingness to comply with all study procedures and medication instructions.

6. Females of childbearing potential have negative (urine) pregnancy test at screening and agree to use at least one of the following birth control methods.
 - a. oral contraceptives
 - b. barrier (diaphragm or cervical cap) with spermicide or condom
 - c. intrauterine progesterone contraceptive system
 - d. levonorgestrel implant
 - e. medroxyprogesterone acetate contraceptive injection
 - f. complete abstinence from sexual intercourse

7.2 Exclusion criteria:

1. Acute, severe psychiatric condition in need of immediate treatment, or imminent suicide risk.
2. Use of tobacco products other than cigarettes.
3. Use of other smoking cessation counseling programs or medication treatments (e.g., Zyban, Wellbutrin SR, or nicotine replacement therapy) currently, or within the last 30 days
4. Use of any investigational drug in the last 30 days.
5. For females of childbearing potential: being pregnant, lactating, or not using the acceptable modes of contraception during the study (see above methods of birth control).
6. Evidence of a medical condition that in the opinion of the site study clinician would put the subject at risk through study participation, including:
 - a. Clinically significant, uncontrolled, hypertension .
 - b. History of clinically significant heart disease including arrhythmia, congestive heart failure, or unstable angina.
 - c. History of allergic or skin reactions to the use of transdermal products, adhesive tape and bandages, or skin disease.
 - d. Other clinically significant medical conditions that preclude study participation

NOTE: Evidence for hypertension: If subjects provide a blood pressure that is higher than 140 mm Hg (systolic) over 90 mm Hg (diastolic) then they will be evaluated by the study physician to determine if they have clinically significant hypertension that is not controlled.

8.0 Study Procedures

The timing of study procedures and clinical assessments is summarized in Table 1.

8.1 Initial Subject Screening

Interested potential participants will contact designated staff members at each CTP. These potential subjects will be asked about their status as: 1) currently enrolled, or interested in enrolling, in drug or alcohol rehabilitation, 2) a cigarette smoker, and 3) having an

interest in quitting smoking. These pre-screening questions will permit a preliminary evaluation of study eligibility. Potential subjects that meet these preliminary criteria will be provided with information about the study and a time will be scheduled for the purpose of obtaining informed consent. This may occur immediately following the initial subject pre-screening or by appointment within a reasonable number of days (preferably within 7 days). Any subjects deemed ineligible for the research study during the initial subject pre-screening will be provided referral for smoking cessation treatment (other community programs, self-help books, etc.).

8.2 Informed Consent

Prior to the initiation of any research procedures or collection of any assessments, the research assistant (or person assuming this role) at each CTP will obtain informed consent for study participation from the potential subject. A sample Informed Consent Form will be provided from the Lead Investigators Node to each participating site. Potential volunteers will be encouraged to ask questions and to take the Informed Consent Form home to review with family or significant others if they wish. Subjects should begin treatment within 30 days of signing consent; otherwise they will need to be re-consented.

Each volunteer who signs an informed consent form will be assigned a Screening Number. The Screening Number will be a 4-digit number assigned sequentially by each CTP starting with the number 0001. Screening numbers may not be used for more than one subject (cannot be “recycled”) and subjects who are re-consented will retain their original screening number.

8.3 Screening Phase

After the subject has completed the informed consent process s/he will meet with the research assistant to begin completing screening assessments.

The research assistant will administer the demographics form, smoking status/ exhaled carbon monoxide (CO) assessment, a urine pregnancy test (for all female participants), the Smoking History survey, obtain medical and psychiatric history and *prior/concomitant* medications information, and collect vital signs and weight. The participant will complete the Curry Reasons for Quitting Questionnaire (CURRY). The research assistant or study clinician (nurse or physician assistant) will complete the DSM-IV Criteria Checklist and Addendum. The study clinician will review the vital signs and weight measurements, urine pregnancy results, and the medical and psychiatric history and *prior/concomitant* medications information. Assessments that must be reviewed by the study clinician may also be completed by the study clinician, if that is preferable at the CTP. Stable methadone or LAAM maintenance dosing, assessed with the help of the *prior/concomitant* medications form, will be determined based on the study physician’s clinical opinion (in consultation with the study clinician).

Once the above has been completed, the study clinician will review the inclusion and exclusion criteria and determine if the subject is eligible for the study.

8.4 Baseline Phase

Prior to randomization the research assistant will administer the following assessments: ASI Lite, Risk Behavior Scale (RBS), Substance Use Report (SUR), urine drug screen, an alcohol breathalyzer test, and prior/*concomitant* medication. The subject will complete the following measures: SF-36 Health Status Questionnaire, Fagerström Nicotine Tolerance Questionnaire, Smokers Beliefs Questionnaire, Beck Depression Inventory (BDI-II), and the University of Rhode Island Readiness to Change Assessment (URICA). Vitals signs and weight will be recorded. The study clinician will review prior/*concomitant* medication information. In addition, a urine sample for cotinine levels must be collected by the research assistant. Assessments that must be reviewed by the study clinician may also be completed by the study clinician, if that is preferable at the CTP.

If the time period between the collection of a screening or baseline assessment and the date of randomization exceeds 21 days, then that assessment must be repeated. The assessments that must be performed with 21 days of randomization are: the urine drug screen, exhaled CO monitor/smoking status test, alcohol breathalyzer, SUR, BDI-II, SF-36, URICA, CURRY, ASI-Lite, prior/*concomitant* medications, and vitals signs and weight measurements.

8.5 Randomization

Randomization: To achieve optimal effectiveness of smoking cessation treatment, counseling groups should start with 6 or more subjects enrolled. In order to reach these numbers, eligible subjects will be randomly assigned in a 2:1 ratio to one of two treatment groups within each site (CTP). The two treatment groups are: *Group 1*) standard substance abuse treatment, plus smoking cessation counseling with nicotine patch medication, *Group 2*) standard substance abuse treatment. No randomized participants will be replaced.

Groups of subjects should be randomized once every 4 weeks* to ensure there is an adequate number of participants in the counseling group.

Group Size: The preferred counseling group size is 6-12 subjects, however smaller group sizes are acceptable before a major holiday or when further recruitment of subjects is unlikely.* If a greater number of subjects are randomized to smoking cessation treatment, then a second group could be run in parallel (e.g., split 16-30 subjects into two groups of 8-15).

* If the number of subjects eligible for randomization is less than 7, then the randomization must be delayed in 1-week intervals until at least 7 eligible subjects are obtained (note: some subjects may need to have consent forms, screening measures, and baseline evaluations re-done according to protocol requirements).

Randomization Schedule: Once the required number of eligible subjects (≥ 7) is obtained, randomization will be scheduled during Wednesday through Friday of the week before start of treatment. Subjects will be instructed to attend a randomization visit during this 3-day window, and randomization may occur in a group or individual setting. If one or more subjects do not attend the day of their scheduled visit they will have until the end of Friday (according to CTP research staff hours) to undergo randomization. Treatment must start on the following week whether or not the minimum of 7 subjects have completed randomization by the end of Friday.

Procedures to promote the completion of randomization for 7 or more subjects will include a \$10 randomization visit compensation and may also include overbooking (≥ 9) of eligible subjects on the randomization day. Subjects that have not completed randomization by the end of Friday are eligible to continue screening until the next cohort of eligible subjects is ready to be randomized (note: these subjects may need to have consent forms, screening measures, and baseline evaluations re-done according to protocol requirements).

The inclusion/exclusion criteria checklist must be re-reviewed by the study clinician or study physician to determine if the subject continues to be eligible for study participation. The final determination of continued study eligibility will be recorded on the randomization CRF, which will be reviewed and signed by the study clinician or study physician. On the day of randomization, the urine pregnancy test will be repeated for female participants.

Randomization List: The statistician at the New York Node will generate one blocked randomization list (block size will be known only to this statistician) for the entire study, starting with randomization number 1001. The randomization list will be generated so that at the end of the specified block, treatment assignment will be balanced. 72 sequential randomization numbers will be assigned to each CTP *a priori*, and set of 72 envelopes (each containing one randomization number) will be sent to each CTP. When a participant satisfies all protocol eligibility criteria, the next available randomization number for their gender will be assigned. All participants who are randomized will receive a randomization number.

Gender: Randomization will be stratified by gender at each CTP. Subjects will be assigned randomization numbers in ascending order, starting with the smallest number (within the block of numbers assigned to the investigator) for males, and assigning numbers in descending order, starting with the largest number (within the block of numbers assigned to the investigator) for females. This method of stratification should permit the study to achieve balance between the two treatment groups with respect to gender, CTP and overall while allowing for each CTP to enroll a different number of men and women.

8.6 Treatment phase

For every set of randomized subjects (Groups 1 and 2) study treatment and assessments will begin on the same calendar day and continue for the next 63 days (see Table 1). Thus, the initiation of study assessments will be synchronized with the initiation of smoking cessation treatment in Group 1, once every 4 weeks*. The start of smoking cessation treatment (Week -1) will be a Monday (Day -7). If Monday is a holiday or if treatment program scheduling constraints exist, initiating smoking cessation treatment on a Tuesday (Day -6) or

Wednesday (Day -5) is acceptable . During study treatment; Week -1 through Week 8,all subjects will come to the clinic for assessments and are expected to attend their standard substance abuse treatment.

Study assessments may be completed in 1 or more visits per study week, if needed. If time is limited during the first visit the research staff is urged to complete, at a minimum, the safety assessments (vital signs and weight, prior/*concomitant* medication information, smoking medication compliance and adverse events) and the following outcome assessments: smoking status/exhaled CO, urine drug screen, and alcohol breathalyzer. On Weeks 4 and 8 the urine pregnancy (females) are also included in the safety assessments. Other weekly assessments may then be completed on a subsequent visit if necessary.

Group 1 will be required to complete, at a minimum, the above listed safety assessments in order to receive their weekly study medication supply. Research assistants are urged to schedule study assessments on the same days as counseling, though this is not mandatory. Note:

- 1) Week -1 assessments must be scheduled to occur at some time point after Session 1 has been completed.
- 2) Week 1 assessments must be scheduled 1-4 days after Session 3

Week -1

During this week the research assistant will administer the following to all subjects: smoking cessation compliance, smoking status/exhaled CO, drug rehabilitation compliance, SUR, urine drug screen, alcohol breathalyzer, vital signs and weight, and prior/*concomitant* medication information. The subject will complete the Withdrawal Scale for Tobacco and the Brief Substance Craving Scale (BSCS). The study clinician will review vital signs and weight measurements, prior/*concomitant* medication information, and will complete an adverse events assessment from all subjects. Compliance with methadone or LAAM dosing will be monitored as a concomitant medication. Assessments that must be reviewed by the study clinician may also be completed by the study clinician, if that is preferable at the CTP.

Weeks 1 – 7

During weeks 1 through 7 the research assistant will administer the following to all subjects: smoking cessation compliance, smoking status/exhaled CO, drug rehabilitation compliance, SUR, urine drug screen, alcohol breathalyzer, vital signs and weight, and prior/*concomitant* medication information. The research assistant will also complete the smoking medication compliance form for those subjects randomized to the smoking cessation treatment (Group 1). The subjects will complete the Withdrawal Scale for Tobacco and the BSCS. The study clinician will review vital signs and weight measurements, prior/*concomitant* medication information, and will complete an adverse events assessment from all subjects. Compliance with methadone or LAAM dosing will be monitored as a concomitant medication. During Week 4, the research assistant will also administer a urine pregnancy test to females and all subjects will complete the BDI-II. Assessments that must be reviewed by the study clinician may also be completed by the study clinician, if that is preferable at the CTP.

Target Quit Day (TQD): The Target Quit Day (TQD) will be the Monday (Tuesday or Wednesday are acceptable if following a Monday holiday or scheduling constraints exist) during Week 1 of the protocol. The TQD is defined as “Day 1” in the protocol schedule (or “Day 2” or “Day 3” if it falls on a Tuesday or Wednesday, respectively). TQD applies only to subjects that receive the study intervention, Group 1.

