CTN-0013

Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Users

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ANCOVA	Analysis of Covariance
ASI-Lite	Addiction Severity Index - Lite
CRF	Case report form
CTN	Clinical Trials Network
CTP	Community treatment program
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
HIV	Human immunodeficiency virus
IRB	Institutional review board
MET	Motivational enhancement therapy
NIDA	National Institute on Drug Abuse
RA	Research assistant
RBS	Risk Behaviors Survey
SIP-R	Short Inventory of Problems – Revised
TAU	Treatment as usual

2.0 STUDY SYNOPSIS AND SCHEMA

2.1 STUDY SYNOPSIS

STUDY OBJECTIVES: The primary objective of this protocol is to evaluate the efficacy of Motivational Enhancement Therapy (MET), compared to treatment as usual (TAU), in increasing treatment utilization in pregnant substance users. Secondary objectives include evaluating the efficacy of MET, compared to TAU, in decreasing substance use and HIV risk behaviors and evaluating the relationship of process and outcome measures to treatment utilization and substance use.

STUDY DESIGN: This is a randomized, parallel, two group study comparing MET to TAU for pregnant substance users. Pregnant women identified as needing substance abuse treatment by the participating CTPs will be randomly assigned to either MET or TAU. The active study phase will be four weeks in duration. Follow up assessments will be conducted at 4 and 12 weeks following the end of the active study phase.

STUDY POPULATION: A total of 200 pregnant substance users, recruited from four CTPs, will be randomized to either MET or TAU.

TREATMENTS: Participants assigned to MET will be offered three MET sessions: an intake session and two individual treatment sessions. These sessions will replace the intake session and the first two individual treatment sessions typically offered at the CTP. MET participants will be encouraged to participate in the other treatment services typically offered at the CTP (e.g., group treatment, etc.). Participants assigned to the TAU condition will be offered the standard

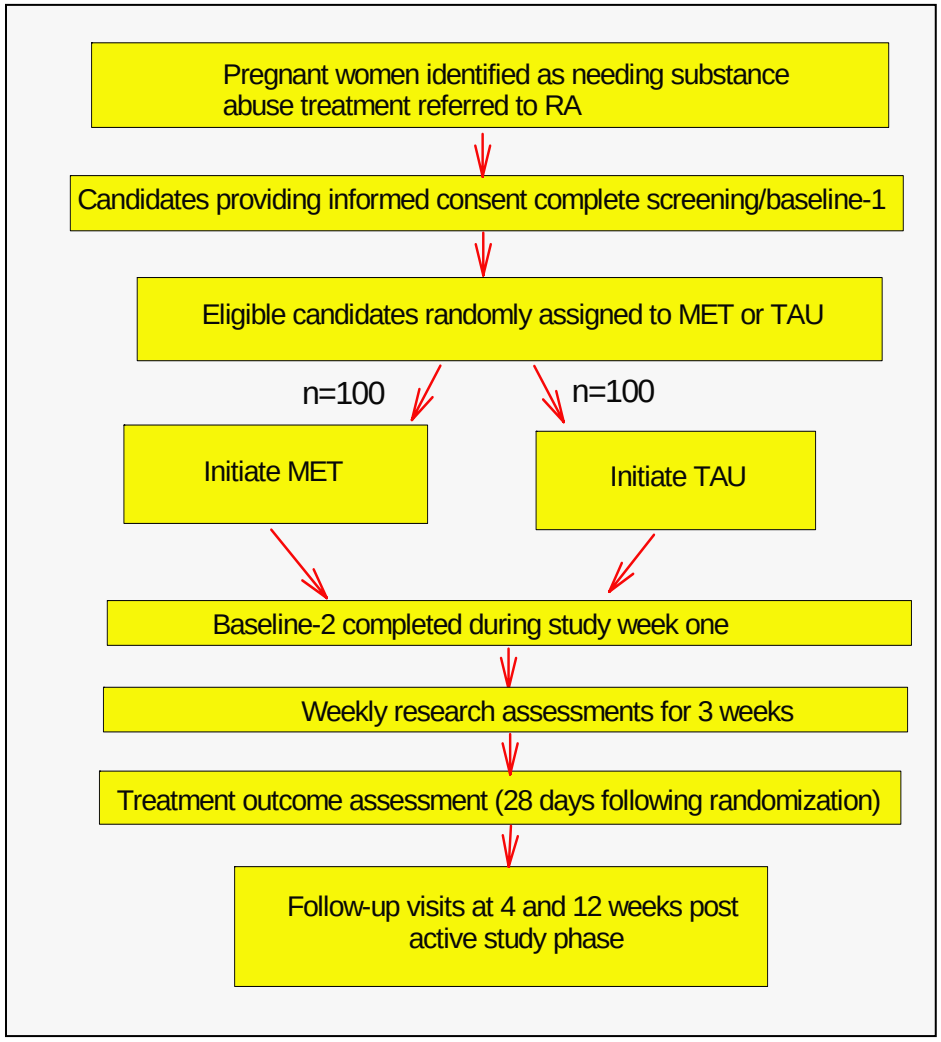
treatment provided by the CTP with the constraint that they are offered at least three individual sessions, including the intake session.

EFFICACY ASSESSMENTS: The primary outcome measure will be treatment utilization (defined as the percent of scheduled treatment hours attended). Secondary outcomes will include substance use, initial engagement into substance abuse treatment, utilization of prenatal care, commitment to abstinence, HIV risk behaviors, and participant satisfaction. Process assessments will include measures of the therapeutic alliance and clinician adherence and competence.

ANALYSIS: Each primary and secondary outcome variable will be analyzed using appropriate statistical methods for the intent-to-treat population. Statistical tests will be two-sided at a 5% Type I error rate for primary outcome analyses and at 1% for secondary outcome analyses.

2.2 STUDY SCHEMA

Figure 1: Study Schema



3.0 BACKGROUND AND SIGNIFICANCE

An estimated 5% of women use illicit substances during pregnancy, with approximately 22% of illicit substance users also reporting the use of tobacco or alcohol (National Institute on Drug Abuse, 1996). The prenatal, neonatal, and postnatal complications associated with illicit and licit substance use during pregnancy represents a major public health care concern (Svikis et al., 1996). In addition, pregnant substance abusers report substantial engagement in behaviors that increase the risk of contracting HIV (Haller et al., 1993). A number of treatment programs have started to offer treatment specifically designed for pregnant substance abusers (Svikis et al., 1997). While these programs generally have greater success rates, compared to programs that do not make provisions for the needs of pregnant women (Chang et al., 1992; Weisdorf et al, 1999), treatment retention continues to be problematic (Haller et al., 1997).

Efforts to increase treatment retention rates are based, in part, on the inverse relationship found between length of treatment received and substance use in the first year following treatment (Simpson et al., 1999). In addition, there is evidence to suggest that longer treatment retention of pregnant substance users is associated with decreased substance use and better birth outcomes (McMurtie et al., 1999). Increasing treatment utilization has thus been identified as an important goal for programs treating pregnant substance users (Howard & Beckwith, 1996).

Brief motivational interventions have been found to increase treatment engagement and improve outcomes in both alcohol (Bien et al., 1993) and drug (Saunders et al., 1995; Swanson et al., 1999, Martino et al., 2000) using samples. While the effectiveness of brief motivational interventions has been studied primarily in problem alcohol users, several studies have evaluated the effectiveness of these interventions for drug users. Saunders et al. (1995) evaluated the effectiveness of a brief motivational intervention for opiate-addicted individuals entering a methadone program. The results indicated that a motivational intervention of approximately one hour in length, compared to a one hour education control condition, resulted in significantly longer treatment retention and fewer self-reported opiate problems at six month follow up (Saunders et al, 1995). A study of the effectiveness of motivational interviewing for dually diagnosed patients found that the addition of an approximately one hour motivational interview prior to discharge from an inpatient setting significantly increased the proportion of patients attending their first aftercare appointment (Swanson, et al., 1999). A small study conducted with dual diagnosis patients in a partial hospitalization program found that a 45 – 60 minute motivational interview, compared to the standard admission interview, significantly improved treatment participation (Martino et al., 2000). Finally, Carroll et al. (2001) reported that, in participants referred for substance abuse evaluation through child protection services, augmenting the evaluation with motivational interviewing techniques resulted in significantly more patients attending an initial substance abuse treatment session.

