

**A FEASIBILITY STUDY OF A TELEPHONE ENHANCEMENT PROCEDURE
(TELE) TO IMPROVE PARTICIPATION IN CONTINUING CARE ACTIVITIES**

Lead Investigator: Robert L. Hubbard, PhD, MBA
NC CTN
Department of Psychiatry
2218 Elder Street, 2B
Durham, NC 27705
US Mail:
Department of Psychiatry, DUMC Box 3419
Durham, NC 27710
Work Phone: (919) 863-4600, ext. 229; (919) 668-3628
E-Mail: hubba014@mc.duke.edu, hubbard@ndri-nc.org

Protocol Project Manager: Kathi D. Lucas

Protocol Development Team:

| | |
|-----------------|------------------|
| Jeff Annon | Jeff Leimberger |
| Sharon Chambers | Michael Liepman |
| Allan Cohen | Kathi Lucas |
| B. J. Dean | Judy McMullen |
| Briar Faulkner | Eileen Pencer |
| Diane Hague | Richard Rawson |
| Len Handelsman | Chris Reiber |
| Louise Haynes | John Schwarzlose |
| Albert Hasson | Susan Silva |
| Robert Hubbard | Theresa Winhusen |

NIDA Collaborators: Mary Ann Chutuape-Stephens
Larry Friedman

NIDA Central Data Repository: Jim Glass

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Protocol Version: 8

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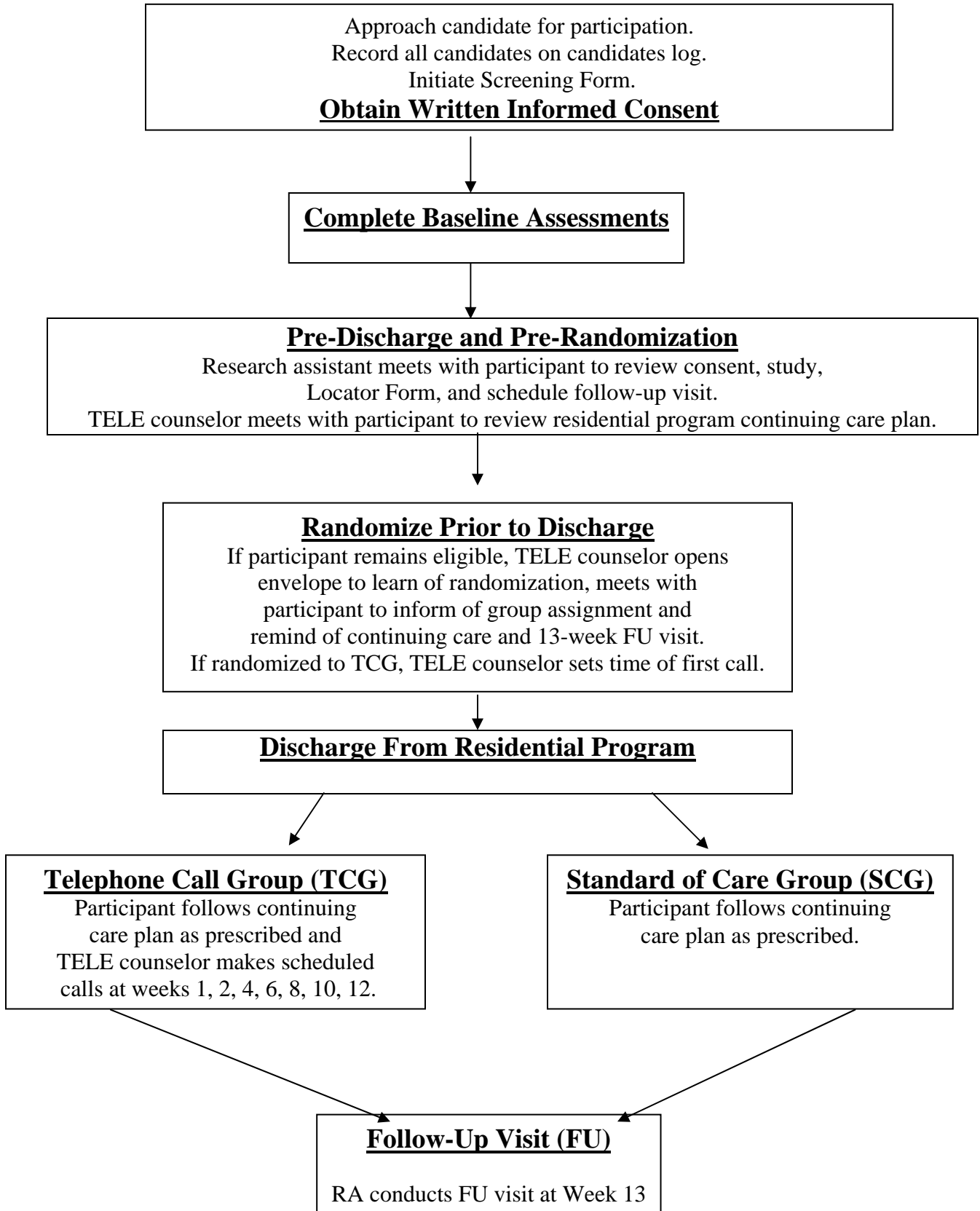
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1.0 LIST OF ABBREVIATIONS

| | |
|----------|--|
| AE | adverse event |
| AIDS | acquired immune deficiency syndrome |
| ASI | addictive severity index |
| ASI-Lite | Addictive Severity Index-Lite |
| BFC | Betty Ford Center |
| CRF | case report form |
| CTN | Clinical Trials Network |
| CTP | community treatment programs |
| DCRI | Duke Clinical Research Institute |
| DHHS | Department of Health and Human Services |
| DSMB | Data and Safety Monitoring Board |
| FDA | Food and Drug Administration |
| FU | Follow-Up |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| IRB | Institutional Review Board |
| LAAM | levomethadyl acetate (L-alpha acetylmethadol) |
| MET | motivational enhancement therapy |
| MIEDAR | Motivational Incentives for Enhanced Drug Abuse Recovery |
| NIDA | National Institute on Drug Abuse |
| QA | quality assurance |
| RBS | Risk Behavior Survey |
| SAE | serious adverse event |
| SCG | standard of care group |
| SCR | Study Completion Report |
| TCG | telephone call group |
| TELE | telephone call support |

2.0 TELE PROTOCOL



3.0 PROTOCOL SYNOPSIS

This study is designed to determine the feasibility of conducting a multi-site evaluation of a telephone call support (TELE) procedure to promote (1) participation in post-residential treatment continuing care activities and (2) improved drug/alcohol abstinence rates at follow-up.

The research question is twofold: First, does a series of follow-up telephone calls to participants after their discharge from a residential treatment program encourage them to engage in the continuing care activities defined in their discharge plans? Second, does this follow-up practice reduce the amount and frequency of their drug and alcohol use?

To measure the effectiveness of the intervention, a randomly assigned control group will receive only usual care after discharge. Both the intervention group (telephone call group [TCG]) and the control group (standard of care group [SCG]) will participate in a data collection follow-up visit 13 weeks after discharge from the residential treatment setting.

Prior to a full-scale study evaluating the TELE procedure, we propose that this 4-site feasibility study be undertaken to explore specific parameters that will be important in a larger trial. For the feasibility study, we will address these questions:

- (1) What proportion of the total eligible participants will volunteer to participate in the study?
- (2) What proportion of consented participants will complete all required residential treatment and baseline assessments, meet eligibility criteria, and be randomized into one of the 2 study groups?
- (3) How many participants can be contacted by phone after discharge, and how many calls will the intervention be delivered of the 7 calls scheduled in the telephone protocol?
- (4) If a structured “script” is used to organize the calls, can telephone counselors be trained to conduct these calls in a standardized manner?
- (5) What is the magnitude of the “effect size” of such a study design?
- (6) What proportion of participants can be contacted for follow-up in the community?
- (7) Can adequate data for a full-scale study be collected in typical community-based treatment organizations?

In the feasibility study, 4 sites will conduct the procedures outlined in this protocol. Procedures have been designed by the TELE protocol group and approved by the Clinical Trials Network (CTN) Steering Committee. The feasibility study will include 360 randomized participants—180 per treatment condition. Each of the sites is expected to randomly assign 60 to 120 participants. If the study shows that it is feasible to deliver the telephone calling intervention and to collect adequate data to compare with a control group, and there is evidence to suggest positive effects of the intervention, recommendations will be made to the CTN Steering Committee for a large-scale trial evaluating the efficacy of the TELE procedure.