Group 1: Subjects in the smoking cessation treatment group will stop smoking on the TQD, following completion of Session 3 of the smoking cessation counseling program scheduled for that day. During Session 3 of the smoking cessation counseling program, subjects will receive a 7-day supply of patches and receive instructions on how to use the medication from their counselor. At the end of this counseling session subjects undergo a quitting ritual and be instructed to place one patch on their upper arm or other skin area with little or no hair. Subjects in Group 1 will be scheduled to attend a second smoking cessation counseling session (Session 4) during Week 1 that will be scheduled to occur 24-96 hours after the TQD. For Weeks 2 through 7, subjects randomized to smoking cessation treatment will continue to receive NicoDerm CQ patches, these will be supplied by the research assistant (who will track all medications dispensed/returned throughout the study).

Week 8 / Termination Visit

Subjects randomized to the smoking cessation treatment (Group 1) will receive their final 7-day supply NicoDerm CQ patches with instructions to use them up until the completion of week 8 (Day 56) and then to return any unused patches at their next visit. The research assistant will administer the following to all subjects: RBS, ASI-Lite, smoking cessation compliance, smoking status/exhaled CO, drug rehabilitation compliance, SUR, urine drug screen, alcohol breathalyzer, vital signs and weight, and the prior/*concomitant* medication information. The research assistant will also complete the smoking medication compliance form for those subjects randomized to the smoking cessation treatment (Group 1) and a urine pregnancy test for female participants. The subjects will complete the Withdrawal Scale for Tobacco, SF-36 Health Status Questionnaire, BDI-II and the BSCS. The study clinician will review vital signs and weight measurements, prior/*concomitant* medication information, and will complete an adverse events assessment from all subjects. Assessments that must be reviewed by the study clinician may also be completed by the study clinician, if that is preferable at the CTP.

During each subjects last scheduled visit, the first follow-up visit (Week 9) will be scheduled, regardless of whether the subject completes the Week 8 assessments.

Early Termination: If subjects are discontinued from the study early, they will be encouraged to come to the clinic for one final visit to complete the above described assessments, however, medication patches will not be dispensed (Group 1) and follow-up visits will not be scheduled. Upon early discontinuation from the study, a Study Termination form will be completed. Treatment options may be reviewed with all subjects in accordance with those available at the CTP or other local providers (e.g. referral for outside smoking cessation counseling, and/or self-help books).

8.7 Follow-Up Phase

There are three visits scheduled during the follow-up phase at weeks 9, 13 and 26 post-TQD. The week 9 visit should be scheduled on the Monday or Tuesday following the last dose of medication, although a weekday later in week 9 is acceptable. For the remaining follow-up visits, effort should be made to schedule them as close to weeks 13 and 26 as possible, although they can be scheduled as early as 3 weeks before or up to 4 weeks after the designated week.

Week 9 Assessments: The research assistant will administer the Smoking Status/exhaled CO, drug rehabilitation compliance, smoking cessation compliance, SUR, urine drug screen, alcohol breathalyzer, vital signs and weight, prior/*concomitant* medications, and the smoking medication compliance form for those subjects randomized to the smoking cessation treatment (Group 1). The subjects will complete the Withdrawal Scale for Tobacco and the BSCS. The study clinician will review vital signs and weight, prior/*concomitant* medications information, and complete the adverse events assessment. Assessments that must be reviewed by the study clinician may also be completed by the study clinician, if that is preferable at the CTP.

At this time the study intervention has been completed and treatment options may be reviewed with all subjects in accordance with those available at the CTP or other local providers (e.g. referral for outside smoking cessation counseling, and/or self-help books). Subjects in Group 2 will also be reminded of their eligibility to receive deferred smoking cessation treatment following the completion of the week 26 follow-up assessment.

Weeks 13 and 26 Assessments: The research assistant will administer the following: RBS, ASI-Lite, Smoking Status/exhaled CO, urine cotinine, drug rehabilitation compliance, smoking cessation compliance, SUR, urine drug screen, alcohol breathalyzer, vital signs and weight, and the prior/*concomitant* medications form. In addition, at Week 26, the Study Termination form will be completed by the research assistant. The subject will complete the SF-36 Health Status Questionnaire and the BDI-II. The study clinician will review vital signs and weight, prior/*concomitant* medications information, and complete the adverse events assessment. Assessments that must be reviewed by the study clinician may also be completed by the study clinician, if that is preferable at the CTP.

8.8 Subject Compensation

Subjects will be compensated \$20 in scrip or cash upon completing screening and baseline measures whether or not they are deemed eligible for the study. Subjects that are eligible for the study will be compensated an additional \$10 in scrip or cash upon being randomized. For each treatment week (Week -1 to Week 8), subjects will be compensated \$10 in scrip or cash after they have completed ALL required study assessments for that week (assessments may be collected over 1 or more study visits). For each follow-up visit, subjects will be compensated \$20 in scrip or cash after they have completed ALL required assessments. In addition, subjects will receive a bonus payment of \$20 in scrip or cash upon completing smoking cessation treatment through week 8 of the study (subjects in the control group will receive this payment for completing study participation through week 8). Subjects discontinued due to missed visits or

protocol non-compliance will not be eligible for the \$20 bonus compensation. Each CTP can determine whether to use scrip (e.g., gift certificate for groceries, to KMART, etc.) or cash.

8.9 Study Compliance

Subjects will be instructed to attend all regularly scheduled substance abuse treatment programs (e.g., group counseling, vocational training, etc.), all smoking cessation counseling sessions, and all study related visits during their participation in the study.

All subjects will be informed that the \$10 randomization compensation will be contingent upon completing randomization procedures during the designated Wednesday-Friday period. All subjects will be informed that the \$10 compensation following the completion of each treatment week will be contingent on the completion of ALL study assessments scheduled for that week (which could involve 1 or more study visits). All subjects will be informed that they will receive an additional \$20 bonus for completing the study through week 8 as long as they have not been discontinued from smoking cessation treatment or deferred treatment eligibility (see section 8.10 for discontinuation criteria) prior to this time point. Subjects will also be informed that they will receive \$20 compensation following the completion of each follow-up visit.

Subjects in Group 1 will also be informed that they are required to complete the weekly safety assessments in order to receive their weekly study medication supply. While receiving patches will not be contingent upon attending smoking cessation counseling sessions, efforts will be made to encourage the subjects to adhere to both modes of treatment.

If subjects continue to smoke after they have begun medication treatment they will be encouraged to set another quit date on their own or with their smoking cessation counselor (whichever comes first) and to try to become smoke-free once again. They will be reminded of medication instructions “not to smoke while using the patch” and will be evaluated at each study visit for signs of nicotine overdose. Simple evidence of continued smoking, without concomitant adverse side effects, will not constitute grounds for discontinuation of medication (patch) treatment. Smoking while on the patch is common, often seen in up to 50% of patients on the patch in clinic trials (Jorenby et al., 1999; Levin et al., 1994; Rose et al., 1994; Fiore et al., 1994; Jimiez-Ruiz et al., 1998; Joseph et al., 1996) and is not associated with an increased rate of adverse events. Previous data from clinical safety studies have demonstrated no additional harm to subjects receiving nicotine patches if they decide to smoke (Joseph et al., 1996; Benowitz and Gourlay; 1997; Jiminez-Ruiz et al., 1998). It has been suggested that this represents the dynamics of nicotine tolerance, self-titration of nicotine dose, and reduced smoking rates in smokers receiving the patch (Rose et al., 1994, 2001).

An inability to meet the above described attendance and study requirements will not constitute grounds for discontinuation from the study, which is described in the next section.

8.10 Treatment and Study Discontinuation

Subjects may be discontinued from study treatment (nicotine patches, smoking cessation counseling) or from study participation (study treatment and assessments) based on guidelines described below.

In the event that a subject is discontinued from study treatment or study participation he/she will continue to be eligible for standard substance abuse treatment at the CTP clinic, in accordance with CTP rules.

8.10.1 Treatment Discontinuation

A. Safety Related Treatment Discontinuation

Subjects may be discontinued from study treatment based on clinical safety issues, including medication related adverse events, serious adverse events, concomitant illness, and pregnancy. Management of these safety issues is the responsibility of the clinician, in consultation with the study physician, at each site. Guidelines for managing safety related treatment discontinuation apply equally to subjects receiving medication during the study (Group 1) or during deferred treatment (Group 2)

Side effects from the nicotine patches may include:

- a) reddening of the skin, swelling or a rash caused by the patch that lasts more than 3-4 days.
- b) irregular heart beat or palpitations
- c) increased blood pressure
- d) insomnia or difficulty sleeping which does not go away by removing patches at night
- e) symptoms of nicotine overdose such as nausea, vomiting, dizziness, rapid heart beat and significant weakness.

1. Management of nicotine patch related adverse events

A. Concomitant Smoking: If a subject experiences clinically significant side effects from the study medication and continues to smoke he/she will be instructed to stop smoking in order to alleviate these symptoms, and be re-evaluated on the following day for signs of reduced side effects. If the subject continues to smoke, and the symptoms continue at a clinically significant level, study medication will be discontinued. Subjects discontinued in this manner may continue attending smoking cessation counseling sessions.

B. No Concomitant Smoking: If a subject experiences clinically significant side effects from the study medication that are not attributed to concomitant smoking, they will be allowed to continue study treatment with a lower dose of study medication. During Weeks 1-6, the patch dose would be lowered from 21 mg/day to 14 mg/day and nicotine side effects would be queried on the following day. If the symptoms do not go away after lowering the nicotine patch dose from 21 mg/day to 14 mg/day, then the subject would be allowed to discontinue patch treatment. In all cases where patch dose is lowered, or discontinued, the subject may continue attending smoking cessation counseling sessions. For those subjects who tolerate the lower 14mg/day dose during weeks 1-6, patch treatment would be discontinued during Weeks 7 and 8 (the next step down).

2. *Pregnancy*

Women who become pregnant at any time following randomization will be discontinued from study medication. Subjects in Group 1 will continue attending smoking cessation counseling, and subjects in Group 2 will maintain their eligibility for deferred smoking cessation counseling. Nicotine patches will not be provided to any subject if they are pregnant or nursing.

3. *Serious Adverse Event or Serious Concurrent Illness*

If a subject has a serious or unexpected adverse event, or develops a serious concurrent illness, that places him/her at risk if study medication treatment is continued the subject will be discontinued from study medication treatment and this event will be monitored until it is resolved or stabilized. Subjects in Group 1 will continue attending smoking cessation counseling, and subjects in Group 2 will maintain their eligibility for deferred smoking cessation counseling. Subjects in Group 2 may regain eligibility for the nicotine patch if the serious adverse event has resolved and all medication related risks have subsided before it is time to initiate deferred treatment.

B. Study Compliance Related Treatment Discontinuation:

A subject may be discontinued from study treatment, at the investigator's discretion, if the subject is unable to comply with the smoking cessation counseling and/or study assessment schedules. A subject not showing up for five or more weeks of study assessments, or not attending counseling sessions for five or more sessions, is considered non-compliant with the protocol and will be discontinued from smoking cessation treatment. Subjects in Group 1 will no longer receive patches and may not attend any further smoking cessation counseling. Subjects in Group 2 will lose eligibility for deferred treatment including both smoking cessation counseling and nicotine patches.

C. Study Treatment Discontinuation Guidelines: Assessments and Compensation

Subjects discontinued from treatment will continue to be eligible for study assessments, and will be encouraged to complete the weekly assessments and the week 9, 13 and 26 follow-up assessments. Subjects will continue to be eligible for \$10 weekly assessment and \$20 follow-up assessment compensation for any subsequent study assessments attended.

Subjects discontinued from study medication due to safety related concerns will continue to be eligible for the \$20 bonus compensation for completing the study through week 8. However, subjects discontinued based on study non-compliance will not be eligible for the \$20 bonus compensation for completing the study through week 8.

8.10.2 Study Discontinuation

The study may be terminated at any time if, in the opinion of the investigator, the study clinician, the study physician, the IRB, or the CTN Steering Committee, 1) continuation of the study would present a serious medical risk to the participants or 2) for other administrative reasons. Individual participation in the study may be discontinued based on the following guidelines.

A. Study Participation Discontinuation based on Administrative Reasons:

The investigator may administratively discontinue a subject if he/she deems it appropriate. Examples of administrative reasons include non-compliance with study protocol and active disruption of study procedures for other participants (e.g., counseling groups, study medications), or non-compliance with CTP rules resulting in expulsion from the CTP clinic. Study discontinuation in this manner should be decided in consultation with the staff at each CTP.