To our knowledge, there have been two evaluations of brief motivational interventions in pregnant substance users. The first involved an evaluation of motivational interviewing in reducing alcohol consumption in a primary care sample of pregnant women (Handmaker et al., 1999). The findings suggest that a one-hour motivational interview, compared with letters informing control participants of the risks of drinking during pregnancy, seemed to significantly benefit the women who had reported drinking the most during the initial interview. Specifically, this subgroup of women assigned to the MI condition reported significantly lower levels of intoxication at the two month follow up than did comparable participants in the control group.

The second study evaluated the efficacy of motivational enhancement therapy and vouchers, vouchers alone, and standard treatment in engaging non-treatment seeking pregnant substance users in substance abuse treatment. Preliminary analyses suggest that the MET plus vouchers condition, compared to standard treatment, was associated with higher birth weights for the infants and fewer positive toxicology screens at delivery for the study participants (H. Jones, personal communication, October 2, 2001).

The present study will evaluate the efficacy of a three session individual MET intervention, compared to TAU, in increasing treatment utilization and decreasing substance use in pregnant substance users.

4.0 STUDY OBJECTIVES

4.1 Primary objectives

1. To evaluate the initial efficacy of MET, relative to TAU, in increasing treatment utilization in pregnant substance users through a four week treatment period.

4.2 Secondary objectives

1. To evaluate the longer-term efficacy of MET, relative to TAU, in increasing treatment utilization through a 3-month follow-up.

2. To evaluate the initial efficacy of MET, relative to TAU, in decreasing substance use in pregnant substance users.

3. To evaluate the longer-term efficacy of MET, relative to TAU, in decreasing substance use through a 3-month follow-up.

4. To evaluate the efficacy of MET, relative to TAU, in reducing HIV risk behaviors associated with a substance abusing life style.

5. To evaluate the relationship of process (e.g., therapeutic alliance, clinician adherence) and outcome (e.g., participant satisfaction level, participant's commitment to abstinence and perceived ability to obtain abstinence) measures to treatment utilization and substance use.

5.0 STUDY DESIGN

5.1 Overview of study design

This is a randomized, parallel, two group study comparing MET to TAU for pregnant substance users. The active study phase will be four weeks in duration and there will be two follow-up visits, one at 4 weeks and one at twelve weeks after the end of the active study phase. The primary outcome measure will be treatment utilization (defined as the percent of scheduled treatment hours attended). Secondary outcomes will include substance use, initial engagement into substance abuse treatment, utilization of prenatal care, commitment to abstinence, HIV risk

behaviors, and participant satisfaction. Process assessments will include measures of the therapeutic alliance and clinician adherence and competence.

5.2 Number of sites and participants

This is a small-scale trial to evaluate the efficacy of MET, relative to TAU, in increasing treatment utilization in pregnant substance users. A total of approximately five CTPs will participate in this initial study. The target sample size is 200 participants. Ideally, each site will enroll between approximately 30 and 90 participants. This flexibility in the number of enrolled participants will allow sites with smaller patient populations to participate in the protocol.

5.3 CTP, participant, and clinician selection

5.3.1 CTP Selection

5.3.1.1 CTP characteristics

Participating CTPs should:

1. have a program targeting pregnant substance users, which seeks to remove traditional barriers to care for this population (e.g., provision of child care, transportation, case management, etc.)

2. see enough pregnant substance users to recruit a minimum of approximately 30 participants within an eighteen month timeframe

3. have at least four clinical staff members willing to participate in this protocol (i.e., 2 for MET and 2 for TAU)

5.3.1.2 Rationale for CTP selection

This protocol is targeting programs that have removed traditional barriers to care for pregnant substance users since increasing patients' motivation for treatment in the context of a program that has barriers to care is unlikely to yield positive outcomes. In other words, if the intervention does succeed in increasing a patient's motivation for treatment but that treatment is not readily available then patient dissatisfaction is most likely to be the end result.

This protocol will include CTPs that offer treatment in a variety of outpatient settings including methadone maintenance programs. This allowed variability in treatment settings is based on the difficulty of engaging pregnant substance users into treatment regardless of the treatment setting.

The requirement of at least two clinicians per condition stems from the need to provide coverage for the study (e.g., covering for sick and vacation leave, termination of employment, etc.). In addition, having at least two clinicians per condition will enable a differentiation between possible clinician and site effects.

5.3.2 Participant Selection

5.3.2.1 Inclusion/exclusion criteria

To be eligible as a training case for the study, an individual must:

1. be pregnant, as confirmed by a positive urine pregnancy test, and not planning to terminate the pregnancy
2. be identified as needing substance abuse treatment via the CTP's usual screening procedure or is already in treatment at the CTP
3. be 18 years of age or older
4. be willing to participate in the protocol (e.g., to have their sessions audiotaped, etc.)
5. be able to understand and provide written informed consent in English
6. be willing to sign a release(s) of information to allow research staff access to the portions of her clinical record(s) required for data collection (e.g., treatment attendance at the CTP, etc.)

Individuals will be excluded who:

1. are a significant suicidal/homicidal risk
2. are more than 34 weeks pregnant

To be eligible for the study, an individual must:

1. be pregnant, as confirmed by a positive urine pregnancy test, and not planning to terminate the pregnancy
2. be identified as needing substance abuse treatment via the CTP's usual screening procedure
3. be 18 years of age or older
4. be willing to participate in the protocol (e.g., to be randomized to treatment, to have their sessions audiotaped, etc.)
5. be able to understand and provide written informed consent in English
6. have a living arrangement of sufficient stability to allow for outpatient treatment
7. be willing to sign a release(s) of information to allow research staff access to the portions of her clinical record(s) required for data collection (e.g., treatment attendance at the CTP, etc.)

Individuals will be excluded who:

8. plan to relocate from the area within four months of signing the study consent form
9. have pending legal charges, other than those requiring the participant to attend treatment, that might lead to incarceration
10. self-report having a condition(s) (e.g., medical complications, psychological problems, etc.) that would necessitate residential/inpatient treatment (excluding detoxification) and willingness to attend such treatment or self-report having a condition that would make study participation difficult
11. are a significant suicidal/homicidal risk
12. are more than 32 weeks pregnant

5.3.2.2 Rationale for participant inclusion/exclusion criteria

The inclusion/exclusion criteria for the study participants (i.e., excluding the training cases) are designed to exclude patients who are likely to be referred to inpatient/residential treatment. Otherwise, relatively broad inclusion criteria are proposed to allow for a representative sample of this already limited population. Participants under the age of 18 have been excluded because at many CTPs the resources devoted to minors differ significantly from those devoted to adults and, thus, minors represent a separate population. Moreover, for non-emancipated minors, a guardian's consent for study participation must be obtained; this is likely to be complicated for pregnant minors who frequently do not wish to disclose the fact of their pregnancy to their guardians.

5.3.3 Clinician selection

The educational background, credentials, and experience of the clinical staff implementing the intervention will vary between CTPs. The term "clinician" as used in the present protocol does not imply a particular educational background or credentialing. Rather, it is used as a short-hand term to refer to the clinical staff members administering the treatment.