The feasibility study will be conducted as follows:

Candidates eligible for randomization will include men and women enrolled in residential substance abuse treatment programs for at least 7 days but no more than 42 days. Participants must be at least 18 years of age and have the ability to understand and provide written informed consent. In addition, they must have been voluntarily admitted (not civilly committed) to the rehabilitation regimen (not admitted for detoxification only) and have a diagnosis for substance abuse or dependence as determined by residential program admission information. Referrals must be from a program servicing the targeted counties at the time of admission, and participants must plan to return to residence in the target counties after their discharge from the residential treatment program. Participants must have no evidence of current suicide intention or recent (≤ 30 days prior to admission) suicide attempt and must complete study requirements prior to departure from the program. All participants must have a working telephone number for contact after their discharge.

Prior to their planned discharge (as close as possible to the date of the participant's planned discharge, ideally within the 2 business days prior to the planned date of discharge or on the actual day of discharge), consenting participants who have met all eligibility requirements for the study will be randomly assigned to one of 2 post-discharge conditions: standard of care group (SCG) or SCG plus 7 scheduled telephone calls (TCG) placed during the first 87 days after discharge. We believe that TCG participants will have greater participation in continuing care activities and that a higher proportion will be abstinent from drugs and alcohol at the time of a follow-up visit, as compared with those in the SCG. Information on participation in continuing care activities (measured by self-report and verification with post-discharge programs), drug/alcohol use (documented by urine tests and breath alcohol tests), and a battery of other measures will be collected at the 13-week follow-up visit for all randomized participants.

Study results will be aggregated across sites and examined within individual sites.

The experience gained through the implementation and operation of this protocol will provide the data necessary to justify a future multi-site trial. If the TELE procedure is ultimately found to be efficacious in a full-scale trial, this work will represent one model for bringing current community-based clinical practice, which has not been extensively evaluated, into the CTN for rigorous empirical examination.

4.0 BACKGROUND AND RATIONALE

4.1 Background

Relapse rates are frequently high during the first 3 months following residential or outpatient substance abuse treatment services and represent a serious clinical problem that can often reverse many of the positive therapeutic changes initiated during the treatment episode. Virtually all treatment programs strongly recommend that, following discharge, participants get involved in defined "aftercare" or "continuing care" activities. The specific activities differ from program to program, but often include a prescribed

schedule of individual and/or group therapies, ongoing psychiatric or family therapies, and a program of self-help attendance. Reports have shown substantially lower relapse and re-addiction rates in participants who comply with the prescribed care plans as compared with those who do not (Fiorentine & Anglin, 1997). Despite these optimistic reports, compliance with the scheduled treatment activities is often poor.

In an attempt to ensure attendance at continuing care activities, some treatment programs use a written agreement or contract with the participant. The degree or extent of the commitment of the contract to attend continuing care varies with the treatment program. In one program that followed participants for 6 months, a greater number of participants who signed a behavioral contract for attendance remained abstinent compared with those who declined to sign (Ahles et al., 1983; Ossip-Klein et al., 1984). Lash and Dillard (1996) found that participants who received only aftercare orientation before their discharge or who received aftercare orientation and signed a treatment contract did not significantly differ in attendance rates from participants who received no additional intervention. These researchers suggest that something more intensive needs to be incorporated in order to substantially improve aftercare attendance.

An alternative approach to increasing continued care participation is implementing an incentive program. Chutuape, Katz, and Stitzer (2001) examined methods for increasing the transition of substance-dependent participants from inpatient detoxification to outpatient aftercare. In their study, 196 participants were randomly assigned to receive standard referral, standard referral with monetary incentive, or staff escort to aftercare with a monetary incentive. Intakes were completed by 24% of the standard condition participants, 44% of the incentive participants, and 76% of the escort/incentive participants. These findings suggest a positive relationship between enhanced support and increased attendance to aftercare programs. The interventions used in the previous studies might be considered passive and patients are not empowered enough to have control maintaining their abstinence. Thus an intervention designed to assist and empower patients, and in which the residential program remains active, could be of use.

A cluster of studies in the substance abuse and mental health research fields suggest that participants who are provided with an assertive outreach post-treatment intervention will have improved compliance with post-treatment aftercare planning and improved outcome status. In chronic alcoholics, a single telephone call or letter expressing interest in the welfare of the participant has been shown to have a significant positive effect on the motivation to participate in aftercare activities (Koumans & Muller, 1965; Koumans, Muller & Miller, 1967). Moreover, multiple calls over an extended period were found to correlate positively with greater utilization of outpatient services. Intagliata (1976) studied the effects of 6 telephone calls over a 10-week period on alcohol-dependent males in recovery and their utilization of outpatient services. Telephone conversations were used to assess the participant's (1) success or difficulties in maintaining abstinence, (2) employment status, (3) the stability of the living situation and (4) incidence of readmission to the hospital. Participants who received these calls made significantly greater use of outpatient services. Additionally, this increase in service utilization was significantly and positively related to abstinence. This effect has been shown to occur regardless of the number of people initiating the telephone call (Intagliata, 1976) or the relationship of the caller to the participant. Lash and Blosser (1999) found that an

automated phone messaging program and appointment cards as reminder prompts over 8 weeks significantly increased and prolonged attendance rates in aftercare group sessions.

The Betty Ford Center recently conducted a pilot evaluation of a very simple, low-cost, post-treatment continuing care intervention. This intervention consists of periodic telephone calls from the Betty Ford Center staff to a selected set of participants. During the call, the staff member expresses interest in the well-being of the participant, inquires about his or her drug/alcohol use status, explores the extent to which the participant is involved in planned continuing care activities, reinforces positive responses, and encourages those who are not attending to increase their participation. The schedule of calls begins with a weekly call for the first month post-treatment, reduces to biweekly calls for 2 months, and monthly calls for 3 months. Preliminary findings from the Betty Ford Center trial are very encouraging. Although a substantial data set is not yet available, reports from participating staff and participants suggest that this relatively low-cost intervention may be valuable for promoting engagement in prosocial behaviors and enhancing the recovery process.

Maintaining contact with discharged participants and encouraging their use of continuing care sessions via telephone calls represent a mode of intervention that is more personal than letter writing and less costly than face-to-face interviews. In addition to the low cost of the actual calls, the time required for a staff member to engage in this type of assertive intervention is relatively minimal. Moreover, 2-way communication is an important facet of telephone contact, allowing the participant to voice concerns or provide explanations for absence from the continuing care activities that a staff member may be able to resolve. A final hidden benefit is that expressing interest in the participants' welfare and encouraging their participation in continuing care activities has been shown to facilitate attendance and prolong abstinence.

If post-residential care calls substantially improve continuing care compliance and reduce relapse to drugs and alcohol, why are they not already being routinely done? There are 2 potential reasons. First, in the present funding climate, treatment programs have to carefully budget every expense. The time and personnel costs associated with the call procedure, although relatively inexpensive, are substantial enough to require a clear justification. Moreover, many residential providers believe that they are responsible for the successful treatment of participants while they are in the residence; however, once discharged, the individual is responsible for following his or her own treatment plan. Without data to clearly demonstrate the value of a post-discharge intervention, a policy change is highly unlikely.

As the literature shows, increasing continuing care attendance has a direct influence on reducing recidivism rates. Considering the previous research methodologies, we hypothesize that a relatively low-cost intervention using periodic contact and reinforcement from program staff could enhance outcomes and significantly reduce relapsing behaviors.

4.2 Rationale

WHY A FEASIBILITY STUDY?

The CTN has been established to move scientifically supported treatments into community treatment settings, and to bring community practices under the scrutiny of rigorous scientific evaluation. The CTN has established models for moving science-based interventions into applied settings (e.g., motivational enhancement therapy [MET], MIEDAR, buprenorphine/naloxone studies). However, no operational model has been established for a community-based clinical practice, with subsequent rigorous empirical examination of its effectiveness. With scientifically based interventions, there are data to support the selection of specific study parameters (e.g., dose and duration of the intervention and methods for measuring its effects). For community practices that are not empirically validated but appear to have promise for demonstrating efficacy, selecting the proper study parameters to collect the necessary confirmatory evidence may be challenging.