B. Study Participation Discontinuation based on Study Participant Request:

A subject may withdraw from this study anytime he/she wishes. Subjects will be considered actively enrolled in the study unless they withdraw their consent.

C. Study Participation Discontinuation Guidelines: Study Treatment, Assessments and Compensation

Subjects discontinued from study participation will no longer receive study treatment; nicotine patches and smoking cessation counseling. Subjects in Group 1 will be discontinued from current treatment and subjects in Group 2 will lose eligibility for deferred treatment. Subjects will not complete study assessments with the exception of final termination visit assessments. If subjects are discontinued from study participation prior to completing week 8, study personnel will attempt (phone calls, and mailed notices (optional)) to schedule termination visit assessments. Such participants will not be scheduled for follow-up assessments. If subjects are discontinued from study participation after completing week 8 they will not be scheduled for any further follow-up assessments. All subjects discontinued from study participation will not be eligible for any further study visit compensation, with the exception of final termination visit assessments. The point of discontinuation from study participation will be based on the last face-to-face contact for a study procedure (assessment or counseling).

8.11 CTP Smoking Survey

A survey of smoking prevalence and interest in smoking will be performed at each CTP participating in the study. The survey will be implemented at the CTP during the first 1-2 weeks of active study recruitment. All subjects, enrolled or seeking to become enrolled in the CTP, will be encouraged to complete the survey. A flier, posted near the survey station, will inform all CTP clients of the survey. The survey will contain instructions to fill out only one form, to answer all relevant questions, and then place it in a clearly marked, locked, ballot box. All surveys will be filled-out anonymously and will contain no personal identifying information. The survey information will be used to assess interest in quitting smoking among the entire treatment population at each participating CTP.

8.12 CTP Program Review

The programs and policies at each participating CTP clinic will be assessed. The CTP local investigator will, in consultation with the clinic's chief administrator, provide a brief list of information regarding the clinic's current practices. This information will be used to assess the feasibility of implementing a smoking cessation program across varying treatment programs participating in the study.

9.0 Study Interventions

At each CTP subjects will receive standard drug abuse treatment plus smoking cessation treatment (Group 1) or standard drug abuse treatment (Group 2). Subjects assigned to receive standard substance abuse treatment, but not smoking cessation treatment, may be eligible for deferred smoking cessation treatment after the end of study participation (6 months).

9.1 Standard Outpatient Treatment

All study participants at each of the CTP's will be enrolled in outpatient treatment that is either 1) a methadone or LAAM maintenance treatment program or 2) a drug-free rehabilitation clinic. All subjects will receive drug and alcohol rehabilitation counseling that is standard care for that CTP. These programs may include individual or group counseling with varying orientation/entry guidelines, eligibility requirements, and treatment philosophies based on program policy.

9.2 Smoking Cessation Counseling

Smoking Cessation Counseling will consist of relapse prevention, cognitive behavioral, and mood management therapy. It includes Counselor and Participant Manuals based on the Mood Management and Cognitive Behavioral Therapy for Smoking Cessation program from the Habit Abatement Clinic, University of California, San Francisco (Munoz et al., 1988; Hall et al., 1994; Patten et al., 1998). Subjects will attend 9 group smoking cessation counseling sessions beginning one week prior to a TQD and continuing for 6 weeks after TQD for a total of 7 weeks of counseling. For the first two weeks of counseling (Days -7 to 7), sessions will be scheduled twice-weekly (Sessions 1-2 during Week -1; Sessions 3-4 during Week 1). For weeks 2-6 of counseling sessions will be scheduled once a week (Sessions 5-9). The scheduling of all counseling sessions is flexible within all study weeks, however, Session 3 must always fall on the TQD and Session 4 should be 1-4 days after the TQD. If subjects miss a group session they are recommended to review that session in the Participant Handout manual and then go over the session briefly with the counselor either: over the phone, or in person before or at the next session. All smoking cessation counselors are required to be non-smokers or ex-smokers. If they are ex-smokers, they cannot have smoked a cigarette within the previous 9 months.

Deferred Smoking Cessation Treatment: Subjects randomized to Group 2, the standard substance abuse treatment group, will be eligible for deferred (6 month) smoking cessation treatment. This will consist of the same, or a similar (based on CTP discretion), program that is employed with Group 1 including both NicoDerm CQ medication and smoking cessation counseling. Due to the high probability of differences in motivation levels, subjects receiving deferred smoking cessation treatment will not be co-mingled with subjects receiving experimental smoking cessation treatment (Group 1).

Non-study Smoking Cessation Treatment: This is an intent-to-treat study design. The use of non-study smoking cessation treatment during the study (Week -1 through Week 26) will be tracked with the Smoking Cessation Compliance and the prior/*concomitant* medications CRFs, but will not be a basis for study or treatment discontinuation. However, referral for outside smoking cessation counseling and/or self-help books will not be provided until subjects have completed the study intervention period (Week 9), or upon early study discontinuation.

9.3 Smoking Cessation Pharmacotherapy

Smoking cessation pharmacotherapy will consist of transdermal nicotine (NicoDerm CQ®) patches supplied courtesy of GlaxoSmithKline Consumer Healthcare. NicoDerm CQ® patches will be provided in two strengths: 21 mg/day and 14 mg/day. Subjects will receive treatment medication for up to 8 weeks. Subjects will begin medication on the TQD and continue through the end of week 8 (Day 56).

Each 21 mg/day patch contains 116-119 mg nicotine mixed with ethylene vinyl acetate that is sandwiched between an impermeable backing plate and a rate limiting membrane of HDEP material that controls the nicotine release rate. The patch dimensions are 22 cm². The 21 mg/day patch delivers a gradual dose of nicotine in the blood stream that reaches peak level, 13-19 ng/ml, which is approximately 40-50% of the levels obtained by smoking a cigarette. Steady state levels are attained within 2 days of initiating transdermal treatment.

Each 14 mg/day patch contains 77-80 mg nicotine mixed with ethylene vinyl acetate that is sandwiched between an impermeable backing plate and a rate limiting membrane of HDEP material that controls the nicotine release rate. The patch dimensions are 15 cm². The 14 mg/day patch delivers a gradual dose of nicotine in the blood stream that reaches peak level, 6-16 ng/ml, which is approximately 15-30% of the levels obtained by smoking a cigarette.

During weeks 1 through 8, subjects in the smoking cessation group will receive patches according to the following dose schedule:

Week 1 (Day 1-7)	21 mg/day patch (22 cm ²), self-administered, QD
Week 2 (Day 8-14)	21 mg/day patch (22 cm ²), self-administered, QD
Week 3 (Day 15-21)	21 mg/day patch (22 cm ²), self-administered, QD
Week 4 (Day 22-28)	21 mg/day patch (22 cm ²), self-administered, QD
Week 5 (Day 29-35)	21 mg/day patch (22 cm ²), self-administered, QD
Week 6 (Day 36-42)	21 mg/day patch (22 cm ²), self-administered, QD
Week 7 (Day 43-49)	14 mg/day patch (15 cm ²), self-administered, QD
Week 8 (Day 50-56)	14 mg/day patch (15 cm ²), self-administered, QD

Transdermal patch therapy will continue for two additional weeks after the last week of counseling.

Following removal of the transdermal nicotine patches plasma nicotine concentrations decline in an exponential fashion with an apparent mean half-life of 3-4 hours.

Week 1: On the TQD, during Session 3 of the smoking cessation counseling program, subjects will receive a 7-day supply of patches from the research assistant and receive instructions on how to use the medication from their counselor. At the end of this counseling session subjects will be instructed to place a single patch on an area with little or no skin hair, such as the upper bicep or shoulder, and to maintain it in place

until the next morning before replacing it with a new patch. They will be instructed to repeat this process on a daily basis, replacing the patch at the same time on each day, for the next 8 weeks. They will be instructed to use only one patch at a time.

If a subject experiences symptoms of nicotine overdose during the first day of medication, or any day thereafter, he/she will be instructed to visit the clinic immediately for a medical safety evaluation and to possibly have their nicotine patch dose lowered to 14 mg/day. Lowering the dose must be done in consultation with the study physician and the subject must be assessed on the following day for reduced symptoms of nicotine overdose.

Weeks 2-8: Subjects will be provided with a 7-day supply of patches at the beginning of each study week and will be instructed to return all unused medication at the end of each week. The research assistant will distribute the 7-day supply of patches after the completion of the safety assessments (vital signs, prior/*concomitant* medication information, smoking medication compliance (Group 1, Wk 1-8), adverse events and urine pregnancy (females: Wk 4 and 8 only)) at a minimum.

Medication Dispensing Schedule Flexibility and Tracking: If in scheduling a subject's next visit it is determined that s/he cannot return within the next 7 days (e.g., after a Monday holiday) then additional patches may be dispensed to the subject to cover the additional days. These extra patches will be taken from a bulk supply and tracked by the research assistant using the smoking medication compliance CRF. If a subject knows that he/she will miss one entire week of the study, that week's study medications may be dispensed in advance (eg. on the Friday before) and tracked by the research assistant using the smoking medication compliance CRF. In cases where dosing flexibility is needed, subjects will be instructed to return all unused patches on the week they return.

All subjects will be instructed to return all unused study medication after the completion of week 8 (Day 56).

Medication Side Effects: The possible side effects of nicotine patches include an irregular heart beat or palpitations, increased blood pressure, insomnia or difficulty sleeping, reddening of the skin, swelling or a rash under and around the patch. Symptoms of nicotine overdose include nausea, vomiting, dizziness and weakness. The topical skin reactions (erythema, pruritis or burning at the application site) have been reported to occur in up to 35% of patients in clinical trials (PDR, 2001) and generally dissipate within 24 hrs. Other than the local effects on the skin, these effects are more frequently observed in non-smokers but not in regular smokers (≥ 10 cigarettes/day) due to their nicotine tolerance.

9.4 Medication Safety and Safety Monitoring

Medication Safety: Subjects receiving study medication will be instructed to keep the patches away from children and pets, not to use the patches if they are pregnant, and not to smoke or use other nicotine products while they are using the patch. They will be instructed not to smoke even when not wearing the patch, since nicotine in their skin will still be entering their bloodstream for several hours after they take off the patch. They will be instructed that if they experience insomnia or difficulty sleeping they may remove the patches at night.

Safety Monitoring: Clinical safety of all study participants will be monitored by weekly assessments of study medication compliance, use of concomitant medications, vital signs and weight, adverse and serious adverse events, and a urine pregnancy test (females, wk 4 and 8 only). For subjects receiving study medication, at each study visit the study clinician will monitor the subject's topical reaction to the patch, and query the subject regarding heart fluttering or palpitations, insomnia or difficulty sleeping, and symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness, and rapid heart beat.

If subjects experience difficulty sleeping while wearing the patch, they may be allowed to remove the patch at night. If subjects experience clinically significant side effects from the nicotine patch they may have their dose of nicotine lowered to 14 mg/day (Week 1-6) or to no patches (Week 7-8). Clinically significant side effects of the nicotine patch include: a) reddening of the skin, swelling or a rash under and around the patch that lasts more than 3-4 days, b) irregular heart beat or palpitations, c) increased blood pressure, d) insomnia or difficulty sleeping which does not go away by removing the patch at night, or e) symptoms of nicotine overdose such as nausea, vomiting, dizziness, rapid heart beat and significant weakness. Lowering the nicotine dose or removing the patch at night (for the purpose of improving sleep) must be done in consultation with the study physician and the subject must be assessed on the following day for reduced symptoms of nicotine overdose or sleep problems. If any side effect of the patch or symptom of nicotine overdose is reported, then it will be noted as an adverse experience and recorded on the appropriate CRF.

Subjects that experience symptoms of nicotine overdose because they are smoking while on the patch will first be told to stop smoking. If the symptoms of nicotine overdose persist after they have stopped smoking, then their dose of nicotine may be decreased to 14 mg/day (Week 1-6) or to no patches (Week 7-8) at the discretion of the study clinician in consultation with the study physician. If the subject does not follow instructions and continues to smoke, and the symptoms persist at a clinically significant level, then decreasing the nicotine patch dose will not be an option and the participant will be discontinued from study medication (see also discontinuation criteria above).