5.3.3.1 Inclusion/exclusion criteria

Clinicians will be eligible for the protocol who:

1. have experience working with pregnant substance users and/or have been trained to work with pregnant substance users
2. are willing to learn and implement a manualized version of MET
3. are willing to be randomly assigned to either the MET or TAU condition
4. are willing to have their sessions audiotaped and then reviewed by a Protocol MET supervisor and/or Independent Rater, to participate in regular supervision sessions, and to complete process ratings (e.g., ratings of the therapeutic alliance) for the duration of the protocol
5. are approved by the CTPs administrative/supervisory staff as appropriate for the study (e.g., reliable, competent, likely to be with the CTP for the duration of the study)

Clinicians will be excluded who:

6. have received credentialing as a MET trainer or who have served as MET clinicians in a prior clinical trial

Clinicians who have received credentialing as MET trainers or who have served as MET clinicians in a previous clinical trial are excluded due to the possibility of their being randomly assigned to the TAU condition, which could lead to MET techniques being included in the TAU sessions. During initial clinician selection, all clinicians who meet the criteria above and are interested in participating in this protocol will be randomly assigned to provide MET or TAU. Random assignment to treatment condition will help ensure the comparability of the clinicians implementing the two treatment conditions. Given the high attrition rates for clinicians at community treatment programs, it is likely that additional clinicians will need to be recruited to replace a study clinician. In these cases, if at all possible, at least two clinicians that meet the inclusion/exclusion criteria outlined above will be identified and one of these clinicians will be

randomly selected to replace the clinician who is not longer participating in the study. For example, if a study clinician from the MET condition is no longer able to participate in the protocol, then a replacement clinician will be randomly selected from two or more eligible clinicians to serve as a MET clinician. If the clinicians assigned to TAU wish to receive training in MET, this training will be provided once data collection for the study has been completed.

5.4 Outcome Measures

5.4.1 Primary Outcome Measure

5.4.1.1 Treatment Utilization

This study will include participants who are referred to a variety of outpatient treatment programs, encompassing both outpatient and intensive outpatient settings and drug-free and opiate replacement programs. The primary outcome measure of treatment utilization will be the percent of scheduled treatment hours attended during the active study phase. Attendance of the intake session, either MET or TAU, will not be counted in the hours of treatment attended. Any treatment session, including the MET sessions, attended after the intake session will be included in the hours of treatment attended. The treatment groups will not differ in the number of available treatment hours. Attendance of the research assessment visits, which will be scheduled independently from the treatment visits, will not be scored as treatment hours. Determination of the hours scheduled and the hours attended will be based on the clinic's records.

5.4.2 Secondary Outcome Measures

Substance Use

Several measures of substance use will be collected in this study:

• Urine Toxicology Screens
A rapid urine screen system that screens for opiates, cocaine, methamphetamines, benzodiazepines, and marijuana will be used to analyze the urine samples collected. Urine samples will be collected using temperature monitoring to help ensure the validity of all samples. Urine samples will be obtained at screening, weekly during the active study phase, and at the two follow-up visits.

• Alcohol Breathalyzer
An alcohol breathalyzer will be completed at screening, weekly during the active study phase, and at the two follow-up visits.

• Substance Use Calendar
The RA will use the Substance Use Calendar to record the participant's self-reported substance use. The substances to be assessed include alcohol, cocaine, marijuana, opioids, benzodiazepines, methamphetamine, 'other' illicit drugs, and cigarettes. The Substance Use Calendar assesses whether or not the participant used these substances on each day within a given timeframe. The Substance Use Calendar will be completed at screening for the 28 days

prior to screening, weekly for each day of the active study phase, and at the 4 and 12 week follow up visits for the 28 and 56 days, respectively, prior to each follow up visit.

ASI-Lite
The ASI-Lite is derived from the Fifth Edition of the ASI, a structured clinical interview that yields scores for seven areas of functioning (McLellan et al., 1992). The ASI-Lite will ideally be completed at baseline-2 but will assess the 30 days prior to randomization. Information from the ASI-Lite will be included in the Personal Feedback report presented to the participant during the second MET session. The ASI-Lite follow-up will be completed at the end of the active study phase, and at the 4 and 12 week follow up visits.

Risk Behaviors Survey
The Risk Behaviors Survey (RBS) is an interviewer-administered assessment of the participant's engagement in activities that increase the likelihood of contracting HIV. The RBS will be completed at baseline-2, at the end of the active study phase, and at the 4 and 12 week follow up visits. The assessment completed at baseline-2 will assess activities prior to randomization.

Commitment to Abstinence
Participants' commitment to abstinence will be assessed with the Thoughts about Abstinence assessment (Hall et al., 1991), modified to assess the participants' thoughts related to alcohol, illicit drugs, and cigarettes. This measure assesses the participant's desire to quit, expected success in quitting and estimated difficulty in avoiding relapse. In addition, it assesses the client's goal for her use ranging from no goal to complete abstinence for life. Significant increases in commitment to abstinence, as measured by this instrument, have been found for participants assigned to Motivational Interviewing compared to standard treatment (Saunders et al., 1995). The Thoughts about Abstinence assessment will be completed at screening and at the end of the active study phase.

URICA
The University of Rhode Island Change Assessment (URICA) (DiClemente & Hughes, 1990) will be used to assess the participants' motivation to change their substance use behavior. The URICA will be completed at baseline and at the end of the active study phase.

Initial Treatment Engagement
Initial treatment engagement is defined as attending at least the initial appointment for the treatment program that the participant is referred to on the basis of the MET or TAU intake session. This first appointment can be attended any time between the completion of the intake session and the completion of the treatment outcome assessment visit. Attendance of any treatment session, including the MET sessions, will be scored as treatment attendance. The treatment groups will not differ in the number of <u>available</u> treatment visits. Attendance of the research assessment visits, which will be scheduled independently from the treatment visits, will not be scored as treatment attendance. Determination of attendance will be based on the clinic's records of treatment attendance.

Weekly Attendance
The number of weeks in which the participant attended at least one treatment session will be assessed. Attendance of the intake session, either MET or TAU, will not be counted as having attended treatment for the week. Any treatment session, including the MET sessions, attended

after the intake session will be scored as treatment attendance. The treatment groups will not differ in the number of available treatment visits. Attendance of the research assessment visits, which will be scheduled independently from the treatment visits, will not be scored as treatment attendance. Determination of attendance will be based on the clinic's records of treatment attendance.

Prenatal Care Utilization
Participant's self-report of scheduled and attended prenatal visits will be assessed weekly by the RA using the Treatment Tracking form. The RA will request that the study participant sign a release of information for her prenatal clinic so that the participant's self-report can be compared with clinic records. The outcome measure of interest will be the percent of scheduled visits attended.

Participant Satisfaction
Participants' satisfaction with treatment will be assessed with a measure derived from measures utilized in Project MATCH and the CSAT multisite marijuana treatment trial. Participant satisfaction will be assessed at the final visit of the active study phase.

Interventions for Non-treatment Attendance
There will be site-specific standard operating procedures detailing the interventions (e.g., calls, visits, etc.) to be made when a study participant misses a treatment appointment. The number and length of interventions made by clinical staff will be assessed weekly.

Pregnancy Assessment
The participant's engagement in activities that are important for a healthy pregnancy will be assessed. The information obtained will also be included in the Personal Feedback report.

5.4.3 Process Measures

Therapeutic Alliance
The strength of the therapeutic relationship will be assessed through the revised Helping Alliance Questionnaire (HAq-II, Luborsky et al., 1996). This assessment will entail the completion of both a clinician and client version of this measure. The HAq-II will be completed after the second MET/TAU session.

Clinician Adherence and Competence
The current study will utilize the adherence and competence instruments developed for use in the CTN 0004 protocol. The instruments developed for the CTN 0004 protocol were based on well-validated instruments including those used in Project MATCH (Carroll et al., 1998).

5.5 Other Measures

5.5.1 Participant Measures

Demographics

This assessment will include questions about the participant's ethnicity, age, employment status, education, and substance use.

Biopsychosocial Functioning
The Biopsychosocial Functioning Assessment will be used to assess each study candidate's self-reported status on six of the study inclusion/exclusion criteria.

Diagnostic Interview
A DSM-IV diagnostic interview will be completed with each study participant. This interview will be used to determine whether potential participants meet DSM-IV criteria for substance abuse or dependence. If sample size allows, a subgroup analysis comparing outcomes for those who do not meet criteria, meet abuse criteria, and meet dependence criteria will be conducted.

Short Inventory of Problems – Revised
To assess the participant's perception of the adverse consequences of her substance use, a short version of the Short Inventory of Problems (SIP-R), will be administered at baseline and at the end of the active study phase. The SIP is modified from the Drinker Inventory of Consequences (DrINC) (Miller et al., 1995), for use with drug users. Its psychometric properties have been found to be acceptable in previous trials (Miller et al., 1995). The baseline information from this instrument will be included in the MET Personal Feedback report.