Proper selection of study parameters is critical to the success of evaluating an intervention. There must be a balance of considerations: testing enough participants to achieve adequate statistical power; delivering an adequate dose (amount and duration) of the independent variable; collecting sufficient and appropriate dependent measures (types of measures, number of data points); considerations of study costs such as staffing and program costs; practicality of the intervention for use in “real world settings”; and the feasibility of being able to actually deliver the study intervention and collect the intended study data in the community sites. For community practice questions, there are often some anecdotal reports that can help support specific study parameters. But more frequently, the choice of specific study parameters is based upon either a somewhat “educated guess” or “common sense.” Unfortunately, this best guess approach requires a huge gamble of money and time, since the conduct of a full scale, multi-site clinical trial needed to establish the empirical value of a procedure is a substantial investment. Even worse, if inappropriate parameters are selected, a major effort costing large amounts of money could culminate in misleading results that fail to provide a meaningful test of the target intervention.

The design of a large-scale trial on the TELE procedure is clearly in the stages of early development. We have thus decided to conduct a feasibility study to answer some preliminary questions and to provide guidance for the design of a full-scale, multi-site efficacy trial to evaluate the procedure. A solid foundation will be established for a larger-scale definitive trial if the results of this feasibility study show promise of a positive clinical impact, with recruitment and follow-up of a sufficient population sample and successful conduct, accuracy, and fidelity of study procedures.

5.0 STUDY OBJECTIVES

5.1 Feasibility

The primary objective of this clinical investigation is to evaluate the feasibility of a randomized clinical trial testing the use of a telephone call support (TELE) procedure to enhance continuing care activities after completion of residential treatment programs for substance abuse. Several aspects of this feasibility study are equally important and failure to complete them would indicate the need for serious reconsideration or restructuring of a future full-scale TELE protocol. The critical aspects of feasibility in this study are listed below:

1. Determining the proportion of the total eligible participants who volunteer to participate in the study
2. Obtaining informed consent on an adequate number of newly admitted residential treatment patients for participation in the study
3. Determining the proportion of consented participants who complete all required residential treatment and data collection activities and are randomized into one of the 2 study conditions
4. Determining whether it is possible to contact this population via telephone after they have been discharged from residential substance abuse care
5. Determining how many of the 7 scheduled calls in the group randomized to the TCG actually have the intervention delivered
6. Determining whether counselors who deliver the calls can be trained to conduct these calls in a standardized manner using a structured “script”
7. Determining the magnitude of the “effect size” within such a design (This information will be needed in power calculations for any future study.)
8. Determining whether adequate data (i.e., sufficient and equivalent follow-up data), which would be required in an adequately powered multi-site trial, are collectible in typical community-based treatment organizations after participants leave the treatment setting

5.2 Efficacy

A secondary goal of this feasibility study is to explore the impact of the TCG condition on participation in post-discharge continuing care activities. In addition, we will examine whether the TELE procedure results in reduced drug and alcohol use of study participants as measured by urinalysis, breath alcohol test, or self-report. Insofar as this study is not adequately powered to answer these experimental questions, the analysis of the TELE efficacy data from the 4 sites will be used to support the conduct of a future full-scale trial and to provide a basis for effect size and power calculations in the future study.

These are specific aims of the secondary analysis:

1. To compare the effect of TCG condition with that of the SCG condition on the basis of participant involvement in aftercare programs. We believe that, compared

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with SCG participants, TCG participants will have an increased participation in continuing care activities.

2. To compare drug and alcohol use measures at 13 weeks post-discharge in the telephone call group (TCG) and standard of care group (SCG). We believe that those who receive the telephone calls will have a higher rate of drug/alcohol abstinence at the follow-up visit.

To determine the effect of the TELE procedure, the following measures will be collected at the 13-week post-discharge follow-up visit:

- Self-reported engagement in continuing care activities prescribed in the continuing care plan prepared by the residential treatment program
- Drug use as measured by urine test
- Alcohol use as measured by breath alcohol test
- Drug and alcohol use during the past 30 days as measured by the CTN Addictive Severity Index-Lite (ASI-Lite) Follow-up Version 1 Form
- Other measures of functioning from the CTN ASI-Lite Follow-up Version 1 Form

The analysis of these data will provide a preliminary overview of the clinical effectiveness of the regimen of telephone calls. Information from this study can then be used to design a full-scale clinical trial.

6.0 STUDY SPONSOR - NIDA

7.0 STUDY SITES

The study will be conducted at 4 community treatment program (CTP) sites of the NIDA Clinical Trials Network:

Node: South Carolina
Node PI: Kathleen Brady
CTP: Morris Village ADATC
2414 Bull Street
Columbia, SC 29202
CTP PI: Kathleen Brady
CTP Contact Person: Louise Haynes
CTP Contact Person Phone: (803) 935-7102

Node: Great Lakes
Node PI: Charles Schuster
CTP: Michiana Addictions and Prevention Services (MAPS)
1910 Shaffer Street
Kalamazoo, MI 49048
CTP PI: Michael Liepman
CTP Contact Person: Elizabeth Thorpe
CTP Contact Person Phone: (269) 226-9221

Node: North Carolina
Node PI: Robert Hubbard
CTP: Julian F. Keith ADATC
301 Tabernacle Road
Black Mountain, NC 28711
CTP PI: Breque Tyson
CTP Contact Person: Breque Tyson
CTP Contact Person Phone: (828) 669-3485

Node: North Carolina
Node PI: Robert Hubbard
CTP: Walter B. Jones ADATC
2577 West Fifth Street
Greenville, NC 27834
CTP PI: John Holter
CTP Contact Person: John Holter
CTP Contact Person Phone: (252) 830-3426

8.0 STUDY DESIGN

This feasibility study is designed as a 4-site clinical investigation to assess the appropriateness and practicality of conducting a larger, more definitive, multi-site trial testing the value of a post-residential care telephone call procedure. There are 60 to 120 participants required for randomization in this study at each site. It is estimated that approximately two thirds of those candidates who sign informed consent will complete the baseline data collection, meet all other eligibility criteria, and be randomized. A minimum recruitment period of 9 months is anticipated. The length of study participation for individual participants is expected to be 13 weeks plus the variable length of the initial residential treatment (7–42 days).

The study will be conducted by using a randomized, parallel-group design in which eligible individuals who enter residential substance abuse treatment programs (7–42 days in length) will have the opportunity to participate in either standard care or in the telephone call protocol. A candidates log will record how many individuals were offered study participation. The Screening Form and the Randomization Form will capture information on consented candidates including if they were subsequently randomized.

Within the first 7 days from admission, eligible participants in residential treatment will be informed of an opportunity to participate in the study. Those expressing interest and who are eligible for the study will give informed consent within the first 7 days from admission, ideally as close as possible to the date of the participant's admission to the residential facility. Then, all baseline assessments must be completed as close as possible to the date of the admission, ideally within the first 7 business days after admission.

Just prior to discharge (as close as possible to the date of the participant's planned discharge, ideally within the 2 business days prior to the planned date of discharge or on

the actual day of discharge), study participants who complete all baseline assessments and have a continuing care (discharge) plan in place will remain eligible and will be randomly assigned to the SCG or TCG (standard of care plus a series of 7 supportive telephone calls distributed over 12 weeks).

Randomization will be performed at each participating residential program by using a randomization sequence developed by the statistician at the Lead Node and provided in sealed, sequentially numbered envelopes to the participating centers. A stratified randomization with permuted blocks will be employed. The randomization scheme will stratify by site (residential program) in order to maintain an approximate balance between treatment groups at each site.

For the TCG participants, calls will be made during weeks 1, 2, 4, 6, 8, 10, and 12 after discharge from residential care. Telephone calls will focus on the participants' self-reported adherence to the continuing care plan that was provided to them at discharge. Contact success and duration of all calls will be documented. A portion of calls will be recorded and at least 10% of successful calls will be randomly selected and scored for fidelity to the intended call procedures.

Participants in each group will be assessed for treatment effects at a follow-up visit expected to occur at 13 weeks after discharge from the residential setting. Day of discharge will be considered as day 0 of follow-up. The window for this visit will be from days 88–116 following discharge from the residential program.

During the study, data will be reviewed by study monitors utilizing the procedures established by the CTN to assess the completeness and accuracy of data collected.

The analysis of the feasibility and efficacy data will be presented to the Steering Committee for consideration in their decision on whether to conduct a larger, multi-site trial.

8.1 Duration of the Study

Enrollment is expected to take place over a period of 9–12 months. Each site is expected to enroll 60 to 120 participants during this period, which restricts the number of participating CTPs to 4 with a large program census. If enrollment is slower than expected, such that 60 to 120 participants are not randomized within 12 months, the trial may be discontinued early. The total duration of study participation will be the 13 weeks of the post-discharge intervention period plus the initial, variable length of residential treatment (7–42 days). Thus, enrollment should be completed and all study data should be collected within 15–18 months.