Subjects receiving study medication, who also use prescription medication for hypertension, asthma or depression, will consult with the study physician regarding the use of these medications during the study. If dose adjustment is warranted, according to the study physician, then the subject will be referred to their prescribing healthcare provider whom will make dose adjustments as clinically indicated.

10.0 Study Assessments

All subjects will have the following evaluations, as indicated in the Schedule of Procedures (Table 1). This information must be recorded on the appropriate case report form. If the subject is unable to read or has difficulty understanding the questions on a participant completed assessment, then the interviewer may read the questions to the subject. The evaluations are listed in alphabetic order.

Addiction Severity Index (ASI Lite)

The ASI (McLellan et al., 1985) is a standardized, multidimensional, semi-structured, comprehensive clinical interview that provides clinical information important for formulating treatment plans as well as problem severity profiles in six domains commonly affected in substance abusers. The domains covered are chemical abuse (alcohol and drug), medical, psychiatric, legal, family/social and employment/support. Composite Scores for each problem domain are derived mathematically. A revised version of the ASI Fifth Edition, 1997 version (ASI Lite), that includes only those questions used to derive the composite scores along with some demographic information will be administered by a research staff member. Composite scores will be calculated according to the procedures described by McGahan *et al.* (1982), Carroll *et al.* (1994).

Adverse Events

AEs will be assessed at each study visit during treatment by a study clinician. Brief assessments for AEs will also be done at week 13 and 26. The study clinician will assess subjects for any medical or psychiatric side effects, and may consult with the study physician when needed. The study clinician will assess AEs by asking the participant “How have you been feeling since I saw you last.” The type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF by the study nurse or physician assistant according to the procedures described in Table 2. The study physician will review all serious AE’s (see sec. 14.3), and all AE’s rated as “severe” (see Table 2) to determine study drug relatedness.

Alcohol Breathalyzer

Alcohol in each subject’s breath is analyzed using an Alco-Sensor IV (Intoximeter, Inc., St. Louis, MO) hand held breath alcohol instrument. It has an automatic breath sampling system designed to give a breath alcohol content (BrAC) reading. When measuring individual levels the subject is instructed to blow into a disposable mouthpiece for approximately 3 sec. Breath samples will be obtained by the research assistant following the collection of the urine sample, preferably during the 3-8 minute sample incubation period required to complete the urine screen test. The BrAC findings will be collected on an Alcohol Breathalyzer CRF.

The Alco-Sensor IV will be calibrated with a standardized alcohol gas tank on a quarterly basis.

Beck Depression Inventory II (BDI-II)

The BDI-II (Beck, 1996) is a subject-administered questionnaire designed to assess the intensity of depression in a subject over the past two weeks. It is also used as a screening instrument to detect depressive symptoms in potential study subjects. The BDI-II results in one total score. Subjects that score in the moderate or high range for depression (total score of 20 or higher) should be assessed by the study physician. Subjects that rate item 9 greater than 0 must also consult with the study physician. The study physician may refer the participant to a CTP mental health professional if the subject is in need of immediate treatment.

Brief Substance Craving Scale (BSCS)

The BSCS is a self-rated instrument assessing the degree of drug craving, excluding nicotine, within the past 24 hours for one primary and one secondary substance that the subject craves the most (these are chosen by the subject). Intensity, frequency, length of time spent craving, number of times craved, and descriptions of the worst day with craving episodes within the past week are assessed. Nicotine craving, measured by the WST, will not be assessed as a primary or secondary substance using this form. A craving score is calculated for each of the two substances.

CURRY Reason for Quitting Questionnaire (CURRY)

The CURRY (Curry et al, 1990) is a subject-administered questionnaire that asks the subject to rate their attitude towards quitting smoking. Subjects are instructed to indicate the extent to which they agree or disagree (from “Not at all true”, to “Extremely, very true”) with a list of 20 statements that include various reasons for quitting smoking on a scale of 0 to 4. In each case, they are to make their choice based on how they feel “right now.” There are 6 scales that are derived from this assessment: Health Concerns, Self-Control, Immediate Reinforcement, Social Influence, Intrinsic Motivation and Extrinsic Motivation.

Demographics

Age, gender, ethnicity, years of education, employment pattern, and drug use history are collected. The Demographics form will be required for all subjects who sign a consent form.

A Basic Data and Locator Questionnaire, including home address, will be completed and kept confidential in the subject’s records. Data collected on the Basic Data and Locator Questionnaire will be used to facilitate contact with the subject during the research and follow-up. Subjects will be asked to provide locator information including their residential street address and a working telephone number, or an address of a relative if they are homeless, as well as the address and telephone number of a non-drug abusing relative or friend who can reach the client in emergencies.

Drug Rehabilitation Compliance

Compliance with standard CTP drug rehabilitation programs will be assessed by recording attendance at drug abuse counseling sessions on a weekly basis in the Drug Rehabilitation Compliance CRF (each week will have a separate CRF).

DSM-IV Checklist

The DSM-IV Checklist (modified from Hudziak et al., 1993) will be administered to determine the participant’s Axis I substance abuse and dependence diagnoses prior to enrollment, as well as the participant’s primary substance of abuse. It will be administered by the research assistant or study clinician, trained in the DSM-IV Checklist, before randomization.

Primary Substance of Abuse (DSM-IV Checklist Addendum): The primary substance of abuse (drug or alcohol) will be defined as that substance which has the highest score on the DSM-IV Checklist based on answers to questions A1-A7 (highest possible score = 7 items present), confirmed by clinical interview with the research assistant or study clinician. If the interviewer does not concur, or if 2 or more items have the same highest score, then the primary substance of abuse will be based on the interviewer's opinion and given a score between 3 and 7 by the interviewer. Any judgement based determination of primary substance of abuse, on the part of the research assistant or study clinician (the interviewer), should be described in the comments section with the interviewer-based score in a specified CRF field.

Subjects stable on methadone or LAAM maintenance (≥ 12 months in treatment), that do not meet DSM-IV Checklist criteria for dependence on alcohol or drugs of abuse, will have opiates defined as the primary substance of abuse. The interviewer will rate the severity of this dependence with a score between 3 and 7 based on their clinical judgement. For tracking this primary substance of abuse, self reported use of opiates, craving for opiates, and urine screens positive for opiates (as opposed to prescribed methadone or LAAM) will be assessed.

Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND) is a brief subject-administered assessment of the subject's smoking habits (Heatherton et al., 1991). What brand of cigarette, how many smoked per day, when cigarettes are smoked, and the relationship of smoking behavior to physical health and social function are determined. The FTND results in one overall total score.

Inclusion/Exclusion Checklist

The eligibility of a participant to be in the study will be determined by review of the screening and baseline evaluations. Subjects that meet all inclusion criteria and no exclusion criteria will have this information verified in the Inclusion/Exclusion Checklist CRF, which is reviewed by the study clinician. For subjects who are not eligible, the reason(s) for not being eligible will be noted on the Inclusion/Exclusion Checklist CRF.

Medical and Psychiatric History Checklist

The medical and psychiatric history checklist will be completed during the screening phase. The psychiatric and medical history is obtained by a research assistant and should be compiled from the subject interview. Chart review, and review of any other available source material may be used to verify and supplement any information obtained during the interview (this will require a release of information form that meets the CTP's local requirements). Each subject will answer whether they have ever been treated for (and if they are currently being treated for) the following categories of psychiatric/neurological disorders: schizophrenia, Tourette's syndrome, major depressive disorder, bipolar disorder, anxiety or panic disorder, clinically significant neurological damage, attention deficit hyperactivity disorder, epilepsy or seizure disorder. Each subject will answer whether they have now, or a history of, the following medical problems: head injury, allergies (including to transdermal medications), liver problems, kidney problems, GI

problems, thyroid condition, heart condition, asthma, high blood pressure, skin disease or problems with skin rashes, routine drug (opiate, non-opiate, or other) or alcohol withdrawal symptoms. Any other medical or psychiatric conditions not mentioned will also be queried for. All medical and psychiatric history forms will be reviewed by a study clinician, and relevance to study participation will be noted, before randomization.

Pregnancy Assessment

Female subjects will be required to have a negative urine pregnancy test at screening and prior to randomization using a JANT ACCUTEST hCG Urine Pregnancy Test Strip. For female subjects, additional pregnancy test will also be performed at the end of the week 4 and week 8 of medication treatment. Female subjects will also be expected to practice an acceptable form of birth control. Women who become pregnant during the treatment phase (week –1 through week 8) will discontinue study medication and be allowed to continue smoking cessation counseling (Group 1) or maintain eligibility for deferred smoking cessation counseling (Group 2). In both cases subjects will continue to be eligible for standard substance abuse treatment services at the CTP. If pregnant subjects voluntarily withdraw from the study the CTP's will provide referral for outside smoking cessation counseling, and/or self-help books.

Prior/Concomitant Medications

The subject will be asked about all medications, prescribed or over-the-counter, he or she has taken over the last 60 days prior to entering the screening phase of the study. This information is obtained during the screening phase of the study (and will be updated prior to randomization) and is used to determine subject eligibility. This information will be obtained by a research assistant and transcribed onto the Prior/Concomitant Medications CRF. All recorded prior medications will be reviewed by a study clinician before randomization.

During the treatment phase of the study, the subject will be asked about medications, prescribed or over-the-counter, he or she has taken since their last visit. This information is used to determine continued subject eligibility. This information will be obtained by a research assistant and transcribed onto the Prior/Concomitant Medications CRF. All recorded concomitant medications will be reviewed by a study clinician on a weekly basis.

Randomization Form

A study clinician or study physician must review the Inclusion Exclusion criteria before a subject is randomized and determine if the subject continues to be eligible for study participation. This determination will be noted on the randomization form. Randomization date, number and group assignment will be collected; and, eligible subjects who are not randomized will have their reasons for non-randomization noted on this form. The Start Date and Target Quit Date will be indicated and the form will be signed by the study clinician or study physician.

Risk Behavior Scale (RBS)

The RBS is based on the Risk Assessment Battery (Navaline et al., 1994). It is an interviewer-administered questionnaire that assesses HIV risk behavior. Information on recent injection drug use and sexual activity are queried. There is no scoring associated with this assessment.

SF-36 Health Status Questionnaire

The SF-36 (Ware and Sherbourne, 1992) is a multi-item, subject administered instrument examining eight general health concepts: general health perceptions, mental health, physical functioning, social functioning, bodily pain, vitality, role limitations due to physical health problems, and role limitations due to emotional problems. In addition, there is a single question that is a measure of health transition. The SF-36 will be completed at baseline and all follow-up visits.

Smokers Beliefs Questionnaire

The Smokers Beliefs Questionnaire (Frosch et al., 1998) is set of two self-administered questions in which the subject is asked to rate the severity of their cigarette addiction and how easy or difficult it would be for them to quit.

Smoking Cessation Compliance

Attendance at each group smoking cessation counseling session will be maintained in a Smoking Cessation Compliance CRF. Any additional smoking cessation treatment (non-CTP) and/or use of self-help brochures or books, before or after completing the smoking cessation intervention (through Week 8), will be recorded. For subjects not receiving smoking cessation treatment (Group 2) non-CTP smoking cessation treatment and/or use of self-help brochures or books will be recorded.

Smoking History Survey

The Smoking History Survey is a modified version of the Mayo Nicotine Dependence Center Patient Questionnaire (1991) administered by the research assistant. It asks subjects the following: how many cigarettes per day they smoke, at what age they started smoking, number of years smoking, how many times they have attempted to quit (including methods), when the last quit attempt occurred, their longest period of cigarette abstinence, and if there are other smokers in their household. Information on other non-cigarette tobacco products will also be noted.

Smoking Medication Compliance

The amount of study medication given to each subject, on each study week, will be recorded on Smoking Medication Compliance CRF (each week will have a separate CRF). Subjects will self-administer medications on a daily basis and medication use will be kept in a weekly Smoking Medication Compliance log. Any unscheduled change in nicotine patch dose, and any deviations from medication administration instruction will also be assessed. The Smoking Medication Compliance log will be maintained by study staff and updated at each scheduled clinic visit.