Treatment Services Review
The types of treatment services received by participants will be assessed weekly with the use of a modified version of the Treatment Services Review (McLellan et al., 1992). This measure will be modified to include information about sessions in which child protective service issues were discussed with participants who have an active child protective services case.

Pregnancy Status
The status of the participant's pregnancy will be assessed at the three month follow-up. This will include questions about whether the participant is still pregnant and, if not, when the pregnancy ended and why it ended (e.g., gave birth, miscarried, etc).

5.5.2 Clinician Measures

Clinician Survey
A substantial amount of treatment outcome variance can often be attributed to clinician effects (Crits-Christoph and Mintz, 1991). It is thus important to characterize the clinicians who participate in the clinical trial. This information will include the clinician's demographic characteristics, years of clinical experience, and training background. The clinician will complete this measure prior to being assigned study patients.

Treatment Session Summary
The Treatment Session Summary will include questions about several important session parameters (length, primary focus, etc.) as well as serving as a checklist for tasks that the clinician needs to complete (e.g., recording the session, etc.).

5.6 Randomization Plan

Randomization of participants will be completed at each CTP. This randomization will be balanced for three dichotomous variables: pressure to attend treatment, self-report of drug and alcohol use, and need for methadone maintenance. Pressure to attend treatment is defined as having jail, the removal of a child (or children), or the removal of housing as the consequence of not attending treatment. The self-report of use variable will be operationalized as the number of days in the past 28 that the participant reports using alcohol and/or drugs (<10 or ≥ 10 days of use in the last 28 days). The third variable, need for methadone maintenance, will be determined by the participant's self-report of substance use and the treatment referral practices followed at the CTP. Balancing for these variables will be accomplished via urn randomization, an algorithm that offers a compromise between complete randomization and strategies that offer complete balance but which can introduce other biases (Lachin et al. 1999). The procedure for completing urn randomization will be that used in CTN-0004. Specifically, urn randomization will be completed by the RA at each CTP with the use of an Access program (or comparable system).

6.0 TREATMENTS

6.1 Treatment as Usual

Participants assigned to TAU will be offered the treatment typically provided at the CTP with the constraint that they receive at least three individual sessions with a clinician, including the intake session. These participants will also be offered the other services typically provided by the CTP (e.g., group treatment, additional individual treatment, case management, etc.). The three individual sessions will be audiotaped to allow for quality assurance checks of the study treatments. The first TAU session will be approximately an hour and a half to two hours in length while the other two sessions will be approximately an hour in length.

6.2 Motivational Enhancement Therapy

The MET intervention is comprised of the brief motivational techniques described by Miller and colleagues (Miller and Rollnick, 1991; Miller, 1999). The MET intervention for this study is based on the MET intervention used in CTN-0004 but has been specifically modified for pregnant substance users. The MET intake session will begin by developing rapport through the use of open ended questions, reflective listening, affirming the participant, and summarizing what the participant has said. In addition, the participant's perceived pros and cons of using substances will be explored. The remainder of the session will be devoted to the clinic's usual assessment and intake procedures. The second session will be devoted to reviewing the participant's individualized personal feedback report concerning the consequences of substance use and the status of her pregnancy. The third session will be devoted to developing a change plan for participants who have expressed a readiness to change and strengthening commitment to change in participants who are not yet ready to change. These three sessions will replace the intake session and the first two individual treatment sessions typically offered by the CTP. The first MET session will be approximately an hour and a half to two hours in length while the other two sessions will be approximately an hour in length. Participants in the MET condition will be encouraged to participate in the other treatment services typically offered at the CTP (e.g., group treatment, case management, etc.).

6.3 Treatment Plans

Each participant will have a treatment plan, which will recommend the current level of treatment for that participant. It will specify the current recommended length and frequency of visits. The treatment plan will be determined at each CTP by its usual assessment procedures. Treatment providers at each CTP will be responsible for monitoring participants for possible clinical deterioration or lack of improvement, and for recommending appropriate changes to the treatment plan.

6.4 Treatment Measures

Clinician treatment adherence and competence

In order to test the efficacy of MET compared to TAU, it must be established that the MET and TAU sessions could be distinguished from each other. This check on therapy will be completed by having raters who are blind to clinician treatment assignment rate the sessions. The current study will utilize the adherence and competence instruments developed for use in the CTN 0004 protocol. The rating of tapes by blind raters will most likely occur after participant recruitment has been completed. During the study, the study sites will send the audiotapes to the lead node, where the tapes will be stored in a locked cabinet. Randomly selected tapes will be sent to the blind raters for evaluation and then sent back to the lead node. The audiotapes will be destroyed by the lead node once the blind raters have completed their evaluation of the tapes. It is estimated that the evaluation by the blind raters will be completed within 8 months of the last participant's completion of the trial.

6.5 Quality Control of Treatments Administered

Quality control for MET implementation will be conducted via the ongoing review of audiotaped sessions by the Protocol MET supervisor. Randomly selected tapes will be sent to the MET Protocol supervisors for rating and then returned to the lead node. Any clinician identified as performing below the standards set for this protocol will be given additional training and more intense supervision until he or she meets or exceeds standards; if the clinician is unable to meet protocol standards then he or she will not be assigned additional cases.

7.0 STUDY PROCEDURES

7.1 Overview of study assessments

Table 1 provides an overview of the participant procedures and assessments. Table 2 provides an overview of the assessments that involve the MET/TAU clinicians.

Table 1: Schedule of Participant Assessments and Procedures

Assessment/ Procedure	Screening/ Baseline-1/ Enrollment	Active Study Phase				Tx Out-come Asses	Follow-Up	
Time (Study day)*	1	2-7	8-14	15-21	22-28	29-35	57-84	113-140
Study Visit	00	01	02	03	04	05	06	07
Approx Visit length (minutes)	115	120	35	35	35	105	70	70
MET/TAU	X**	**Need to complete all 3 MET sessions within 4 weeks**						
Screening Assessments								
Informed consent	X							
Urine pregnancy test	X							
Study Eligibility form	X							
Randomization form	X							
BiopsychFunct	X							
Audiotape consent	X							
Efficacy Assessments								
Treatment Tracking			X	X	X	X	X	X
Substance Use Calendar	X		X	X	X	X	X	X
Urine Toxicology	X		X	X	X	X	X	X
Breathalyzer	X		X	X	X	X	X	X
Thoughts about Abstinence	X					X		
ASI- Lite		X				X	X	X
Risk Behaviors Survey		X				X	X	X
URICA	X					X		
Pregnancy Assessment	X					X		
Process Assessments								
HAq-II			X♦					
Other Assessments								
Demographics	X							
Locator Information	X					X	X	
Diagnostic Interview		X						
SIP-R	X					X		
Treatment Services Review			X	X	X	X		
Pregnancy Status						X		X
Participant Satisfaction						X		

* The study days on which a particular visit can be completed, each visit will be scheduled as early as possible; **Ideally, a MET/TAU session will occur at the initial study visit but this initial session can occur at subsequent visits. ♦The HAq-II will be completed after the second MET/TAU session.

Table 2: Assessments Related to MET/TAU Clinicians

Assessment	Purpose	Collection Schedule
Clinician Eligibility form	Document clinician study eligibility	Pre-study initiation
Clinician Survey	Characterize the participating clinicians	Pre-study initiation
Treatment Session Summary	Checklist for tasks that the clinician needs to complete; description of session	Completed for each MET/TAU session
Supervisor Tape Rating	Quality control checks of MET sessions	Completed for each audiotaped session reviewed by a MET Protocol Supervisor
Supervision Record	Documentation that supervision was provided as outlined in protocol	Completed each time supervision is provided to MET clinicians
HAq-II (clinician)	Measure of therapeutic alliance	Completed after each study participant's second MET/TAU session
Independent Tape Rating	Treatment Integrity Check	Completed for each audiotaped session reviewed by Independent Rater

7.2 Screening/Study Enrollment

Pregnant women identified as needing substance abuse treatment will be referred to the RA. After signing the Informed Consent Form, the study candidate will complete screening and baseline-1. Ineligible individuals will continue into the CTP's standard intake assessment and treatment program. Study participants will ideally attend the initial treatment session (MET or TAU) immediately following randomization. In order to avoid overwhelming participants on this initial visit, a minimal number of instruments will be completed prior to enrollment and randomization. The remaining measures for which a baseline is needed will be collected at the second study visit, which ideally will take place within seven days of the initial visit.