9.0 SUBJECT SELECTION

Participants enrolling at participating residential facilities for treatment of substance abuse who meet basic inclusion/exclusion criteria should be considered for the TELE protocol. There are 60 to 120 participants required for randomization in this study at each site. It is estimated that approximately two thirds of those candidates who sign informed consent will complete the baseline data collection, meet all other eligibility criteria, and

be randomized. Some participants may not complete the treatment program and may leave without a continuing care plan in place; others may withdraw consent prior to randomization.

9.1 Eligibility Criteria

Eligible candidates in the participating residential program will be informed of the study as soon as practical, but within 7 days from their admission to the residential program (days 1–7, recommended by day 3).

Eligible candidates include men and women who are at least 18 years of age and have the ability to understand and provide written informed consent. Candidates must be voluntarily admitted (not civilly committed) to a residential program for rehabilitation treatment (not admitted for detoxification only) and must have had a diagnosis for substance abuse or dependence for a minimum of 7 days and a maximum of 42 days. Candidates should be referred by a program servicing the targeted counties on admission and should plan to return to residence in targeted counties after discharge. Candidates must be able to be contacted via phone after discharge. Candidates will be excluded from consideration for the study if they have evidence of current suicide intention or recent (≤ 30 days prior to admission) suicide attempt.

Participants must complete all study procedures and assessments in the specified order, but flexibility in timing is permitted within the ranges provided. Participants must give informed consent to participate in the study within 7 days of residential facility admission (recommended by day 3), and all baseline measures must be completed as close as possible to the date of the admission, ideally within the first 7 business days after admission.

Randomization will occur as close as possible to the date of the participant's planned discharge, ideally within the 2 business days prior to the planned date of discharge or on the actual day of discharge. To be eligible for randomization, individuals must have completed all consent and baseline assessment measures, have been provided a continuing care plan from the residential program, and met with the research assistant.

Participants will be withdrawn from study eligibility, if, after being consented during the first 7 days of their residential treatment, they do not complete the study baseline measures as close as possible to the date of admission to the residential facility, ideally within the first 7 business days after admission, or if they leave the treatment program for any reason without completing and discussing a continuing care plan, or if they leave without being randomized.

See sections 9.1.1 and 9.1.2 for a complete list of inclusion and exclusion criteria.

Based upon estimates from the CTP staff, approximately 67.5% of those signing informed consent forms will complete the data collection and treatment planning activities (study baseline), will meet all other eligibility criteria, and will be randomized. Data on the number of participants giving consent and the number randomized will be collected for feasibility study purposes.

9.1.1 Inclusion Criteria

1. Men and women at least 18 years of age
2. Ability to understand and give written informed consent within the first 7 days of admission to the residential facility
3. Voluntary admission (not civilly committed) to the residential facility for rehabilitation treatment (not admitted for detoxification only)
4. Diagnosis of substance abuse or dependence (excluding nicotine and caffeine) according to residential facility records
5. Referral by a program servicing the targeted counties, with plans to return to residence in targeted counties after discharge from the residential treatment facility
6. Ability to be contacted via phone by research staff upon release from residential treatment

9.1.2 Exclusion Criteria

1. Unable or unwilling to provide informed consent
2. Failure to complete prescribed treatment, study baseline measures, or no provision for a continuing care plan prior to departure from the residential center
3. Evidence of current suicide intention or recent (≤ 30 days prior to admission) suicide attempt
4. Enrollment in a residential treatment program for < 7 or > 42 days

10.0 STUDY PROCEDURES (must occur in this order)

10.1 Screening and Obtaining Written Informed Consent

10.1.1 Candidates Log

In order to track the number of individuals who are invited to participate in the study, a log will be maintained by the research assistant, recording the number of candidates who received an invitation to participate in the study. Of those who were approached for participation, aggregated data will be provided to the Lead Node at the conclusion of the trial for those candidates who were excluded from study participation and thus did not sign a written consent form. These data will include the summary of the number of males and the number of females, categorization of age (e.g., how many candidates were between 20 and 29 years old), and categorization of the reasons candidates were not consented who were approached for participation.

Additional information will be collected on the Screening Form and the Randomization Form on all participants who sign the consent form. This information will record whether each consented candidate completed all study requirements to be randomized into the study. For candidates who fail to achieve randomization, the reason for this outcome will be recorded (e.g., premature discharge, failure to meet all eligibility criteria).

10.1.2 Initial Candidate Screening & Informed Consent

Each eligible candidate should be informed by the research assistant about the TELE feasibility study, as early in their residential stay as possible, following whatever plan the particular center has developed, but this must occur within the first 7 days of the candidate's admission to the program. The candidate should receive a detailed explanation of the study, with the opportunity to ask questions, and then be invited to participate in the study.

Candidates who agree to participate in TELE should be given a copy of the IRB approved consent form, with ample time to review the form. The research assistant should remain available to answer any questions the candidate might have about the study or explain any language in the consent the candidate does not understand.

Candidates who agree to participate will sign the informed consent and be given a copy of the signed agreement. At that time, or at a suitable time as close as possible to the date of the participant's admission to the residential facility, ideally within the first 7 business days after admission, the information for all baseline measures is collected by the research assistant.

10.2 Baseline Assessments

Baseline assessments must be completed as close as possible to the date of the participant's admission to the residential facility, ideally within the first 7 business days after admission to the facility following written informed consent, and will consist of completion of the following case report forms and other information gathering tools:

1. CTN Addiction Severity Index-Lite Version 1
2. HIV Risk Behavior Survey (RBS)
3. Screening Form
4. Randomization Form
5. Locator Form

10.3 Study Assessments Prior to Discharge

10.3.1 Pre-Discharge Interview

All participants will receive their program's routine continuing care plan (discharge plan), developed by their residential counselor or developed as usual at the specific treatment program.

All participants will meet with the research assistant prior to randomization as close as possible to the date of the participant's planned discharge, ideally within the 2 business days prior to the planned date of discharge or on the actual day of discharge. At the meeting, the research assistant will do the following:

1. Review the consent form signed by the participant to assure that the participant continues to understand and be a willing participant in the TELE study

2. Review the locator form previously completed by the participant and update as needed
3. Discuss the week-13 post-residential program follow-up visit:
 - a. Describe the visit (participant will be expected to answer questions, provide a urine sample, and perform a breath alcohol test).
 - b. Attempt to schedule the date, time, and the location of this visit. The participant should be given an appointment card (or equivalent) with the agreed-upon date for the follow-up visit.
 - c. Provide each participant with contact information for the research assistant who will conduct the follow-up visit, in case the participant needs to reschedule the week 13 visit and the locator information changes during the 13 weeks following discharge.
 - d. Obtain signed release form(s) for program(s) to which the participant is referred for post-discharge continuing care activities in order to verify compliance and release form(s) for arrest and conviction records to possibly verify self-reported criminal justice activity that occurred after discharge from the residential facility.

10.3.2 Review of the Continuing Care Plan and Randomization

All participants will meet with the TELE counselor prior to randomization as close as possible to the date of the participant's planned discharge, ideally within the 2 business days prior to the planned date of discharge or on the actual day of discharge, to review the continuing care plan. If a thorough review has been performed by the residential program counselor, the TELE counselor only needs to ensure participant comprehension of this plan. Subsequently, the TELE counselor will perform the manual randomization (of participants remaining eligible) to either telephone counseling calls (TCG) or standard of care (SCG). This will be done as close as possible to the date of the participant's planned discharge, ideally within the 2 business days prior to the planned date of discharge or on the actual day of discharge.

A set of envelopes, numbered sequentially and provided to each site prior to the recruitment of participants, will be used to determine a participant's random assignment. At the time of randomization, the TELE counselor will remove the envelope with the next sequential number. Upon opening the envelope, the TELE counselor will inform the participant of the group to which he or she is randomized. If the participant is randomized to SCG, the TELE counselor should remind the participant of his or her planned continuing care and the 13-week visit, and conclude the meeting. If the participant is randomized to the TCG, the TELE counselor should schedule the first call during this meeting. The participant should be reminded of his or her planned continuing care and the week 13 follow-up visit, and the interview should be concluded. Refer to the Counselors Manual for more details.

The goal of this pre-discharge meeting is to establish rapport with all study participants to avoid bias of the study results, which might occur if only the group randomized to follow-up phone calls had had the pre-discharge meeting.