Smoking Status/Expired CO

Each subject will be asked if they have been continuously cigarette abstinent since the last clinic visit. If they have smoked cigarettes, they will be asked the average number of cigarettes smoked per day. They will also be asked whether they have used any other tobacco or nicotine products.

Expired CO will be measured at each study visit. Carbon Monoxide (CO) in each subject's breath is tested using a standard calibrated CO gas-monitoring device connected to a disposable mouthpiece. When measuring individual CO levels the subject is instructed to blow into the mouthpiece for approximately 5 sec. This procedure is performed twice for each visit and documented separately on the CRF. Time of day that CO samples are collected will be noted in the Smoking Status/CO monitor CRF. Study staff should attempt to collect samples at a uniform time (in morning, right after subject arrives and before other assessments or counseling sessions begin).

Subjects with primary marijuana dependence will be queried for recent marijuana smoking if a $CO \geq 10$ ppm is obtained, and any such corresponding marijuana smoking episode will be entered in the SUR.

Study Enrollment

All subjects that sign a consent form to participate in the study, and begin screening and baseline evaluations, will be so designated by use of Study Enrollment CRF.

Study Termination

Subjects that are discontinued from the study prior to the Week 26 follow-up will be noted as discontinued from the study on the Study Termination CRF. Subjects that complete the treatment intervention and assessments (Study Completers) will also be noted on this CRF. Reason(s) for discontinuation will be noted.

Substance Use Report (SUR)

The SUR assesses the following areas of substance use: alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, marijuana (cannabinoids), methadone, methamphetamines, opiates, and PCP. Using a 7-Day Time Line Follow-Back styled format, the SUR tracks the use of each substance for the preceding week. There will be one SUR for each study week. If a study participant comes to the clinic after having missed more than one week of study visits the research assistant will obtain drug use information for all days back to, and including, the date of the last study visit.

University of Rhode Island Readiness to Change Assessment (URICA)

The URICA is a subject-administered questionnaire that asks the subject to rate their attitude towards their own problems and how they might approach them. Subjects are instructed to indicate the extent to which they agree or disagree with a list of 32 statements about their problems and attitudes towards treatment on a scale of 1 to 5. In each case, they are to make their choice

based on how they feel “right now”, not how they felt in the past or would like to feel. For all the statements that refer to “problem”, the subject is instructed to answer in terms of problems related to drug and/or alcohol abuse. Four Scales are derived from the URICA: Pre-Contemplation, Contemplation, Action and Maintenance.

Urine Cotinine Assay

Cotinine is the primary metabolite of nicotine and can be measured in saliva and urine. A urine sample will be collected during a baseline visit and during each of the follow-up visits. Each sample will be split in 2 and the primary sample will be sent to a central contractor for the analysis of quantitative urine cotinine and creatinine levels. The back-up sample will be stored in a standard freezer (-20 °C) and may be discarded when assay results are obtained from the contractor and all data queries have been resolved.

Urine Drug Screen

Urine samples are to be collected at each study visit. An FDA-approved one-step test, the Accutest Multi-Drug Screen (for immunoassay of 9 drugs of abuse and TCAs; JANT Pharmaceutical Corporation) will be used for drug screening. Following collection of the urine sample into a urine collection cup, staff will dip this multi-drug screen cassette into the cup and wait for the results. Results are obtained in 3-8 minutes. It is not necessary to monitor the collection of urine samples. The nine drugs of abuse are: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methadone, methamphetamines, opiates, and phencyclidine. Results are to be recorded on the Urine Drug Screen CRF by the research assistant. The results are confidential and should not be shared with the patient or non-research CTP staff.

Vital Signs and Weight

Vital signs to be assessed include oral temperature, blood pressure, respiration rate and heart rate. In addition, the participant’s weight will be entered onto this form. Oral temperature will be collected with a standard thermometer; blood pressure and heart rate with an automated BP/Pulse detector (LifeSource, Auto-Inflation Wrist Cuff) or equivalent equipment, and respiration will be determined by a 15 sec observation of breathing. Vital signs will be assessed with the subject in a sitting position, at rest for at least 3 minutes. Vital signs and weight are collected during screening, at baseline and then weekly during the study for all study subjects. Vital signs information will be reviewed by a study clinician each week.

Withdrawal Scale for Tobacco (WST)

The WST is a modified version of the Minnesota Withdrawal Scale (Hughes et al, 1991; Hatsukami et al, 1997; Hughes and Hatsukami, 1986). The WST is a subject completed questionnaire which asks subjects to rate 9 items of withdrawal on a scale from 0=None to 4=Severe. A Total score is then computed from the responses to these 9 items. In addition, the 9 items are also examined separately.

CTP Program Review

Each site participating in the study will be asked to complete the CTP Program Review prior to starting the study. The information from this assessment will be used to characterize the CTP in exploratory analyses.

A research assistant, in consultation with the clinic's chief administrator and/or the CTP site investigator, will complete this form. This assessment provides a brief list of information regarding the clinic's current practices. The information listed will be:

1. Primary Service Setting: HMO, hospital, freestanding program, social service center, etc.
2. Standard outpatient programs offered: methadone/LAAM, drug abuse rehabilitation, alcoholism treatment, other
3. Standard length (duration) of treatment program
4. Substance abuse counseling platforms employed: cognitive behavioral, relapse prevention, 12-step, AA, other
5. Substance abuse counseling schedule: daily, 2x/week, 1x/week, open-ended, other
6. Random urine collection policy: 2x/week, 1x/week, 2x/month, 1x/month, none, other
7. Clinic patient census
8. Staff census: number of counselors that smoke, and that don't smoke.
9. Clinic smoking policy:
 - a) smoke free, or non-smoke free
 - b) smoking allowed in clinic vicinity (i.e. outside, during breaks, etc.), or not allowed in clinic vicinity
 - c) nicotine addiction integrated into substance abuse counseling, or not integrated into substance abuse counseling

CTP Smoking Survey

Each site participating in the study will also be asked to collect information clinic-wide in order to assess interest in smoking cessation at their clinic. This will be done during the first 1-2 weeks of active study recruitment at the participating site. This assessment may be filled out by anyone enrolled in the clinic, not just study participants.

All patients, enrolled or seeking to become enrolled in the CTP, will be informed of a clinic wide smoking survey and encouraged to fill it out. The survey will contain the following questions:

1. What is your gender?
2. What is your age?
3. Do you use tobacco products?
4. Are you a cigarette smoker? If yes:
 - a) How many cigarettes do you smoke per day?
 - b) How many years have you been smoking?
 - c) Are you interested in quitting smoking?

d) Would you like to enroll in a smoking cessation treatment program?

All surveys will be filled-out anonymously and will contain no personal identifying information. Surveys will be available at a table in a public space (such as a waiting room) that is manned by a research assistant who will answer questions and make sure that no one individual submits more than one survey. Once the surveys are completed they will be placed through a slot into a locked box that is clearly identified as the container in which finished surveys should be placed.

11.0 Statistical Analyses

11.1 Efficacy Measures

Primary Efficacy Measure

Smoking abstinence will be the primary smoking cessation treatment outcome and the primary efficacy parameter for the study. Smoking abstinence at a specific study visit is defined as a self-report of no smoking since the last study visit according to the Smoking Status Survey, and expired CO levels ≤ 10 ppm. Participants reporting no smoking and providing CO levels ≤ 10 ppm will be considered abstinent for that visit; otherwise they will be considered non-abstinent. If no data is available for a given week, the value for the smoking abstinence measure will be missing.

Secondary Efficacy Measure

Abstinence from the participant's primary substance of abuse will be the secondary efficacy parameter for the study. Abstinence at a specific study visit is defined as no use of the primary substance of abuse since the last study visit according to the Substance Use Report, and a urine drug screen or alcohol breathalyzer result negative for the primary substance of abuse. Participants reporting no use of the primary substance of abuse and providing a negative drug/alcohol sample will be considered abstinent for that visit; otherwise they will be considered non-abstinent. If no data is available for a given week, the value for the secondary efficacy measure will be missing. The primary substance of abuse for each participant is defined based on the DSM-IV Checklist Addendum.

Retention of participants in treatment, number of weeks abstinent from the primary substance of abuse, and number of weeks smoke free will be additional secondary efficacy parameters. Retention in smoking cessation treatment, substance abuse rehabilitation treatment, and study participation will be measured using smoking cessation counseling and drug rehabilitation attendance records, date of enrollment and date of termination from the study.

Additional Measures

The ASI composite scores, weekly scores from the Withdrawal Scale for Tobacco and Brief Substance Craving Scale, and secondary drug or alcohol use based on the urine drug screens and alcohol breathalyzer results and the Substance Use Report, will be additional outcome measures. In addition, changes in the total score from the Beck Depression Inventory (BDI-II) and the overall health score from the SF-36 will be used to measure changes in the psychological and health assessment of study participants.

Cigarette addiction, tolerance and interest in quitting among the study participants will be measured by total scores from the baseline Fagerström Test for Nicotine Dependence, Smokers Belief, and CURRY questionnaires, as well as Smoking History values for number of years smoked, number of previous quit attempts, and age of onset as a regular smoker. These variables will be used to characterize the participants at baseline.

The CTP Program Review will be used to measure CTP clinic program practices and policies; and, to characterize the clinics (e.g., methadone versus drug-free). The CTP Smoking survey will be used to measure smoking prevalence, clinic-wide interest and willingness to quit smoking. These three measures will be used to assess “feasibility.”

11.2 Sample Size/Power

Sample size was determined using logistic regression with unequal group size (2:1) using the PASS 2000 sample size program. These sample size estimates are used for both the primary and secondary efficacy measures; and, for males and females. In order to compute sample size for logistic regression, an adjustment is required for the regression of treatment group on the other independent variables in the regression model (CTP, sex, and week). R-Squared values of 0.3 and 0.5 were used. The following table provides the sample size estimates for 80% power at a 0.05 significance level.

Required Total Sample Size given different values for: Probability of Abstinence in SC group (P1) and in TAU group (P2) When Power = 80% and Alpha = 0.05								
		P1						
P2		0.10	0.15	0.20	0.25	0.30	0.35	0.40
R-Squared = 0.3	0.05	1433	468	252	164	117	89	70
	0.10		2227	653	328	203	140	103
	0.15			2921	813	394	236	159
	0.20				3515	947	447	263
	0.25					4008	1057	489
	0.30						4402	1141
	0.35							4695
R-Squared = 0.5	0.05	2006	655	353	229	164	125	98
	0.10		3118	914	460	285	197	145
	0.15			4090	1138	551	331	223
	0.20				4921	1326	626	369
	0.25					5612	1480	685
	0.30						6163	1598
	0.35							6573

Primary Efficacy Measure

Previous research on the effects of smoking cessation on smoking abstinence rates have indicated that nicotine patch plus counseling is less effective in females than males (Perkins, 2001). Therefore effect size estimates for this primary outcome measure apply to each gender separately.

Males: For the outcome of *smoking abstinence*, assuming a 26% abstinence rate in the smoking cessation treatment group (Group 1) and a 4% abstinence rate in the control group (Group 2), 45 subjects in the control group and 90 subjects in the smoking cessation treatment would provide 80% power to detect this or a larger between-group difference as significant, using a two-sided alpha level of 0.05. Thus, a total of 135 participants would be needed when R-squared is 0.3 (or 189 when R-squared is 0.5).

Females: For the outcome of *smoking abstinence*, assuming a 19% abstinence rate in the smoking cessation treatment group (Group 1) and a 4% abstinence rate in the control group (Group 2), 78 subjects in control group and 156 subjects in smoking cessation treatment group would provide 80% power to detect this or a larger between-group difference as significant, using a two-sided alpha level of 0.05. Thus, a total of 235 participants would be needed when R-squared is 0.3 (or 329 when R-squared is 0.5).

Secondary Efficacy Measure:

Previous research on the effects of smoking cessation on drug and alcohol use has not demonstrated any clear difference between male and female populations. Therefore, effect size estimates for this secondary outcome measure will apply across both genders.

For the outcome of *drug or alcohol abstinence*, assuming a 25% abstinence rate in the smoking cessation treatment group (Group 1) and a 15% abstinence rate in the control group (Group 2), 271 subjects in the control group and 542 subjects in the smoking cessation treatment group would provide 80% power to detect this or a larger between-group difference as significant, using a two-sided alpha level of 0.05. Thus, a total of 813 participants would be needed when R-squared is 0.3 (or 1138 when R-squared is 0.5).