7.3 Active Study Phase

The active study phase is four weeks in duration. During this time, participants in both treatment conditions will be offered at least three individual sessions with a clinician. The first individual session must be completed by study day seven in order for the participant's data to be included in the primary data analysis. There is a 28-day time frame, starting from enrollment, for the participant to receive the three MET/TAU sessions with the constraint that no more than two sessions are allowed in a single business week. In addition to receiving MET, MET participants will be offered the treatment normally provided by the CTP. Participants in the TAU condition will be offered the treatment typically provide by the CTP with the constraint that they will be offered at least three individual sessions, including the intake session. Participants in both conditions will meet with the RA weekly to complete study assessments as outlined in Table 1, with the constraint that there must be at least two days between the urine toxicologies performed

for a given participant for the research study. The treatment outcome assessment will be completed after the end of the active study phase.

7.4 Follow-up

Follow-up visits will be conducted at 4 and 12 weeks following the active study phase. The measures to be collected during the follow-up phase are delineated in Table 1. Attempts will be made to complete follow up visits with all participants who enroll into the study. There will be a 28-day time frame in which to complete each follow-up visit (i.e., between weeks 4 and 8 for follow-up one and between weeks 12 and 16 for follow-up two).

7.5 Participant Reimbursement

Participants will be reimbursed for their transportation, inconvenience, and time. This reimbursement will be in the form of retail scrip or vouchers. It is recommended that participants receive $30 for longer research visits (i.e., visits 00, 01, 05 and each of the two follow-up visits) and $25 for the shorter research visits (i.e., visits 02, 03, and 04). However, participant reimbursement might vary across study sites to take into account local IRB guidelines, as well as special circumstances and geographic differences across sites. The Lead Node should be informed of any changes in level of participant reimbursement.

8.0 REGULATORY AND REPORTING REQUIREMENTS

8.1 IRB Approval

Prior to initiating the study, the 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 each IRB for approval prior to implementation. Annual progress reports and local Serious Adverse Event reports will be submitted to each IRB, according to its usual procedures.

8.2 Informed Consent

All potential study participants will be given a current copy of the Informed Consent Form. At sites requiring consent forms for clinicians, each potential study clinician will be given a current copy of the clinician Informed Consent form. For both study participants and clinicians, all aspects of the study will be explained in lay language and all of the candidate's questions will be answered. A brief "comprehension tool," in which the candidate is asked about important elements of the study (e.g., study participation is voluntary, etc.), will be completed and discussed before the candidate signs the Informed Consent Form. Candidates who appear to be incapable of understanding the basics of the study will be excluded from study participation. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

8.3 Clinical Monitoring

Study Medical Monitors:

All study participants will be enrolled in treatment at one of the participating CTPs. Each of these CTPs has an established program for treating pregnant substance users. Within this larger treatment context, the participants will attend either three sessions of MET or three sessions of TAU and will meet with an RA for study measures. Each of the CTPs has established practices for managing medical and psychiatric emergencies and the study staff will be trained to utilize these procedures. The treatment plan for a given participant will be determined at each CTP by its usual assessment procedures. Treatment providers at each CTP will be responsible for monitoring participants for possible clinical deterioration or lack of improvement, and for recommending appropriate changes to the treatment plan.

The LI has appointed a medical monitor for this study, who will review or provide consultation for the LI's review of each Serious Adverse Event (SAE). These reviews will include an assessment of the possible relatedness of the Event to the study intervention or other study procedures. The medical monitor will also provide advice for decisions to exclude, refer, or withdraw subjects for medical reasons. For any adverse event that is related to the trial, a qualified clinician will ensure that adequate medical care is provided to the subject until the event is resolved. In addition, NIDA will appoint a medical safety officer to this study to independently review the safety data, present it to the DSMB for periodic review, and provide LIs with summary reports of SAEs, or a Safety Letter when necessary. The study staff will be trained to monitor specific adverse events and Serious Adverse Events (see section 8.6).

Node Monitors: Monitoring visits will be conducted at each site by qualified node personnel, before, during, and after the trial. These visits will occur as often as needed to detect and correct problems at the study sites, and will examine the data, in up to 100% of participants, as specified in the QA Plan. The node monitors will verify that each subject's consent for study participation has been properly obtained and documented, confirm that research participants enrolled into the study meet inclusion and exclusion criteria, verify that study treatments are properly provided, ensure that submitted data are accurate and in agreement with source documentation, and ensure that all essential documentation required by Good Clinical Practice guidelines are appropriately filed.

NIDA Contract Monitors: Investigators will allow NIDA contract monitors to periodically audit, at mutually agreed upon times, all CRFs and corresponding source documents for each participant. These monitoring visits allow for an independent evaluation of the progress of the study and of potential problems at the study sites. The contract monitors will also verify subjects' consents, confirm that participants meet inclusion and exclusion criteria, verify that study treatments are properly provided, ensure that submitted data are accurate and in agreement with source documentation, and check that guidelines for Good Clinical Practice documentation and other study procedures are carefully followed.

Data and Safety Monitoring Board (DSMB): An independent CTN Data and Safety Monitoring Board (DSMB) will examine accumulating data, to assure protection of subjects' safety, while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether

there is support for continuation of the trial, or evidence that study procedures should be changed or the trial should be halted, for reasons relating to the safety of the study subjects, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment of subjects).

Any serious adverse events (SAEs) that occur during the study will be reported through NIDA to the DSMB. After each meeting, the DSMB will communicate its recommendations and a summary report of all 'possibly' related Serious Adverse Events to the LI and the participating Node PIs, to be conveyed to each IRB involved in the study.

8.4 Study documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

8.5 Confidentiality

8.5.1 Confidentiality of Data

By signing this protocol the investigator affirms to NIDA that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

8.5.2 Confidentiality of Participant Records

To maintain subject confidentiality, all CRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Subject information will not be released without written permission, except as necessary for monitoring.

8.6 Adverse Events

In general, the risks associated with trials employing behavioral interventions are presumed minimal relative to those evaluating pharmacologic interventions. Based on the experience from the MET/MI trials already underway, the risk from the MET intervention is low. Still, for the present trial, the population studied is a vulnerable population and possibly at higher risk given the nature of the disorder and the population (i.e. substance use and pregnant women). Thus, the following events, which are not defined as Serious Adverse Events, and which occur during the

active study or the follow-up periods will be tracked on an Adverse Events case report form (CRF) for each participant:

1. Vaginal bleeding
2. Severe abdominal pain
3. Leaking fluid prior to week 37 of pregnancy
4. Persistent uterine contractions (i.e., 4 in 20 minutes or 8 in 60 minutes) prior to week 37 of pregnancy
5. Changes in vision (e.g., blurred vision, tunnel vision)
6. Severe headache (e.g., two extra strength Tylenol do not alleviate it)
7. Significant swelling of face or hands
8. Decreased fetal movement (i.e., less than 10 "kicks" within a 2 hour period) for participants who are more than 28 weeks pregnant)
9. Suicidal ideation
10. Homicidal ideation

Serious Adverse Events (SAEs) will also be initially captured on the Adverse Events CRF. An SAE is defined as any event that occurs during the 'active' phase of treatment, or the follow-up periods, and either: (1) results in death, or (2) requires inpatient hospitalization (**EXCEPT for** the instances specified below) or a prolongation of existing hospitalization, or (3) is a congenital anomaly/birth defect, or (4) results in persistent or significant disability / incapacity, or (5) is life-threatening, or (6) requires intervention to prevent one of the above outcomes.

For the purposes of this study, several exceptions to an episode of inpatient hospitalization will be specified, and will not be reported as a Serious Adverse Event. These Exceptions are: (A) normal delivery of a term infant, (known pre-term deliveries, or prolongation of the normal length of hospital stay for a delivery, must still be reported.) (B) admission to a hospital or free-standing residential facility for the treatment of drug abuse, and (C) admission to a hospital for elective surgery or pre-scheduled diagnostic tests.