10.4 Intervention after Discharge

Following discharge, a total of 7 telephone contacts at weeks 1, 2, 4, 6, 8, 10, and 12 will be made by the TELE counselor to all participants randomly assigned to the TCG. Each contact will follow the scripted procedure outlined in the Counselors Manual. The same procedure will be followed upon each contact. Up to 3 attempts will be made to contact the participant for each of the 7 scheduled calls, regardless of the outcome of the previously scheduled call.

Unless consent to participate is expressly revoked by the individual, he or she will continue to be contacted as scheduled. Attempts to contact the participant and the outcome of the call will be recorded on the participant contact form in the CRF. The SCG participants will not be contacted by the TELE counselor following their pre-discharge session.

A portion of calls will be recorded and at least 10% of successful calls will be randomly selected and scored for fidelity to the intended call procedures. Each node supervisor will provide supervision to the TELE counselor, per standard practice for the particular program.

In order to provide standardization across all TCG calls, the TELE Counselors Manual provides directions for conducting these calls. Information obtained during the course of the call will not be used as research data with the exception of serious adverse events. These events disclosed by the participant will be documented and reported as described in section 12.0.

The manual also provides minimal instructions for handling medical emergencies such as suicidal threats. Each facility is expected to have a written plan in place for emergency situations. If a plan is not in place, a procedure will be developed by the facility and should be available for review by the node quality assurance (QA) monitor prior to enrollment. Each facility has the responsibility for training its research staff on the facility's emergency plan.

10.5 Participant Initiated Contacts Between Discharge and Follow-Up Visit

If a TCG or SCG participant initiates contact with the original residential program and/or a TELE research staff member after discharge, he or she will be referred to the appropriate program staff member. If there is a change of locater information, the research staff will ensure that the information is updated on the participant's locater form. Additionally, the research staff will maintain a log of any study participant contacts made between discharge and the 13-week follow-up visit. Subsequently, they will be asked to provide this information to the Lead Node.

10.6 Week 13 Follow-Up

10.6.1 Week 13 Follow-Up Visit

At week 13 post-discharge, all participants will meet face-to-face with the designated research assistant from the CTP. There is a 4-week window of opportunity for the 13-week follow-up visit. The follow-up visit should document the following:

1. CTN Addiction Severity Index-Lite Follow-up Version 1
2. HIV Risk Behavior Survey (RBS)
3. Breath alcohol test
4. Urine sample collection for drug screen
5. Continuing Care Compliance Form
6. Serious adverse events
7. Study Completion Report (SCR)
8. Additional signed program-specific release form if participant attended a program that was not specified on the continuing care plan

If there is difficulty contacting the participant to schedule and/or confirm the 13-week visit, the research assistant may need to look at residential program records for possible updated locator information.

If the research assistant is informed by the participant of an emergency situation during the call to schedule the visit or during the follow-up visit, the research assistant will intervene per the facilities emergency plan.

10.6.2 Verification of Continuing Care Compliance after Follow-up Visit

After completion of the 13-week follow-up visit, participation in continuing care will be verified, where feasible, by confirming attendance/participation in the assigned program as identified on the continuing care (discharge) plan.

In order to verify this information, participants will be asked to sign a program-specific release form at the pre-discharge interview. If the participant attended a program that was not specified on the continuing care plan, an additional program-specific release form will be obtained during the follow-up visit. Attendance and participation in at least one counseling session will be recorded on the follow-up CRF.

Additionally, if approved by the local IRB, the research staff may confirm the participant's self-reported information on criminal justice activity by using the release signed at the pre-discharge interview and/or reviewing public records (e.g., court records, arrest logs, probation and parole records).

10.6.3 Verification of Continuing Care Compliance for Missed Follow-up Visit

If the follow-up visit is missed (e.g., the participant is a 'no-show'), the research staff will use release forms signed at the pre-discharge interview to verify attendance and

participation in the continuing care activities as identified in the residential program's continuing care plan. Additionally, if approved by the local IRB, the research staff may use the release signed at the pre-discharge interview to verify self-reported criminal justice activity that occurred after discharge from the residential facility.

10.7 Participant Compensation

Participants will be compensated \$25 in scrip or cash by the residential program for the time spent in providing the baseline data; each participant will also receive \$25 in scrip or cash by the research assistant at the 13-week follow-up visit for the time spent in the interview. Each CTP will determine the type of scrip most appropriate for its site. All compensation offered must be listed in the ICF and must be approved by the local IRB.

10.8 Participant Withdrawal

Participants are free to withdraw from participating in the study at any time. If they withdraw during the course of the study, they should be encouraged to complete the follow-up assessments that are expected to be obtained at the 13-week follow-up visit.

The principal investigators from each node retain the right to withdraw a participant from the study if the participant is determined to be a threat to self, staff, or other participants. Those participants who are withdrawn from the study by administrators will be provided appropriate referrals to alternative treatments in the area.

All participants randomized to one of the treatment conditions will be included in the data analysis regardless of their subsequent compliance with study procedures. Hence, any randomized participant who withdraws, discontinues, and/or is lost-to-follow should not be replaced.

10.9 Study Outline and Timeline

Table 1 summarizes the step-by-step study schedule and procedures. Steps must be followed within the indicated time intervals. Table 2 provides a timeline of the study.