Sample size calculations for this secondary outcome measure are presented for informational purposes.

Sample Size Determination:

The final sample size determinations were based on the above sample size calculations, and consideration of potential factors: variability that may exist between CTP's, % female clients enrolled at participating CTP's (approximately 33% based on a year 2002 survey), the possibility that some CTP's will not achieve 100% of targeted enrollment, and the desire to have high enough power to detect a difference in the secondary outcome measure of substance abuse. Based on these factors, and a study design that is optimal at a recruitment rate of 9 subjects per month (3 control, 6 experimental), and consideration of block sizes for the randomization scheme, a total of 72 subjects per CTP across 12 CTP's was selected as the sample size. This results in a total sample size of 864.

For the primary efficacy analysis, the required sample size is 705 (of which 33% = 235 are females). For the secondary efficacy analysis, the required sample size is 813. For the randomization scheme, we chose a multiple of 3, 6, 9, 12, 18 or 36. Since 72 is the next larger number that meets these criteria, we selected 72 per site, for 12 sites which gives a total sample size of 864.

11.3 Participant Subsets

The primary efficacy analysis will be based on data from all randomized participants ("intent-to-treat analysis" participants).

11.4 Types of Analyses**11.4.1 Logistic Regression**

Logistic Regression, as implemented in SUDAAN, will be used to analyze binary outcome measures. The statistical issues arising from clustering of participants within a site, and from repeated measures over time on a participant, requires appropriate statistical methods for analysis of clustered binary data. SUDAAN permits the specification of clustering at many levels, including repeated measures. Treatment group, CTP and gender will be categorical effects in the model and week will be a continuous variable. Two

levels of clustering will be considered: CTP and participant. The parameter estimates, standard errors and 95% confidence intervals will be presented. Treatment groups will be tested at the adjusted 0.05 level based upon the interim analysis.

11.4.2 Survival Analyses

Time to dropout measures will be analyzed using survival analysis techniques. Survival analyses will be performed using a Cox Proportional Hazards model (Cox, 1972). The Cox proportional hazards model permits the evaluation of the effects of covariates in the analyses. A survival analysis is based upon events occurring. The survival distribution functions will be estimated using the Kaplan-Meier estimator and the results will be plotted for graphical presentations (Lee, 1992; Lawless, 1982).

11.4.3 Mixed Effects Models

Mixed Effects Models (MEMs) will be used to analyze continuous outcome measures. The statistical issues arising from clustering of subjects within a site requires appropriate statistical methods for analysis of clustered data, namely Mixed Effects Models (MEM). MEMs are also used to analyze repeated measurements of data over time. The repeated measurement on an individual over time are usually correlated and thus represent another cluster in addition to the clustering of subjects within a site.

In all mixed effects models, site (or more explicitly, CTP) will be a random effect reflecting our desire to make a global inference among all CTPs, as opposed to treating them as fixed effects which would correspond to local inference related to only the particular CTPs used in the study. The estimated variance of the random effects corresponding to sites and site by treatment interaction will give a measure of the expected variability in the efficacy of SS between CTPs. PROC MIXED in SAS® [SAS Institute Inc. Cary, NC] will be used to carry out the MEM analysis.

The covariance structure for any particular model will be determined by modeling several possible covariance structures. For example, the course of an efficacy measure over time will be modeled as auto-regressive of order one, compound symmetry, and unstructured. Selection of which structure to be used will be based upon review of both Akaike's Information Criteria and Schwarz's Bayesian Criteria.

11.4.4 Chi-square Analyses

For the comparison of proportions in the two treatment groups, a Mantel-Haenszel chi-square analysis, controlling for (stratified by) CTP and gender will be used (Agresti, 1990). This analytic method will be used for Secondary Efficacy Hypothesis 4.

11.5 Analysis of Specific Hypotheses

11.5.1 Primary Efficacy Analysis

Hypothesis 1: At the end of treatment, smoking cessation treatment will be more effective than standard substance abuse treatment with respect to smoking abstinence rates.

This hypothesis will be tested using Logistic Regression with an independent working correlation and robust variance estimates (resulting in a GEE logistic model). Smoking abstinence will be determined for each treatment week in the study (Week –1 through Week 8) for each participant. Follow-up time points will not be included in this analysis. The weekly abstinence scores for smoking will be the repeated measure. Treatment group, CTP, and gender will be categorical effects in the model. Week-by-treatment group and gender-by-treatment group interactions will also be included in the model. Linear functions of time (week) will be used to represent the course of smoking during the study; however, if necessary, quadratic terms could be incorporated. We anticipate that there will be a significant interaction of treatment and week, which would correspond to differences in abstinence rates over time between the two treatment groups, which would result in a difference between the treatments at end of the treatment.

If there is a significant gender-by-treatment group interaction, then the model will be run separately for males and for females.

11.5.2 Secondary Efficacy Analysis

Hypothesis 2: At the end of treatment, smoking cessation treatment will be more effective than standard treatment with respect to measures of retention in drug rehabilitation treatment.

This hypothesis will be tested using a Cox Proportional Hazards model on time to dropout from drug rehabilitation. Gender and treatment group will be covariates in the model. CTP will be entered into the model as a stratification variable. Since survival analysis is based upon events occurring, the event of interest is time of discontinuation from drug rehabilitation. Participants who drop out of drug rehabilitation will be considered to have “the event of interest” at the time of their last clinic visit. Participants who complete drug rehabilitation or who finish the treatment phase of the study will be censored at that time.

Hypothesis 3: At the end of treatment, smoking cessation treatment will be more effective than standard substance abuse treatment with respect to primary substance of abuse abstinence rates.

This hypothesis will be tested using Logistic Regression with an independent working correlation and robust variance estimates (resulting in a GEE logistic model). Abstinence from primary substance of abuse will be determined for each treatment week in the study (Week –1 through Week 8) for each participant. Follow-up time point will not be included in this analysis. The weekly abstinence scores for primary substance of abuse will be the repeated measure. Treatment group, CTP, gender and primary substance of abuse will be categorical effects in the model. Week-by-treatment group interaction will also be included in the model. Linear functions of time (week) will be used to represent the course of primary substance of abuse abstinence during the study; however, if necessary, quadratic terms could be incorporated. We anticipate that there will be a significant interaction of treatment and week, which would correspond to differences in abstinence rates over time between the two treatment groups, and would result in a difference between the treatments at end of the treatment.

Hypothesis 4: At the end of treatment smoking cessation treatment will be more effective than standard substance abuse treatment with respect to smoking abstinence rates.

This hypothesis will be tested using a Cochran-Mantel-Haenszel Chi-square statistic for general association, stratified by gender and by CTP. A person will be considered a “success” if they are abstinent during weeks 7 and 8; otherwise the subject will be considered a “failure.” If there is evidence of non-homogeneity between the sex strata, then separate analyses will be performed for males and females separately.

Hypothesis 5: At the end of treatment, smoking cessation treatment will be more effective than standard treatment with respect to measures of retention in study.

This hypothesis will be tested using a Cox Proportional Hazards model on time to dropout from study. Gender and treatment group will be covariates in the model. CTP will be entered into the model as a stratification variable. Since survival analysis is based upon events occurring, the event of interest is time of discontinuation from the study. Participants who drop out of the study will be considered to have “the event of interest” at the time of their last clinic visit. Participants who complete the study will be censored at the time of their last clinic visit.

11.5.3 Supplementary Analyses

To gain a better understanding of the results of the study and to explore which variables may be important to the treatment outcomes, the following analyses are proposed. Due to the number of tests being proposed here, any significant findings will be interpreted with caution.

Weekly scores from the Withdrawal Scale for Tobacco and the Brief Substance Craving Scale will be evaluated using MEMs. The repeated measurements from the ASI, the BDI and the SF-36 will also be analyzed using MEMs.

11.5.4 Exploratory Analyses

In addition, exploratory analyses will be performed to determine if any demographic or pre-randomization characteristics are prognostic or influence efficacy outcome measures. In particular, CTP type, CTP prevalence of smoking, CTP interest level in quitting smoking, race, gender, age, concomitant methadone dose (restricted to data sets from methadone programs), and primary substance of abuse will be evaluated. Additional exploratory analyses for smoking outcomes will evaluate the impact of smoking history, cotinine levels and FTND score.

Drug abuse treatment outcomes in smoking abstinent vs. non-abstinent participants, and smoking cessation treatment outcomes in drug abstinent vs. non-drug abstinent participants will also be evaluated.

The level of study vs. non-study smoking cessation intervention in each group will be evaluated by descriptive statistics.

11.6 Demographic and Baseline Characteristics

The number of participants enrolled into the study will be summarized by CTP, by treatment group, and by gender. For participants who are screened but not randomized, a distribution of the reasons for non-randomization will be provided for each site separately.

Treatment groups will be compared descriptively with regard to baseline characteristics (e.g., age, sex, race) using proportions when the data are categorical or means and standard deviations when the data are quantitative. These descriptive statistics are being computed to describe the subjects in the different randomization strata (gender, CTP and Treatment group).

The categorical demographic variables to be examined are: sex, race, marital status, usual employment pattern in the past 3 years and age group. The quantitative demographic variables to be examined are age in years, years of education, substance use in the past 30 days, as well as, use of substances during the participant's lifetime. Quantitative baseline characteristics are the Fagerström tolerance score, CURRY Reasons for Quitting score, urine cotinine levels; and, the four stages of changes scores (pre-contemplation, contemplation, action and maintenance) from the URICA.

For Baseline efficacy parameters, the following quantitative variables will be examined: the seven composite scores from the ASI (medical, employment, alcohol, drug, legal, family and psychiatric); BDI-II total score, baseline cigarette usage, and, primary drug craving score from the Brief Substance Craving Scale.

11.7 Safety Analysis

Adverse Experiences

For each individual adverse experience, each participant will be categorized by the maximal severity reported during the randomization phase. Adverse experiences occurring during screening but ending prior to randomization, or those starting during screening and continuing into the randomization phase with the same or less severity will be excluded. The severity categories are: none (if the participant never had the adverse experience), mild, moderate, or severe. If a participant has an adverse experience more than once, then the most severe evaluation will be used in the analysis.

Vital Signs

Vital sign data (weight, temperature, respiration rate, systolic and diastolic blood pressure, and pulse rate) will be summarized for each week separately, by treatment group and by treatment group stratified by CTP. An exploratory analysis of covariance may be performed on the change from baseline to Week 8 for each vital sign measure. The model will include factors for treatment group, CTP and treatment group by CTP interaction and use the baseline value as a covariate.

11.8 Interim Analysis

An interim analysis of substance use for the subject's primary substance of abuse will be performed for safety reasons.

Abstinence from the subject's primary substance of abuse will be used as the parameter for the interim analyses. Subjects who do not have any post-randomization data will be excluded from the analysis. Overall, a subject will be considered abstinent if they report not using their primary substance of abuse AND they have a negative urine drug screen for all visits in the 7-day timeframe for the week. The proportion of subjects who are abstinent will be compared for the two treatment groups using the same analytic approach as for the primary analysis. The EaSt-2000 statistical package for interim analyses was used for designing the interim analyses. The designs created by using EaSt 2000 are based on a family of power boundaries proposed by Wang and Tsiatis in 1987 where by the shape parameter value determines the boundaries. A value of zero will produce the O'Brien-Fleming type boundaries; while a value of 0.5 will produce the Pocock boundaries.

Two possible plans were considered for an interim analysis. Plan 1 had 1 interim analysis after 310 subjects had completed the treatment phase; and, Plan 2 had 2 interim analyses after 209 and 418 subjects had completed the treatment phase. The probability of stopping under the null (H_0) hypothesis for Plan 1 is 0.005. For Plan 2 the probabilities of stopping under the null hypothesis are 0.0005 and 0.014. The power associated with these analyses are 0.26 for Plan 1; and, 0.04 and 0.48 for Plan 2. Since the probability of stopping under either the null or alternative hypotheses are so small for Plan 2, we have selected Plan 1. Under Plan 1, the alpha level will be 0.005 for the interim analysis and 0.045 for the final analysis. A statistician other than the lead node statistician will perform the interim analysis.