After capture on the AE CRF, the SAE form will be initiated by the RA, and the following individuals will be notified by facsimile transmission within 24 hours of the site's initial receipt of the information: (1) the Investigator at the site (e.g., the Executive or Clinical Director, etc.), who will direct the appropriate review, then complete and sign the follow-up SAE Form, (2) the Node Regulatory staff person, who will notify the appropriate Node IRB and/or CTP site IRB according to their procedures, (3) the Project Coordinator, (4) the Study Medical Monitor, who will review the event for relatedness to the study, then will prepare and sign the SAE summary report, and (5) the NIDA Medical Safety Officer, who will independently review each SAE for relatedness.

Following the initial 24 hour SAE report, additional information will be gathered to enable an assessment of the event for relatedness. For example, psychiatric history, baseline severity of illness, treatment compliance, and verbal or objective information about drug use at the time of the event are pertinent. The site Investigator will attach copies of source documents to the

follow-up SAE form, which will be provided to the Study Medical Monitor for review and forwarding to the NIDA Medical Safety Officer within 2 weeks of the initial SAE report. In addition, the Study Medical Monitor will prepare an SAE summary report, which will be sent to the NIDA Medical Safety Officer within two weeks of the initial SAE report. The NIDA Medical Safety Officer will accumulate individual SAE reports from all sites involved in the study, and summarize them in a table of SAEs. The cumulative SAEs will be sent to the DSMB each quarter, to review for possible study-related toxicities. Recommendations from the DSMB will be communicated via NIDA in a summary letter to the LI; it is the LI's responsibility to forward this letter to the Node PIs, who in turn will convey it to their appropriate IRB(s).

9.0 DATA MANAGEMENT

9.1 Data Collection

The study data will be managed at the level of the node and, thus, several different data management systems will be utilized for the present protocol. Data will be collected at the study sites on either electronic (paperless) or paper case report forms (CRFs). In accordance with policies developed by the CTN Data Management and Analysis Subcommittee (DMAS), the Ohio Valley Node Data Management Center (DMC) will provide final CRFs for the collection of all data required by the study. While the study data content of these CRFs may not be changed, it is understood that CRFs may be modified for incorporation into each node's data management system. Each node is responsible for distributing study CRFs to its participating CTPs.

CRFs 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 and complete records, and for tracking CRFs for each participant. All corrections to paper CRFs must be initialed and dated by the individual making the correction. Data entry onto electronic CRFs shall be performed by authorized individuals. Corrections to electronic CRFs shall be tracked electronically by documenting the time, date, individual making the change, both the old and new data values, and the reason for the correction.

9.2 Data Submission and Monitoring

The Ohio Valley Node DMC will provide a data dictionary that defines each data element. This data dictionary will be developed in accordance with CTN DMAS policies and will specify checks for missing, illogical, and out of range data. This will provide necessary specifications for Node DMCs to implement comprehensive error checking/tracking procedures and data quality assurance monitoring as outlined in the published CTN DMAS error monitoring SOPs.

Data will be submitted to each node's data management center and processed in accordance with the CTN DMAS Data Timeliness, Accuracy, and Completeness Standard Operating Procedure (SOP).

9.3 Test Data

Prior to initiation of the protocol, the Ohio Valley Node will make available a set of test CRFs as specified in the CTN DMAS Test CRF Creation Standards SOP. Each node will be required to process this test data and submit it to the NIDA central data repository in accordance with the CTN Data Transfer and Testing Validation SOP.

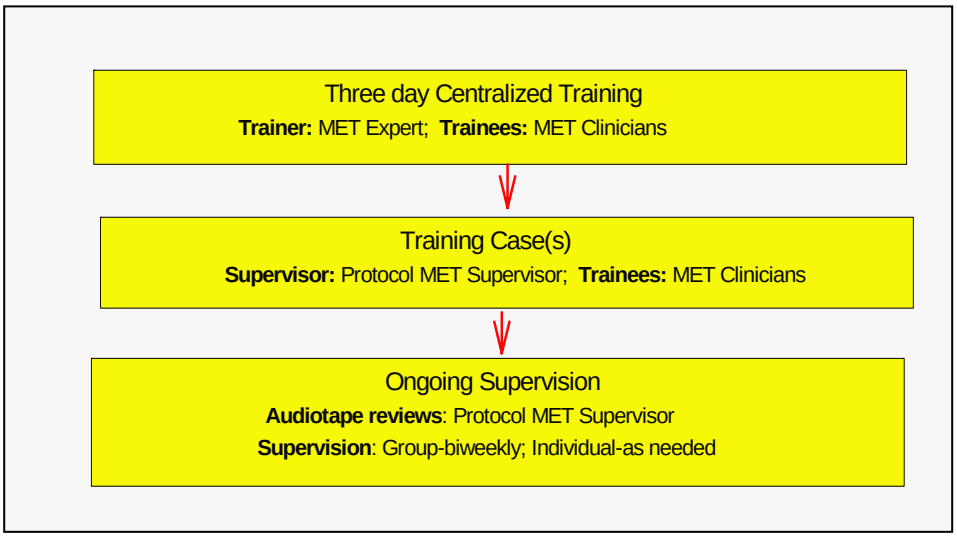
9.4 Central Data Repository

In accordance with published CTN DMAS data transfer SOPs, all nodes will transmit data to the NIDA central data repository (managed by Information Management Consultants (IMC)) on a monthly basis. The Ohio Valley Node will receive study data from the central repository on a monthly basis to allow for ongoing data quality assurance review. Upon study completion, all data will be transmitted from the NIDA central data repository to the Ohio Valley Node for data analysis and production of the final study report. The Ohio Valley Node will transmit the data set used for final analysis back to IMC/NIDA for archiving and storage.

10.0 MET TRAINING

The procedures for training clinicians and supervisors on MET have been derived from those used in the CTN 0004 protocol. An overview of MET training procedures can be found in Figure 2.

Figure 2: MET Training and Supervision Schema



10.1 Training Model

The present study will utilize a centralized training and supervision model.

10.2 Centralized Clinician Training

An expert in MET interventions will conduct the three-day clinician training. At least two clinicians from each participating CTP should complete this training. This three-day training will be focused on learning about brief motivational techniques in general and on the specific MET manual for the protocol. Training will include a lecture format as well as role playing exercises specifically involving scenarios with pregnant substance users.

10.3 Training cases

Following completion of the clinician training, each clinician will complete at least one training case. The training cases will be supervised by a Protocol MET supervisor via ratings of the audiotaped session for clinician adherence and competence. Clinicians will be assigned study participants if they receive an average rating (4 on 7-item scales) on half of the MET rating scale items for both adherence (frequency and extensiveness) and competence (skillfulness). Otherwise, the clinician will receive additional training and will complete additional training cases; a clinician who is unable to meet the criterion will not be assigned study participants.

Participants who serve as training cases will undergo all of the study procedures that will be completed by participants in the main study (see Table 1) with the exception of randomization to treatment condition. Like the participants in the main study, the training case participants will be offered three MET sessions as well as the other treatment offered by the CTP.

10.4 Ongoing Clinician Supervision and Training

A Protocol MET supervisor will have primary responsibility for supervising the clinicians' implementation of the MET manual. It is expected that the Protocol MET supervisor typically will have a teleconference with the clinicians for group supervision on a biweekly basis, contingent upon the clinicians having active cases to discuss. In addition, the Protocol MET supervisor may provide individual supervision at his/her discretion. The supervision sessions will include a review of audiotaped sessions including strengths and deficits of the sessions.

11.0 ANALYTICAL PLAN

11.1 Statistical Hypotheses

The primary hypothesis is that MET, relative to TAU, will increase participants' utilization of substance abuse treatment.

11.2 Outcome Measures

11.2.1 Primary Outcome

The primary hypothesis will be tested by comparing the MET and TAU participants on the percent of scheduled treatment hours attended during the active study phase.