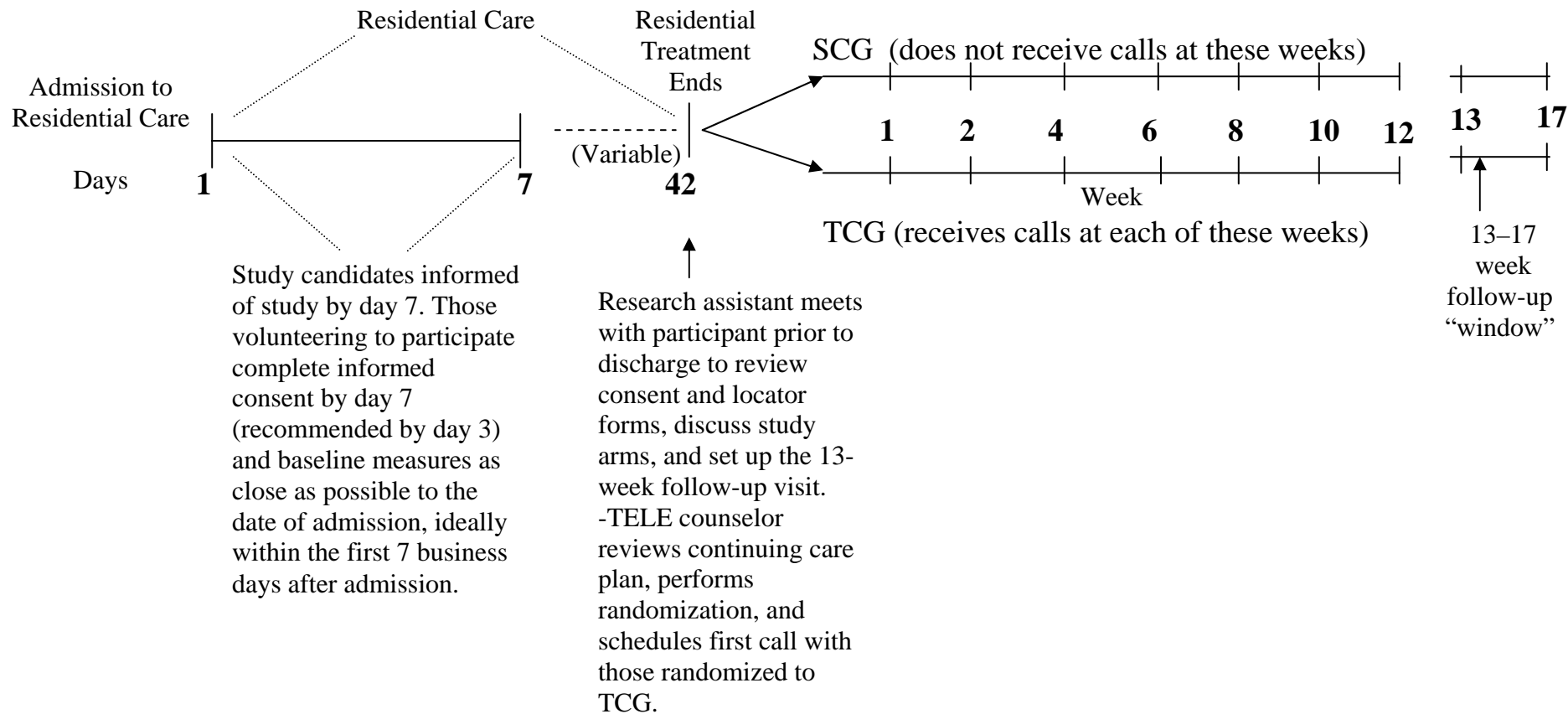
Table 1: Study Outline

| Activities During Residential Treatment | | | |
|---|--|--------------------------------|----------------------------------|
| Activity | Time Interval | | Responsible Staff |
| Inpatient treatment admission | Program day 1 | | Residential program intake staff |
| Recruitment/ Informed consent <small>(must be obtained prior to other activities)</small> | Program day 1–7 | | Research assistant |
| Completion of baseline assessments | Program day 1–7* | | Research assistant |
| Initiation of program continuing care plan | Program day 1–7 | | Residential program staff |
| Variable Residential Stay (7–42 Days) | | | |
| Pre-discharge interview | Discharge minus 2 days† | | Research assistant |
| Review of continuing care plan and randomization | Discharge minus 2 days† | | TELE counselor |
| Activities Following Discharge From Residential Treatment | | | |
| Week | 12-Week Telephone Contact Schedule for TCG Only | | |
| 1 | TELE call 1 | Discharge + 4–10 days | TELE counselor |
| 2 | TELE call 2 | Discharge + 11–17 days | TELE counselor |
| 4 | TELE call 3 | Discharge + 25–31 days | TELE counselor |
| 6 | TELE call 4 | Discharge + 39–45 days | TELE counselor |
| 8 | TELE call 5 | Discharge + 53–59 days | TELE counselor |
| 10 | TELE call 6 | Discharge + 67–73 days | TELE counselor |
| 12 | TELE call 7 | Discharge + 81–87 days | TELE counselor |
| Week | Post-Intervention Activities for Both Groups | | |
| 13–17 | Follow-up data collection | Day of discharge + 88–116 days | Research assistant |

* As close as possible to the date of the participant’s admission to the residential facility, ideally within the first 7 business days after admission.

† As close as possible to the date of the participant’s planned discharge, ideally within the 2 business days prior to planned discharge or on the actual day of discharge.

Table 2: Study Timeline Algorithm



11.0 ASSESSMENT METHODS

11.1 Screening Form

The Screening Form will be completed on all patients consented for participation in the TELE protocol. Initially, it may serve as a guide to recruit participants for the study.

11.2 Locator Form

A Locator Form will be completed by each consented participant and will be kept confidential in the participant's records. Data collected on the Locator Form will be used to facilitate contact with the participant for the follow-up aspects of the project.

Participants will be asked to provide locator information, including a residential street address, working telephone number, driver's license and social security numbers, as well as the addresses and phone number of individuals who may know of their whereabouts. Additionally, participants will be asked to provide the name, address, and phone number of an individual who may be contacted in the event of an emergency. The information will be collected at baseline and reviewed and updated by the research assistant during the participant's pre-discharge interview, prior to randomization.

11.3 HIV Risk Behaviors Survey

The Risk Behavior Survey (RBS), an abbreviated version of the Risk Behavior Assessment (RBA) developed by NIDA for the Cooperative Agreement, will be used to measure risk behaviors related to human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Risk behaviors in the areas of drug use and sex in the previous 30 days are measured. Reliability and validity assessments of the RBS support its adequacy as a research tool for populations of drug users, including intravenous drug users (Darke et al., 1991; Weatherby et al., 1994; Needle et al., 1995).

11.4 CTN Addiction Severity Index-Lite Version 1 and Follow-up Version 1

The CTN Addiction Severity Index-Lite Version 1 and Follow-up Version 1 forms are multidimensional, semi-structured, comprehensive clinical interviews, which provide clinical information important for formulating treatment plans, as well as problem severity profiles in 6 domains commonly affected in substance abusers (McLellan et al., 1985). The domains covered are chemical abuse (alcohol and drug), medical, psychiatric, legal, family/social relations, and employment/support status. Composite scores for each problem domain are derived mathematically and used as change measures or outcome indicators as a function of treatment intervention.

These instruments also provide clinically necessary information on whether the participant is at imminent risk for suicide, thus permitting evaluators to implement any

needed immediate and/or early intervention strategies. The CTN ASI - Lite forms will be administered by a research staff member with a bachelor's degree in the social sciences or equivalent training and experience, as determined by the site's investigator. Composite scores will be calculated according to the procedures described by McGahan et al. (1982), and Carroll et al. (1994).

The CTN ASI - Lite Version 1 form will be administered during the baseline assessment and the CTN ASI - Lite Follow-up Version 1 will be administered at the 13-week follow-up visit.

11.5 Randomization Form

Prior to randomization, through review of the Randomization Form, the research assistant will confirm the participant's eligibility for randomization. If the participant remains eligible, the subject will be randomized and the treatment group assignment will be recorded on this form. If the participant is not randomized, the reason for ineligibility for randomization will be captured on this form as well.

11.6 Urine Drug Screen

Urine samples are to be collected by the research assistant at the 13-week follow-up visit by use of collection cups with temperature-controlled monitoring strips. These cups will be provided by the manufacturer as noted in the Operations Manual, and will provide a rapid measure of the presence of the following: opioids, methadone, benzyloecognine (a cocaine metabolite), amphetamines, cannabinoids, and benzodiazepines.

11.7 Breath Alcohol Test

A breath alcohol test for measuring the presence of alcohol will be administered by the research assistant at the 13-week follow-up visit. The results will be recorded on the breath alcohol form, which is a common battery form for the CTN. The details of the manufacturer and the process for obtaining and recording results of this test will be defined in the Operations Manual.

11.8 TCG Participant Contact Form

The TCG participant contact form will capture the TELE counselor's attempts to contact a participant (randomized to the TCG only) and the actual successful contact information.

11.9 Week 13 Continuing Care Compliance Form

This form will document the extent of all participants' involvement, knowledge, and satisfaction in their prescribed continuing care plan.

11.10 Serious Adverse Events CRF

Serious adverse events, as defined in section 12.3.3.1, if reported to the TELE counselor during telephone contacts made at weeks 1, 2, 4, 6, 8, 10, and 12, or as elicited by the research assistant during the 13-week follow-up visit, will be addressed by the TELE counselor or the research assistant. Serious adverse events (which occurred from the time of randomization through the 13-week follow-up visit, and not previously recorded) which are reported to the TELE counselor during the scheduled telephone calls, or which are elicited by the research assistant during the 13-week visit, will be recorded on the SAE CRF and reported, as described in section 12.3.3.2.

Prior to study implementation, each site will have a documented plan describing their procedures in cases of suicidal or homicidal threats or attempts or other medical emergencies. During the course of the intervention period and at the follow-up visit, if participants are found to be in acute need of psychiatric attention for threats of these types or to have any condition requiring medical attention, the participant will be referred per the CTPs documented plan to community referral resources, including a medical care facility, readily available community hotlines, or other appropriate resources.

All SAEs determined to be related (refer to section 12.3.3.3) are to be brought to the attention of NIDA/CCTN medical monitor, the Lead Node medical monitor, and the local node/site PI within 24 hours of learning of the event and the local Institutional Review Board (IRB) per local requirements.

11.11 Study Completion Report

The Study Completion Report (SCR) is a brief tracking instrument used to officially record the time at which participants become inactive with respect to the study protocol. The SCR will be completed by the research assistant at the follow-up visit or the last planned contact, or upon early termination from the study, whichever occurs first.

11.12 Schedule of Instrument Administration:

Table 3 shows the timepoints at which each instrument is to be administered.

Table 3. Schedule of Instrument Administration

| Instruments | Baseline | Randomization | TELE Counselor Calls by Week | | | | | | | Follow-up Visit (13–17 Weeks) |
|---|----------|---------------|---------------------------------|---|---|---|---|----|----|----------------------------------|
| | | | 1 | 2 | 4 | 6 | 8 | 10 | 12 | |
| Screening Form | X | | | | | | | | | |
| Randomization Form | | X | | | | | | | | |
| Locator Form | X | X | | | | | | | | |
| HIV Risk Behavior Survey (RBS) | X | | | | | | | | | X |
| CTN ASI-Lite V1 | X | | | | | | | | | |
| CTN ASI-Lite Follow-up V1 | | | | | | | | | | X |
| Urine drug screen | | | | | | | | | | X |
| Breath alcohol test | | | | | | | | | | X |
| TCG Participant Contact Form | | | X | X | X | X | X | X | X | (TCG only) |
| Week 13 Continuing Care Compliance Form | | | | | | | | | | X |
| Serious adverse events CRF* | | | | | | | | | | X |
| Study Completion Report (SCR)* | | | | | | | | | | X |
| Verification Form* | | | | | | | | | | X |

* To be collected at termination of study participation.