Special data transmissions to the NIDA data repository and to the statistician performing the interim analysis may be necessary in order to analyze the interim data in a timely manner. The interim analyses will be based upon cleaned data, however; if the SOPs developed by the Data Management and Analysis Subcommittee are followed (i.e., Data Timeliness and Completeness, Data Accuracy and Validation, and Error Tracking SOPs), this should not result in any significant delays.

In conjunction with the interim analysis, descriptive statistics by gender and treatment group for retention in drug rehabilitation, and study vs. non-study smoking cessation interventions, will be provided. For retention, the length of time in drug rehabilitation treatment will be displayed graphically for each treatment group (combining sexes), and for the four subgroups (male-group 1, female-group 1, male- group 2, and female-group 2), where group 1 is the smoking cessation therapy plus standard drug abuse treatment and group 2 is standard drug abuse treatment. For the graphical display, Kaplan-Meier estimates of the proportion still in treatment will be computed for each week; however, no statistical comparisons of the two treatment groups will be performed.

The decision to continue or discontinue the study will be based on all available data, of which the formal interim analysis is only a piece. The decision will be based on both clinical and ethical considerations. Clinical guidelines recommend study discontinuation if the rate of abstinence from primary substance of abuse in the intervention group (Group 1) is 15% lower than the control group

(Group 2) (e.g., if Group 2 has a value of 25% abstinence, any value for Group 1 of 10% or lower would be grounds for study discontinuation).

Data on client recruitment and retention will be monitored according to DMAS SOPs (see section 12). In addition, after every 100 subjects, recruitment by gender will be examined to ensure that CTPs are enrolling a percentage of women into the protocol that reflect the percentage of female clients in their programs (as determined by survey data received by the Lead Node when enlisting study sites; average for the 12 sites=33.5%). Each month, non-study treatment will be assessed (both groups combined) and rates of use of non-study treatment will be reviewed for each site and overall.

12.0 Data Management

The New York Node Data Management Center (DMC) will coordinate data management activities and provide ongoing consultation and assistance to participating nodes through out the study. All procedures will be in accordance with the Standard Operating Procedures (SOPs) developed by the CTN Data Management & Analysis Subcommittee (DMAS). The DMAS SOPs are in accordance with the Food & Drug Administration regulations, which NIDA has adopted as the data collection and management standards for all CTN studies.

Lead Node Responsibilities

The New York Node Data Management Center will provide final Case Report Form (CRF) specifications for the collection of all data required by the study. While the study data content of the CRFs cannot be changed, it is understood that CRFs may be modified for incorporation into each participating node data management system as appropriate. The New York Node DMC will also provide data dictionaries for each CRF that will comprehensively define each data element. The data dictionary will specify missing, illogical, out of range, and inconsistent value checks for each data element as well as within-CRF logic checks and across-CRF logic checks. The data dictionaries provide the specifications necessary for each node to develop an automated data acquisition and management system that will be designed in accordance with standards established by DMAS. The New York Node Data Management Center will also provide specifications necessary to conduct data monitoring activities and meet the requirements of all other DMAS SOPs.

Data Collection

Data will be collected at the study sites on either electronic (paperless) or paper case report forms (CRFs). Forms completion instructions will also be provided for each CRF.

Each participating node Data Management Center (DMC) will coordinate the preparation of paper CRFs and the distribution of these CRFs to participating Community Treatment Programs (CTPs) within their node. These forms are to be completed on an ongoing basis during the study. Forms should be completed according to the instructions provided. Each node is responsible for maintaining accurate, complete and up-to-date records and for tracking CRFs for each participant. Paper CRFs must be completed legibly with

black ballpoint pen. Any corrections must be made by striking through the incorrect entry with a single line using a ballpoint pen and entering the correct information adjacent to the incorrect entry. Corrections to paper CRFs must be initialed and dated by the person making the correction.

Data Submission, Editing and Monitoring

Completed forms/electronic data will be submitted to each participating node DMC in accordance with Data Timeliness and Completeness SOP established by the DMAS. Only authorized individuals, in accordance with each participating node's DMC policies, shall perform data entry into electronic CRFs. Corrections to electronic CRFs must be tracked electronically with time, date, and individual making the change, both the old data value and new data value, and the reason for the correction. Each node DMC will implement comprehensive error checking and data management procedures as per the Error Tracking SOP established by DMAS. Data monitoring will be the responsibility of the DMC at each node. Data monitoring will be performed as specified in the Data Timeliness and Completeness SOP, Data Accuracy and Validation SOP, Participant Progress Monitoring SOP, and other data monitoring SOPs as published by the DMAS.

Automated Data Acquisition and Management Systems

Each node is responsible for the development of a comprehensive automated data acquisition and management system in accordance with guidelines and SOPs published by NIDA and DMAS. The New York node DMC is willing to discuss the use of the New York automated data acquisition and management system if it is not desirable or cost effective for a node to develop an independent data acquisition and management system.

Central Data Repository

Data will be transmitted by the participating node DMC to the NIDA central data repository on the 1st of every month. The New York Node DMC will receive aggregated data from the NIDA central data repository on a monthly basis for data completeness, timeliness and accuracy quality assurance review. At the completion of the study, all data will be transmitted from the NIDA central data repository to the New York Node DMC for data analysis and the development of the final study report. The New York DMC will conduct final data quality assurance checks and "lock" the study database from further modification in accordance with the Database Lock SOP developed by the DMAS. The New York DMC will send the final analysis dataset back to NIDA for storage and archive.

13.0 Regulatory and Reporting Requirements

13.1 IRB Approval

Prior to initiating the study, the Principal Investigator at each study site will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the Principal Investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials (Homework Sheets and Self-help Handout Material) given to the subject.

13.2 Informed Consent

The informed consent document provides a summary of the research study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant.

All potential candidates for the study will be given a current IRB approved copy of the Informed Consent Form to read. The investigator, sub-investigators, or study physician at each site will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. The reason for refusal or withdrawal will be noted on a CRF.

A sample informed consent form is will be provided from the Lead Investigators site to each participating site.

13.3 Drug Accountability

Upon receipt of study medications (NicoDerm CQ® patches), the investigator is responsible for taking inventory of the investigational agent (s) and providing secure storage at the CTP. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent(s) shall be returned to the sponsor (or responsible party) unless otherwise instructed.

13.4 Investigator Assurances

Prior to initiating the study, the Principal Investigator at each study site will sign a protocol signature page, providing assurances that the study be performed according to the standards stipulated therein. The original signed copy of this document will be sent to the Lead Investigator site for record keeping and a copy will be maintained in the site's regulatory binder.

13.5 Outside Monitoring

The NIDA-CTN Data and Safety Monitoring Board, NIDA-CTN contracted Clinical Monitors, representatives from the Lead Investigators Node, and Quality Assurance representatives from the participating Node, will be given access to facilities and records to review and verify data pertinent to the study.

A. Data and Safety Monitoring Board (DSMB):

An independent Data and Safety Monitoring Board (DSMB) will monitor the conduct of this trial. The Board will examine accumulating data to assure that the risks and benefits of participation remain acceptable and that the results of the trial will be considered scientifically reliable. The conditions under which the Board will examine this data are described below.

In accordance with the Board's SOP, presentation of primary and other efficacy outcome data and other data not intended to evaluate safety will be presented for all treatment groups combined, further broken down by study node and, if feasible, by CTP. No statistical penalty will be taken for this blinded interim analysis of efficacy data that will be conducted for the sole purpose of assessing the acceptability of safety results.

Adverse event data and other data intended for the monitoring of safety will be presented to the DSMB in an open-label fashion. Since the trial is not powered to demonstrate statistically significant differences in adverse events or other safety outcomes, p-values will not be calculated for any differences observed unless specifically requested by members of the Board to assist in the evaluation of a potential safety concern. No adjustments will be made for the number of interim analyses in the final report.

B. Clinical Monitors

All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to inform the sponsor of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that study medications are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and good clinical practice's guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the sponsor's representatives will be scheduled at appropriate intervals, more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will advise on storage of study records and return of unused study medication. All sites should anticipate visits by NIDA and the Lead Investigator's Protocol Team.

C. Quality Assurance

The primary goal of quality assurance is to protect the rights and safety of participants; and, to ensure that the study results are credible. The final document will provide specific guidelines developed for this protocol based on the QA Policy and Required Elements developed by the NIDA CTN QA Subcommittee. In general, 100% of the informed consent forms, 100% of Inclusion/Exclusion criteria, 100% of the primary outcome measures (smoking abstinence), all case reports forms for participants experiencing a serious adverse event, and all case report forms for the first 10 participants will be reviewed. A random 10% sample of the remaining participants will have all case report forms reviewed. In addition the randomization process will be reviewed at each

monitoring visit to ensure that the protocol procedures are being followed. Thus, it is expected that the case report forms for 16 or 17 participants will be reviewed in sites experiencing no serious adverse events. The Quality Assurance procedures to be covered during each monitoring visit, and a checklist for those activities, will be provided by the Lead Investigator Node to each participating site as a study operations manual.

13.6 Records Retention

Clinical records for all subjects studied including history and physical findings, laboratory data, audiotapes of counseling sessions, and results of consultations are to be maintained by the investigator in a secure storage facility. These records are to be maintained in compliance with IRB, State and Federal requirements, whichever is longest. It is the investigator's responsibility to retain copies of the completed case report forms until notified in writing by the sponsor.

13.7 Confidentiality Certificate

To further safeguard confidentiality, the NY node has obtained a Certificate of Confidentiality from NIDA.

13.8 Training

Protocol specific training are required for research staff directly involved in subject treatment and assessment. Three days of protocol training took place in New York City. Protocol training was attended by the CTP study RN or PA, 1-2 CTP study Research Assistants, participating Node Training and/or QA Specialists, and the participating CTN Node designated Study Investigator (Local PI). The Lead Investigator, Protocol Manager, NY Node Training Subcommittee representative, and a NY Node Data Management representative provided the training.

Smoking cessation counseling training and orientation to the counseling manual will be required for the designated Study Counselor from each CTP, and a participating CTN Node designated Counseling Supervisor. A back-up Study Counselor may also attend the counselor training, though this is not required. The role of the Counselor Supervisor is to monitor the smoking cessation counselors at each participating Node for adherence to the counseling program and to provide refresher training if necessary. In addition, the Counseling Supervisor will train replacement counselors when necessary. The smoking cessation counseling training took place in April 2002 in San Francisco, CA and involved 3 days of training and practice sessions. The Lead Investigator, NY Node Training Subcommittee representative, and the Counseling Manual Consultants Team directed training of counselors. The Counseling Manual Consultants Team has extensive experience with this smoking cessation program across a wide variety of nicotine dependent populations, and has trained numerous counselors on this program over the last 10 years. The Counseling Manual Consultants Team consists of: Sharon Hall, Ricardo Muñoz, Gary Humfleet, and Kim Norman. Training of replacement counselors will be performed at Node level and will involve a minimum of 1 day of training and 1 day of practice sessions with the Node Counseling Supervisor.

Study operations manuals, for counselor and protocol specific training, were provided by the Lead Investigator's Node to each participating site. In addition to protocol specific training, all study personnel having direct contact with research participants are

required to complete Good Research Practice training course provided by the local CTN Node. Research Assistants will be required to complete CAB training by the Node Training Expert on the ASI-Lite, Demographics, RBS, and DSM-IV assessments. Study investigators are also required to attend a training course for the responsible conduct of research involving human subjects. This program should be provided by the CTN Node host university or affiliate and must fulfill the Office for Human Research Protections (OHRP) requirements for human subject training for all research investigators. It includes review of the roles and responsibilities of the IRB, responsibilities of investigators, and institutional policies governing human subject research.

14.0 Reports

14.1 Safety and Efficacy

Clinical safety of all study participants will be monitored by weekly assessments of study medication compliance, use of concomitant medications, vital signs and weight, adverse and serious adverse events, and a urine pregnancy test (for females). For subjects receiving nicotine patches, at each study visit a study clinician will monitor the subject's topical reaction to the patch, and query the subject regarding heart fluttering or palpitations, insomnia or difficulty sleeping, and symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness, and rapid heart beat. If any side effect of the patch or symptom of nicotine overdose is reported, then it will be noted as an adverse experience and recorded on the appropriate CRF.