11.2.2 Secondary Outcome

Several secondary outcome measures that will further elucidate the efficacy of MET, compared to TAU, have been included in this study. The two treatment groups will be compared on the following measures:

1. utilization of substance abuse treatment through a 3-month follow-up

2. substance use (defined as days of self-reported substance use, with partial confirmation by urinalysis and breathalyzer) during the active study phase

3. substance use (defined as days of self-reported substance use, with partial confirmation by urinalysis and breathalyzer) through the 3-month follow-up

4. engagement in behaviors that increase the risk of contracting HIV, as measured by the Risk Behaviors Survey

5. the seven areas of functioning measured by the ASI- Lite (medical status, employment status, drug use, alcohol use, family status, legal status, psychiatric status)

6. commitment to abstinence and expected success in quitting and remaining abstinent as measured by the Thoughts about Abstinence assessment

7. the percent attending an initial session for the treatment referral received as determined by clinic records

8. the number of weeks in which at least one treatment session is attended as determined by clinic records

9. the percent of scheduled prenatal visits attended as determined by the Treatment Tracking form

10. motivation to change alcohol/drug use behavior as determined by the URICA

11. satisfaction with treatment as measured by the Participant Satisfaction form

12. engagement in activities that are important for a healthy pregnancy as measured by the Pregnancy Assessment form

13. the amount of clinical staff time spent trying to contact participants who are not attending treatment as measured by the Interventions for Non-treatment Attendance form.

14. the length of time that participants are retained in treatment as measured by the Treatment Tracking form

11.3 Analysis Plan

11.3.1 Efficacy Analysis

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat population. Parametric tests will be conducted on all continuous outcome measures that satisfy parametric assumptions; non-parametric tests will be conducted on those measures failing to satisfy parametric assumptions. For all hypotheses, residuals from the statistical analysis will be examined to determine that distributional assumptions are met. Where appropriate, transformation of variables will be employed to more closely approximate the parametric distribution (i.e. normal). A statistical test will be conducted at a 5% Type I error rate (two-

sided) for the primary efficacy measure. The Type I error rates will be adjusted to 1% (two-sided) for tests of secondary outcomes, because of the multiplicity of outcomes.

11.3.1.1 Primary Efficacy Measure

The purpose of the first primary analysis is to determine if giving a participant MET, versus TAU, impacts the average rate of attended/scheduled treatment hours during the active study phase. The analysis will be carried out assuming a Poisson regression model and a log 'link' function. The mean (or expected value) of the number of attended hours given the number of scheduled hours will be estimated by using the number of attended hours as the response variable, and including the number of scheduled hours as a weighting factor or offset variable. The primary independent variable will be modeled by including an indicator variable for treatment type (MET or TAU). Indicator variables for categorically modeled treatment level (outpatient, intense outpatient) will also be included to control for a possible confounding effect of treatment level on the relation between treatment type and hours attended.

The primary focus of the analysis is to compare the treatments (MET versus TAU). The model assumes a common attendance rate per scheduled hour for each visit within the same category of study group and treatment type. The Poisson distribution is commonly used to model count data and appropriate ratio data. The analysis will be carried out using the method of generalized estimating equations (GEE), implemented by the SAS procedure PROC GENMOD. In order to provide valid results of hypothesis testing, correlations between pairs of observations on the same subject will be modeled. A compound symmetric and unstructured correlation matrix will be tried. If results are similar, the compound symmetric correlation structure will be assumed because of ease of interpretation. In order to test the sensitivity of the results to model specification, the analysis will be repeated assuming a binomial model with a response variable of hours attended / hours scheduled. This analysis will be carried out using PROC GENMOD. This similar outcome variable (average attendance per scheduled hour) will be related to treatment (MET vs. TAU) and group (outpatient, intense outpatient) in this model also. In addition, descriptive statistics will be obtained summarizing the average attendance rates by categories of treatment and patient groups for inpatient, intense outpatient and outpatient treatments.

11.3.1.2 Secondary Outcome Measures

Substance Use

For a subset of study days, <u>both</u> self-report and objective measures of substance use will be obtained. The concordance rate between self-report and urinalysis and breathalyzer results will be calculated. Based on analyses of recent NIDA data sets, a concordance rate between 70 and 90% is expected. Corrections to the data will be made for participants whose concordance rate falls below 70%. These corrections will include adjusting the participant's self-report to be consistent with the urinalysis and breathalyzer results and completing the analyses with and without the participants whose concordance rate is below 70%. A third form of correction, in which missing urines are imputed as being positive will also be utilized. A GEE similar to that described for the primary analysis will be used to compare the two treatment groups on days of substance use during each week of the active study phase. Similarly, a GEE will be used to

compare the groups on days of substance use during the active study and during the two follow-up periods.

Other Secondary Outcome Measures

The data from the ASI-Lite, Risk Behaviors Survey, Commitment to Abstinence, URICA, and Pregnancy assessments will be analyzed with an Analysis of Covariance (ANCOVA) in which the baseline score is controlled for; one set of analyses will be conducted on just the active study phase data while another set will include the data from both the active study phase and follow-up periods. A Chi-square will be used to compare the treatment groups on the percent of participants who attend an initial treatment session. The number of weeks in which at least one treatment session is attended during the active study phase, interventions for non-treatment attendance, and participant satisfaction will each be analyzed with an independent measures t-test. Data on the number of weeks in which at least one treatment session is attended during the active study phase and during the two follow-up periods will be analyzed with GEE. Finally, a survival analysis will be performed on the data from the entire study period using a Cox Proportional Hazards model to compare the TAU and MET participants on the length of time to first treatment drop out while the participant is still pregnant. First treatment drop out is defined as failure to attend any treatment provided by the CTP, whether in the clinic or in the community, for three consecutive weeks. Estimates of the survival function for each treatment group will be calculated using the Kaplan-Meier method.

11.3.1.3 Process Measures

Regression analyses will be used to evaluate the relationship of process (e.g., therapeutic alliance, clinician adherence) and outcome (e.g., participant satisfaction level, participant's commitment to abstinence and perceived ability to obtain abstinence) measures to treatment utilization and substance use. In addition, we will evaluate the process measures as potential mediators of treatment effect with the use of hierarchical regression analysis.

11.4 Sample Size Estimate

The present study is an initial evaluation of the efficacy of MET, compared to TAU, in increasing treatment utilization and decreasing substance use in pregnant patients. Because this is an initial evaluation, it is desirable to limit the overall sample size and, hence, the cost of the study. The difficulty associated with a limited sample size lies in having adequate statistical power to answer a number of possible questions. This study has been powered to detect differences between the treatment groups when the data are pooled across sites. Thus, this study is not powered to detect potential site or site by treatment interaction effects and, consequently, the detection of these effects will be sacrificed for this small study. Should this initial trial suggest that MET is a promising intervention for pregnant substance users then a larger scale follow-up study can be conducted. The information gathered from this trial will also provide preliminary data on variability across sites to aid in the planning of a larger follow-up study.

The t-test module in PASS 2002 (Hintze, 2001) was used to conduct a power analysis for the primary outcome measure. This power analysis did not account for attrition since we will be able to get 100% of the data for this primary outcome measure (e.g., those who fail to return to the clinic after the first session would receive a score of 0 on the measure, etc.). Based on prior

studies, it is assumed that the percent of scheduled treatment hours attended will be lower for TAU participants compared to MET participants. Assuming 100 participants per treatment group and a level of significance equal to .05 (two-sided), the power to detect a moderate treatment effect size (D=.40; Cohen, 1988) would be 80%. This would translate, approximately, into 20% greater treatment attendance by the MET group compared to the TAU group, when the largest possible standard deviation, 0.5, is assumed for the primary outcome measure.

11.5 Descriptive Statistics

The baseline characteristics of the study sample and for the participants in each treatment group will be summarized. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups.

11.6 Interim Analyses

This trial will not involve over 1000 participants, will not involve treatments of 6 months duration or longer, and will not use death or serious adverse events as an efficacy measure. The trial will evaluate a behavioral intervention for which published information supports efficacy in the treatment of the addiction under study, and is not considered inconsistent. Moreover, this protocol is not considered likely to provide evidence of "overwhelming efficacy" of one treatment over another. Accordingly, interim analysis of accumulating efficacy data by treatment assignment is not planned and will only be conducted if needed to assess the acceptability of safety results.