12.0 REGULATORY AND REPORTING REQUIREMENTS

12.1 Institutional Review Board Approval

Prior to initiating the study, the investigator at each study site will obtain written Institutional Review Board (IRB) approval for the protocol and the participant informed consent form. Should changes to the study protocol become necessary after initial IRB approval is obtained, protocol amendments will be prepared by the Lead Node and must be submitted in writing to each participating Node’s IRB by the investigator for his or her CTP. Written IRB approval is necessary prior to implementation of the protocol. In addition, IRBs will approve all advertising materials used for participant recruitment and any educational materials planned to be provided to the participant.

12.2 Informed Consent

All candidates for the study will be given a copy of the informed consent form approved by their IRB to read. The consent form may be read to any participant who is unable to read. The research assistant at each site will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study.

Any individual who wants to participate in the study will be asked to sign the informed consent. A copy of the signed consent form will be made and given to the participant. No information for the study will be obtained, or any study procedure performed, prior to the informed consent being signed by the participant.

Individuals who refuse to participate in the study or who withdraw from the study after providing consent will be treated without prejudice or penalty. The reason for refusal or withdrawal will be noted in the screening/enrollment log.

Because of the potential time lapse between actually obtaining written consent and randomization, the research assistant will remind each participant just prior to randomization of the voluntary nature of study participation and the right to withdraw consent to participate at any time.

12.3 Data and Safety Monitoring Plan

12.3.1 Clinical Monitoring

Prior to site enrollment, the Lead Node and node QA monitor is responsible for assuring that proper study-related documentation exists. The Lead Node QA monitor also assists in training investigators and other site personnel in study procedures and good research practices. Additionally, the Lead Node QA monitor will conduct a site initiation visit. The TELE Protocol Initiation Endorsement Form will be signed by the node PI, the lead investigator, and the NIDA representative to authorize site enrollment.

All investigators will allow representatives of their local node, Lead Node, and NIDA or its representatives to periodically visit the participating CTP at mutually convenient times during and after the study. The purpose of these visits will be to assure that submitted data are accurate and in agreement with source documentation, and that all essential documentation required by good research practice guidelines is appropriately filed. In order to complete the required monitoring, these periodic monitoring visits will occur more frequently at the beginning of the study and as needed for the remaining duration.

In order to provide adequate monitoring for this feasibility trial of limited duration for subject participation (3 months) and minimal risk to participants, the following are the minimum requirements to be performed by the node QA monitor at each site:

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- All informed consent documents will be reviewed to verify that consent for study participation has been properly obtained and documented prior to performance of any study specific procedures.
- All reportable serious adverse events (as defined in section 12.3.3.3) will be reviewed.
- All source data verification will be performed on a minimum of 5% of randomized participants.

Additionally, these monitoring visits provide the local node with the opportunity to evaluate the progress of the study at each of their sites and to inform the Lead Node or/and NIDA of potential problems at the study sites. Prior to leaving the site, the node monitor will conduct an exit meeting with the site investigator and/or study personnel to review and clarify preliminary findings, which include any outstanding items and the appropriate plan of action. These activities and findings will be documented in a visit report by the node QA monitor and will be distributed to the site investigator, node PI, Lead Node PI, and NIDA.

Throughout the trial, the Node QA Monitor or designee will maintain phone contact with participating sites to address study progress.

At the end of the study, the node QA monitor will perform close-out activities necessary to conduct a final review of the study administrative and regulatory records, to ensure that all outstanding issues are resolved, and to review record maintenance and archival requirements with the site.

12.3.2 Data and Safety Monitoring Board

12.3.2.1 Review of Data

The NIDA Clinical Trials Network Data and Safety Monitoring Board (DSMB), appointed by the NIDA CTN director, will conduct periodic reviews of safety and conduct of this trial. The DSMB will also review amendments to the study protocol. The DSMB will review data independently from the study sponsor, investigator(s), and IRBs to evaluate whether the accumulating data support continuing the trial for reasons relating to the randomization of study subjects and the safety of the study subjects. The DSMB will be provided with listings of SAEs to allow monitoring of patient safety, in summary tables of events or other formats preferred by the DSMB for their review. In conducting its reviews and making recommendations to NIDA regarding the status of this trial, the DSMB will assure that the safety of study subjects is protected while the scientific goals of the study are being met.

In addition, the DSMB will review the feasibility indicators of the trial to determine whether study procedures need to be changed to improve enrollment or whether attempts to accrue participants or access efficacy outcomes of the treatment under study are futile for the trial to continue. Since this is a feasibility trial, the DSMB will not base a

recommendation to terminate the trial early on either positive or negative efficacy trends, but instead on whether the efficacy data can be collected by the sites.

In order to assure the integrity of this study, DSMB members must agree to respect the confidentiality of the data they are asked to review. Members of DSMB will be asked to sign a statement of confidentiality confirming their agreement not to disclose data other than under the terms of this document.

12.3.2.2 Interim Analysis

Interim analysis: No formal interim analysis plan is necessary for this feasibility trial of limited duration for subject participation (3 months) and minimal risk to participants (telephone calls to engage participants in continuing care plans).

12.3.3 Collection and Reporting of Serious Adverse Events

12.3.3.1 Adverse Events - Definitions

An *adverse event* (AE) is any reaction, side effect, or untoward event that occurs during the study, whether or not it is considered study-related or clinically significant. AEs will include events reported by the patient or observed by clinic or study staff. A new illness, symptom, sign, or worsening of a preexisting condition or abnormality is considered an AE. Stable chronic conditions that were present prior to study entry and do not worsen are not considered AEs.

A serious adverse event (SAE) is an adverse event (as defined above) that results in one of the following outcomes: Death, life-threatening, persistent or significant disability/incapacity, requires or prolongs hospitalization and a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Requires or prolongs hospitalizations does not include hospitalizations related to normal child birth, elective hospital admissions scheduled prior to the study and hospitalization for an elective procedure or Emergency Room visits.

A *related adverse event* is an AE that is a result of the patient's participation in this study and/or a result of study intervention.

12.3.3.2 Collection and Recording of Serious Adverse Events

AEs meeting serious criteria (as defined in 12.3.3.1) will be collected from the time

of randomization through the 13-week follow-up visit and captured on the CRF (refer to section 11.10). The SAE CRF will include a description of the event, the date of onset, the severity of the event, whether or not the event is study related, and the outcome of the event. All CTPs should have a consulting physician available to review AEs in order to determine their seriousness and causality. Non-physician LIs/PIs are expected to obtain medical consultation as necessary.

All SAEs that are both serious and study related (result from the patient's participation and/or related to study intervention) will be reported by fax to NIDA/CCTN Medical Monitor, the lead investigator, Robert H. Hubbard, PhD, and DCRI Safety Surveillance in accordance with section 12.3.3.3. All SAEs will be followed by study investigators until event resolution, stabilization, or through the completion of the final 13-week follow-up visit, whichever occurs first.

Any AE that does not meet SAE criteria as defined in the protocol will not be captured for the purposes of this research study.

12.3.3.3 Expedited Reporting of SAEs

SAEs that are related to study intervention or/and participation must be reported **within 24 hours** of the learning of the event according to the following procedures:

Initial notification of the event should be reported by fax to the following:

NIDA/CCTN Medical Monitor

Phone number: 301-443-6697

Fax number: 301-443-2317

Robert H. Hubbard, PhD, MBA, Lead Investigator

Phone number: 919-863-4600 ext. 229

Fax number: 919-863-4601

DCRI Safety Surveillance

Phone number: 919-668-8624

Fax number: 919-668-7138

The fax notification should include a Serious Adverse Event Report Form and a copy of the SAE CRF page along with copies of any applicable supporting documentation, if available. DCRI Safety Surveillance will review and data base the information received, query the submitting node for missing and/or additional information, write a case summary and obtain Medical Monitor review. The DCRI Safety Surveillance Medical Monitor will perform a medical review of the SAE data, perform an independent evaluation of causality and seriousness, query DCRI Safety Surveillance for any additional information needed from the node, and approve the case summary within 2 business days of initial receipt of the

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SAE form. DCRI Safety Surveillance will provide a copy of the SAE Report Form, SAE CRF page, case summary, any applicable supporting documentation to the lead investigator and the NIDA Medical Monitor within 5 calendar days of initial receipt of the SAE forms.