Subjects receiving nicotine patches, who also use prescription medication for hypertension, asthma, or depression, will consult with the study physician regarding dose adjustment as necessary.

Safety Reports will include data summarizing the total number of randomized subjects that have experienced medication related side effects: adverse topical reactions to the patch, irregular heart beat or palpitations, insomnia or sleeping problems, significant increase in blood pressure, and symptoms of nicotine overdose. All subjects receiving concomitant prescription medication for hypertension, depression, asthma will be noted and records of such dosing (including need and time of any dose changes) will be provided. The CTP investigator will provide safety reports, generated by the data management center of that CTP's sponsoring node, to the Lead Node Investigator on a semi-annual basis.

The DSMB is responsible for an efficacy-monitoring plan, which may be done as an interim analysis. This analysis will be based on the accrued data, which is forwarded on a monthly basis from each participating Node's Data Management group to the NIDA Data Repository.

14.2 Adverse Events Reporting.

In accordance with USDHHS reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the specific instructions detailed in this section of the

protocol. The occurrence of AEs will be assessed weekly during smoking cessation treatment and at the 9, 13 and 26 week post-TQD follow-up visits.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related or clinically significant (see Table 2). For this study, AEs will include events reported by the subject. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present (and documented) prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE Form. The AE Form is also used to record follow-up information for unresolved events.

Each week, a study investigator and/or CTP clinician (physician, nurse or physicians assistant) must review the AE Form completed for the previous week for any events that were reported as continuing. Study investigators will follow all AEs, regardless of severity, until satisfactory resolution. AEs may be reported up to 5 weeks following completion of smoking cessation treatment.

14.3 Serious Adverse Events (SAE)

A studyclinician (in consultation with the study physician) will classify each AE as serious or non-serious and will follow all appropriate reporting procedures. Serious adverse events (SAEs) are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, any congenital anomaly, or any event that requires intervention in order to prevent permanent impairment/damage. An unexpected event is one that is not described with respect to nature, severity, or frequency in the current PDR (2001) description for NicoDerm CQ.

The study physician will assess all SAE's prior to submitting reports to the Project Clinical Director, Lead Investigator, NIDA or the appropriate IRB. Any SAE (including death) due to any cause, which occurs during the course of this investigation, whether or not related to the investigational medication, must be reported within 24-hours by telephone, accompanied by a faxed copy of the initial SAE form, to one or more of the following individuals (in order of priority):

Paul Casadonte, M.D.,
New York V.A. Medical Center, 116A
423 E. 23rd Street
New York, NY 10010
phone: 212-686-7500 x7985
fax: 212-951-6891
e-mail : paul.casadonte@med.va.gov

Malcolm S. Reid, Ph.D.
New York V.A. Medical Center, 116A

423 E. 23rd Street
New York, NY 10010
phone: 212-686-7500 x7983
fax: 212-951-6891
e-mail: malcolm.reid@med.va.gov

John Rotrosen, M.D.,
New York V.A. Medical Center, 116A
423 E. 23rd Street
New York, NY 10010
phone: 212-686-7500 x7979
fax: 212-951-6891
e-mail: john.rotrosen@med.nyu.edu

CTN-0009 Protocol Manager, Frank Flammino, Ph.D.
New York V.A. Medical Center, 116A
423 E. 23rd Street
New York, NY 10010
phone: 212-686-7500 x4444
fax: 212-951-6891
e-mail: frank.flammino@med.nyu.edu

In addition, SAEs must be reported to NIDA within 24 hours to:

NIDA CCTN Medical Officer
Clinical Trials Network
National Institute on Drug Abuse
6001 Executive Boulevard, Rm 4234, MSC 9557
Bethesda, MD 20892
phone: 301-443-6697
fax: 301-443-2317

The telephone report is to be followed by receipt of a follow-up SAE Form with demographic information and a narrative explanation of the event within 2 weeks to all of the above listed individuals (this may be provided by fax, with copies in the mail). Attached to the SAE Form should be a cover letter and the Smoking Medication Compliance and the Medical and Psychiatric History forms from the

subject's CRFs. Unexpected serious medical events are also to be reported immediately to the responsible institutional review board according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to NIDA, the local institutional review board, and the study medication supplier, GlaxoSmithKline Consumer Healthcare.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with USDHHS regulations governing the reporting of SAEs. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA so that sponsor can comply with these regulations.

In the event that a study subject either withdraws from the study or an investigator decides to discontinue the subject from the study due to a SAE, the subject must have appropriate follow-up medical monitoring. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

15.0 Resources

Estimated costs per CTP are calculated with certain assumptions regarding subject attrition: an estimate of approximately 70% of screened subjects will become randomized (to get 72 randomized participants will require screening 103 subjects), of the 72 randomized subjects 65% will complete through week 8 and 40% will complete all follow-ups. In addition, in the control group (Group 1) approximately 50% will enroll in deferred smoking cessation treatment. The following information is offered as a guideline. Study budgets and staffing requirements will be finalized at the Node level.

A. Staff.

Additional staffing required at each CTP will include a Smoking Cessation Counselor (50%FTE), a Study Clinician, such as a nurse or physician assistant, necessary to screen subjects and evaluate clinical status on a weekly basis (RN: 25% FTE), and 1-2 Research Assistants to recruit, screen and assess subjects and manage data entry (1-2 x 100% FTE). A Study Physician should be available for consultation in the event of serious adverse events or study medication complications, but is not necessary for determining study eligibility. Each Node will provide a Smoking Cessation Counselor Supervisor who will monitor counseling quality and provide refresher and/or replacement training as necessary (5% FE).

B. Training

Protocol specific training will be required for research staff directly involved in subject treatment and assessment. Two to three days of protocol training will take place in New York City prior to study implementation. Protocol training will be attended by: the CTP study nurse or physicians assistant, 1-2 CTP study Research Assistants, participating Node Training and/or QA Specialists (optional), and the participating Node Study Investigator (Local PI). Smoking cessation counseling training and orientation to the counseling manual will be required for the designated Study Counselor from each CTP, and a Counseling Supervisor from each participating Node. A back-up Study

Counselor from each CTP may also attend, though this is not required. The smoking cessation counseling training will take place in April of 2002 in San Francisco with the assistance of the UCSF scientists whom developed this program. Subsequent training of individual CTP counselors will be performed at Node level and will involve a minimum of 1 day of training and 1 day of practice sessions.

C. Supplies and Equipment

Necessary research supplies/costs at each CTP include a computer, photocopier, tape recorder, assessment forms/copies, tapes, ballot box, counseling manuals and subject handouts, fax machine, blood pressure monitor, stethoscope, weight scale, CO monitor, Alcohol Breathalyzer, urine cotinine sampling supplies, Accutest urine toxicology kits, urine pregnancy test kits (@ 20 females/72 participants) and a standard freezer.

Note: Accutest urine toxicology kits, and urine pregnancy test kits (@ 20 females/72 participants) will be provided through a central NIDA CTN contract. These costs need not be covered by the CTP budget.

D. Services and Assays

Services and assay costs at each CTP include internet access, urine cotinine screens, and medication packaging and labeling services.

Note: Urine cotinine screens, and medication packaging costs will be provided by a central NIDA CTN contract. These costs need not be covered by the CTP budget.

E. Medication and Counseling Manual

Study medication will be provided free of charge from GlaxoSmithKline and the Smoking Cessation Counseling Program will be made available from the UCSF Habit Abatement Clinic and the authors Sharon Hall, Victor Reus and Ricardo Munoz free of copyright fees.

16.0 Protocol Signature Page

SPONSORS REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____

INVESTIGATOR (S)

- I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of subjects.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.
- I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.
- I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

Typed Name	Signature	Date
Principal Investigator _____	_____	_____
Sub-Investigator _____	_____	_____

Sub-Investigator

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THIS PAGE IS INTENTIONALLY LEFT BLANK **TABLE 1. TIME AND EVENTS SCHEDULE**

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Activity	Time (min)	Interviewer/ Provider	Pre-Screen	Screen	Base	Pre-TQD	Post-TQD								Follow-Up		
							-1	1	2	3	4	5	6	7	8	9	13
Study Week																	
CTP Smoking Survey	5	RA	X														
CTP Program Review	5	RA	X														
Drug Abuse Counseling		CTP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking Cessation Counseling	90	SC				2X	2X	X	X	X	X	X	X				
Smoking Cessation Medication		RA					X	X	X	X	X	X	X				
Screening/Safety Assessments																	
Informed Consent/Study Enrollment	30	RA	X														
Randomization	5	RA/NURSE			X												
Inclusion/Exclusion Checklist	5	RA/NURSE		X													
Demographics	15	RA		X													
DSM-IV Checklist/Addendum	25	RA/NURSE		X													
Medical and Psychiatric History	5	RA/NURSE		X													
Prior/Concomitant Medications	5-10	RA/NURSE		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Assessment	5	RA/NURSE		X	X+				X					X			
Vital Signs (incl. Weight)	5	RA/NURSE		X*	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	5	NURSE				X	X	X	X	X	X	X	X	X	X	X	X
Baseline Assessments																	
Beck Depression Inventory-II	5	P			X*				X					X		X	X
SF-36	5	P			X*									X		X	X
URICA	5	P			X*												
Smoking History Survey	10	RA		X													
Fagerström Test	5	P			X												
Risk Behavior Scale	10	RA			X									X		X	X
CURRY Reasons for Quitting	5	P		X*													
Smokers Beliefs Questionnaire	1	P			X												
Urine Cotinine	5	RA			X										X	X	
ASI-Lite	35	RA			X*									X		X	X
Treatment Outcome Assessments																	

Smoking Cessation Compliance	5	RA				X	X	X	X	X	X	X	X	X	X	X	X
Smoking Medication Compliance	5	RA					X	X	X	X	X	X	X	X	X		
Smoking Status/Exhaled CO	5	RA		X*		X	X	X	X	X	X	X	X	X	X	X	X
Withdrawal Scale for Tobacco	3	P				X	X	X	X	X	X	X	X	X	X		
Drug Rehabilitation Compliance	5	RA				X	X	X	X	X	X	X	X	X	X	X	X
Substance Use Report (SUR)	5	RA			X*	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug and Alcohol Breathalyzer	15	RA			X*	X	X	X	X	X	X	X	X	X	X	X	X
Brief Substance Craving Scale	3	P				X	X	X	X	X	X	X	X	X	X		
Study Termination†	5	RA/NURSE															X†

*These assessments need to be repeated if not performed within 21 days of randomization. +Performed on Day of Randomization, prior to Randomization. †To be performed at Week 26 or final visit if discontinued early.

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Table 2. Instructions for Evaluating and Reporting Adverse Events

A. General Instructions

The Adverse Events (AE) form must be completed at each study visit.

If no new AEs occur, answer the question as “no”, sign and date form.

Enter all AEs that occur during the study.

Enter only **one** AE per form.

Record the patient’s description of the event, including all signs/symptoms reported.

Report the severity of the event according to the grading scale below.

Report the relatedness of the event to the study intervention (see section C. below for guidance in determining relatedness).

B. Definitions – Severity of Events

1 = Mild: Awareness of symptom, but easily tolerated.

2 = Moderate: Discomfort enough to cause interference with usual activity.

3 = Severe: Incapacitating with inability to work or do usual activity.

C. Definitions – Relatedness of Events

Study clinician (nurse or physician assistant) must review the information and offer an educated opinion about the relatedness of the event to the study intervention. Do not use ‘UNKNOWN’ unless there is absolutely no information available upon which to base an opinion. Do not leave blank. Use codes provided:

1 = **Definitely** – The adverse event:

- a) Follows a reasonable temporal sequence from drug administration/initiation of study intervention.
- b) Abates upon discontinuation of the drug (de-challenge).
- c) Is confirmed by reappearance of the reaction of repeat exposure (re-challenge).

2 = **Possibly** – The adverse event:

- a) Follows a reasonable temporal sequence from drug administration/initiation of study intervention.
- b) Could have been produced by the patient’s clinical state or by other modes of therapy administered to the patient.

3 = **Definitely not** – The adverse event is definitely produced by the patient’s clinical state or by other modes of therapy administered to the patient.

9 = **Unknown**