11.7 Post-hoc Analyses

In addition to the analyses described above, a number of post-hoc analyses will be completed. Each primary and secondary outcome variable will be analyzed for the evaluable subsample, which is defined as the subjects who are randomized to treatment and who receive at least the intake session (either MET or TAU). Some examples of possible analyses include an exploration of participant baseline variables that are predictive of treatment outcome and of clinician characteristics associated with treatment outcome. In addition, if MET is found to effect longer-term outcome, we will explore models by which MET might exert this effect. Further, we will evaluate the degree to which therapist effects and types of treatment services provided impacted treatment outcome.

12.0 REFERENCES

Bien, T., Miller, W., Tonigan, J. (1993). Brief interventions for alcohol problems: a review. Addiction, 88, 315-336.

Carey, K.B., Purnine, D.M., Maisto, S.A., & Carey, M.P. (1999). Assessing readiness to change substance abuse: a critical review of instruments. Clinical Psychology: Science and Practice, 6, 245-266.

Carroll, K.M., Connors, G.J., Cooney, N.L., DiClemente, C.C., Donovan, D.M., Longabaugh, R.L., Kadden, R.M., Rounsaville, B.J., Wirtz, P.W., & Zweben, A. (1998). Internal validity of project MATCH treatments: discriminability and integrity. Journal of Consulting and Clinical Psychology, 66, 290-303.

Carroll, K., Libby, B., Sheehan, J., Hyland, N. (2001) Motivational interviewing to enhance treatment initiation in substance abusers: an effectiveness study. Am J Addictions (in press).

Cohen, J. (1988). Statistical Power Analysis of the Behavioral Sciences. Lawrence Erlbaum Associates, Hillsdale NJ.

Chang, G., Carroll, K.M., Behr, H.M., Kosten, T.R. (1992). Improving treatment outcome in pregnant opiate-dependent women. Journal of Substance Abuse Treatment, 9, 327-330.

Crits-Christoph, P., Mintz, J. (1991). Implications of therapist effects for the design and analysis of comparative studies of psychotherapies. Journal of Consulting and Clinical Psychology, 59, 20-26.

DiClemente, C.C., & Hughes, S.O. (1990). Stages of change profiles in alcoholism treatment. Journal of Substance Abuse, 2, 217-235.

Hall, S., Havassy, B., Wasserman, D. (1991). Effects of commitment to abstinence, positive moods, stress, and coping on relapse to cocaine use. Journal of Consulting and Clinical Psychology, 59, 526-532.

Haller, D., Knisely, J, Elswick, R., Dawson, K, Schnoll, S. (1997). Perinatal substance abusers: factors influencing retention. Journal of Substance Abuse Treatment, 14, 513-519.

Haller, D., Knisely, J, Dawson, K, Schnoll, S. (1993). Perinatal substance abusers: psychological and social characteristics. Journal of Nervous and Mental Disease, 181, 509-513.

Handmaker, N.S., Miller, W.R., & Manicke, M. (1999). Findings of a pilot study of motivational interviewing with pregnant drinkers. Journal of Studies on Alcohol, 60, 285-287.

Hintze, J. (2001). PASS (Version 2002). [Computer Software]. Number Cruncher Statistical Systems. Kaysville, Utah.

Howard, J., Beckwith, L. (1996). Issues in subject recruitment and retention with pregnant and parenting substance-abusing women. In E. Rahdert(Ed), Treatment for drug exposed women and

their children: Advances in research methodology (NIDA Research Monograph No. 165, DHHS Publication No. 96-3632, pp 52 – 67).

Jones, H.E., Haug, N.A., Stitzer, M.L., Svikis, D.S. (2000). Improving treatment outcomes for pregnant drug-dependent women using low-magnitude voucher incentives. Addictive Behaviors, 25, 263-267.

Lachin, J.M., Matts, J.P., Wei, L.J. (1988). Randomization in clinical trials: conclusions and recommendations. Controlled Clinical Trials, 9, 365-374.

LaFazia, M., Kleyn, J., Lanz, J., Hall, T., Nyrop, K., Stark, K., Hansen, C. & Watts, D. (1996). Case Management: A method of addressing subject selection and recruitment issues. In E. Rahdert(Ed), Treatment for drug exposed women and their children: Advances in research methodology (NIDA Research Monograph No. 165, DHHS Publication No. 96-3632, pp 52 – 67).

Laird, N. M. & Ware, J. H. (1982). Random-effects models for longitudinal data. Biometrics, 38, 963-974.

Liang, K.Y. and Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. Biometrika, 73, 13-22.

Littell, R. C., Milliken, G. A., Stroup, W. W. & Wolfinger, R. D. (1996). SAS Systems for mixed models. Cary, NC: SAS Institute Inc.

Luborsky, L., Barber, J.P., Siqueland, L. & Johnson, S. (1996). The revised Helping Alliance questionnaire (Haq-II). Journal of Psychotherapy Practice and Research, *5,* 260-271.

Martino, S., Carroll, K.M., O'Malley, S.S., & Rounsaville, B.J. (2000). Motivational interviewing with psychiatrically ill substance abusing patients. American Journal on Addictions, 9, 88-91.

McLellan, A.T., Alterman, A.I., Cacciola, J., Metzger, D. & O'Brien, C.P. (1992). A new measure of substance abuse treatment. Initial studies of the treatment services review. Journal of Nervous and Mental Disease, 180, 101-110.

McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., & Argerious, M. (1992). The fifth edition of the Addiction Severity Index. Journal of Substance Abuse Treatment, 9, 199-213.

McMurtie, C., Rosenberg, K.D., Kerker, B.D., Kan, J., Graham, E.H. (1999). A Unique Drug Treatment Program for Pregnant and Postpartum Substance-Using Women in New York City: Results of a Pilot Project, 1990-1995. AM. J. Drug Alcohol Abuse, 25(4), 701-713.

Miller, W.R. (Consensus chair). (1999). Enhancing motivation for change in substance abuse treatment. SAMHSA Treatment Improvement Protocol Series Volume 35, DHHS Publication No. (SMA) 99-3354. Rockville, MD: Substance Abuse and Mental Health Services Administration Center for Substance Abuse Treatment.

Miller, W.R., & Rollnick, S. (1991). Motivational interviewing: Preparing people to change addictive behavior. New York: Guilford.

Miller, W.R., Tonigan, J.S., & Longabaugh, R. (1995). *The Drinker Inventory of Consequences (DrInc): An instrument for assessing adverse consequences of alcohol abuse. Test manual.* NIAAA Project MATCH Monograph Series Volume 4. Rockville, Maryland.

National Institute on Drug Abuse. (1996). National pregnancy and health survey (NIH Publication No. 96-3819). Rockville, MD: Author.

Saunders, B., Wilkinson, C., Phillips, M. (1995). The impact of a brief motivational intervention with opiate users attending a methadone programme. Addiction, 90, 415-424.

Simpson, D., Joe, G., Fletcher, B., Hubbard, R., Anglin, M. (1999). A national evaluation of treatment outcomes for cocaine dependence. Arch Gen Psychiatry, 56, 507-514.

Singer, J. D. (1998). Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. Journal of Educational and Behavioral Statistics, 24(4), 323-355.

Svikis, D, Huggins, G. (1996). Substance abuse in pregnancy: Screening and intervention. Contemporary Obstetrics and Gynecology, 41, 32-52.

Svikis, D., Lee J.H., Haug, N.A., & Stitzer, M.L. (1997). Attendance incentives for outpatient treatment: effects in methadone- and nonmethadone-maintained pregnant drug dependent women. Drug and Alcohol Dependence, 48, 33-41.

Swanson, A.J., Pantalon, M.V., & Cohen, K.R. (1999). Motivational interviewing and treatment adherence among psychiatric and dually diagnosed patients. Journal of Nervous and Mental Disease, 187, 630-635.

Weisdorf, T., Parran, T.V., Graham, A., Snyder, C. (1999). Comparison of pregnancy-specific interventions to a traditional treatment program for cocaine-addicted pregnant women. Journal of Substance Abuse Treatment, 16, 39-45.