The initial SAE report should include the relationship (causality) to study intervention and/or to the patient's involvement in the study. This assessment should be determined by the principal investigator. In the case where the principal investigator is not a physician, this assessment must be made by the delegated qualified physician for the CTP. All SAE forms must also include the principal investigator's signature, or in the case where the principal investigator is not a physician, the signature of the delegated qualified physician for the CTP making the assessment of causality. If the principle investigator or qualified physician is not available to sign the form within 24 hours of the site's knowledge of the event, please fax the SAE Report Form and SAE CRF within 24 hours and send a signed form as soon as it becomes available.

DCRI Safety Surveillance will continue to work with the site to obtain all relevant information for the SAE and/or until the final outcome is determined. A follow-up Serious Adverse Event Report Form and SAE CRF page should be sent as soon as any additional significant information concerning the SAE in the same format and timeframe (within 24 hours) as outlined above. Events not resolved at the end of the trial will have an outcome of "ongoing".

Note: Reports and supporting documentation will be sent by the site in a blinded fashion, and the participant will only be identified by the participant number on each page of supporting information.

The investigators in this study are responsible for promptly reporting all events meeting the defined SAE criteria above, so that NIDA can comply with regulations and adequately monitor the safety of participants. Local IRB procedures and requirements for the reporting of AEs and SAEs may differ. It is important that the staff at each participating node be aware of the requirements of their IRB and report AEs and SAEs as required.

The DSMB will review all relevant safety data as directed by the NIDA/CCTN Medical Monitor and make recommendations of actions required and/or changes needed to the protocol, as necessary. These recommendations will be communicated to all nodes by the lead investigator, as needed.

12.3.4 Data Management QA Plan

A detailed document that contains the Data Management QA Plan will be maintained at the Duke Clinical Research Institute, the Lead Node's Data Management Center. This document will describe the procedures, i.e., data entry, storage and manipulation of the

data, and the output of data, which are used to ensure that the information collected, is the same as the information sent to NIDA.

12.4 Study Documentation and Records Retention

Study documentation includes all case report forms, data correction forms, electronic data files, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments; Ethics Review Committee or IRB correspondence, approved consent form and signed participant consent forms; and clinical supplies records).

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 an exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial for at least 6 years or until the study is completed, whichever is longer.

12.5 Confidentiality

To safeguard confidentiality, the Lead Node PI will apply for a Certificate of Confidentiality from NIDA on behalf of all participating sites.

12.5.1 Confidentiality of Data

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

12.5.2 Confidentiality of Study Records

By signing the protocol, the investigator agrees that within local regulatory restrictions and ethical considerations, NIDA (the study sponsor) and its representatives, or any regulatory agency may consult and/or copy study documents in order to verify case report form data.

12.5.3 Confidentiality of Counselor Phone Calls

During the pre-discharge meeting for TCG participants and as deemed appropriate during the TELE procedure, the counselors will clarify specific calling guidelines with each participant as a means to maintain the participants' confidentiality. The counselors should list all restrictions for the telephone calls noted by the participant. The counselor should address any concerns or questions participants might have regarding the call process

during the pre-discharge meeting or during the subsequent calls to avoid problems later. Participants should have reassurance that their confidentiality will be strictly maintained, that no information will be disclosed to anyone, with the exception of threats of self-harm or suicide, child/elder abuse, or domestic violence. The purpose of the call procedure is to encourage the participant to engage in continuing care activities, not to collect information to disclose to anyone. With the exceptions noted above, no information will be disclosed to anyone, including the primary care counselor or residential facility. Participants should be encouraged to disclose any pertinent information themselves, with support and encouragement from the TELE counselors. Reassurance may help reduce the participant's uncertainty or anxiety about being contacted.

13.0 ANALYTICAL PLAN

13.1 Analytical Considerations

This clinical investigation serves 2 purposes: (1) to evaluate the feasibility of the study within the CTN and (2) to explore the effectiveness of TCG as compared with the SCG. The later analysis will be used to augment the feasibility data by providing preliminary findings that can be incorporated in the power and sample size determinations for a future large-scale study. Descriptive statistics will be used to address the primary feasibility issues, while a combination of descriptive statistics and hypothesis-testing methods will be used to explore treatment effectiveness.

Descriptive statistics presented for continuous variables will include the mean \pm 1 standard deviation, the median and 25th and 75th percentiles, as well as 95% confidence intervals of the mean. Categorical variables will be presented as proportions, with 95% confidence limits. Inclusion of the confidence intervals will allow investigators to ascertain the values of the point estimates likely to be found in a larger efficacy trial. Summary data will be presented across all sites, as well as by site.

13.2 Feasibility Indicators

Feasibility information will be gathered to determine the proportion of (1) total eligible participants who volunteer and thus consent to participate in the study, (2) consenting participants completing all required residential treatment and baseline assessments, (3) consenting participants meeting the eligibility criteria, (4) consenting participants randomized into one of the 2 treatment conditions, (5) randomized participants contacted by phone after discharge, (6) randomized participants who could be contacted for follow-up visit, and (7) randomized participants completing the follow-up during the visit.

In order to determine 1–7 above, we will need to collect the following information:

- Number of participants entering the residential program
- Number asked to participate in the protocol
- Number agreeing to participate in the protocol
- Of those who agree, the number who complete the baseline assessments
- Of those who agree, the number who complete the residential program

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- Of those who complete the residential program, the number who meet eligibility criteria for the study
- Number of participants randomly assigned to a treatment group;
- Number of patients successfully contacted to schedule week 13 visit
- Number of week 13 visits completed for the randomized patients
- Of those who complete a week 13 visit, time interval between discharge and the follow-up visit

For the TCG participants, logs of phone calls and attempted contacts will be compiled to examine the proportion of participants in which the 7 phone contacts were delivered and the average number of phone contacts delivered per participant. To determine whether it is possible to reach participants by telephone after they have been discharged from residential substance abuse care, the following data will be collected:

- Number of scheduled phone contacts attempted
- Number of scheduled phone contacts completed (delivered)

For the TCG condition, fidelity procedures have been included in the study to evaluate whether counselors who deliver the calls can conduct these calls in a standardized manner when provided with a structured “script.” A portion of calls will be recorded and at least 10% of successful calls will be randomly selected by the Lead Node statistician for analyses for treatment integrity and fidelity.

If the above items are successful in terms of their implications for feasibility, what is the magnitude of the “effect size” of such a study design? This will be done by assessing the efficacy outcomes from this preliminary study (which reflect actual participant outcomes) and comparing results from various other analyses to arrive at a reasonable estimate of the effect size.

Taken together, the results derived from the feasibility indicators will be reviewed by experienced investigators at the nodes and in the leadership of the CTN, and decisions will be made concerning whether the pattern of participant availability is amenable to the conduct of a full-scale study of the telephone protocol.

13.3 Efficacy Outcomes

Comparisons of the TCG and SCG groups will be made with regard to the following: (1) participant engagement in aftercare programs and (2) drug and alcohol use abstinence at 13 weeks post-discharge. We believe that those who receive the telephone calls during the post-discharge period will have better compliance with aftercare programs and a higher drug/alcohol abstinence rate at the follow-up visit than those who do not receive calls.

The main efficacy measures will be—

- Self-reported engagement in aftercare activities prescribed in the continuing care plan prepared by the residential treatment program, derived from the number of treatment and self-help activities the patient engaged in/attended during the 13-week post-discharge period
- Drug use as measured by urine test
- Alcohol use as measured by breath alcohol test

Self-report measures that will be examined as part of a supplemental analysis include—

- Drug and alcohol use during the past 30 days as measured by the CTN ASI-Lite forms
- Other measures of functioning from the CTN ASI-Lite forms
- HIV and HCV risk behaviors as measured by the HIV Risk Behavior Survey (RBS)
- Client satisfaction with the continuing care plan, as measured by the 13 Week Continuing Care Compliance form

13.3.1. Analysis of the Efficacy Outcomes

The efficacy analyses will be used to guide future research and provide preliminary data to estimate the effect size and required sample size for a clinical trial. To this end, descriptive statistics will be presented for each outcome as described in Section 13.1. Although the main goal of this study is to evaluate feasibility, a set of hypothesis-testing methods will be applied to provide a preliminary evaluation of the treatment effects. The later analysis will provide a preliminary overview of the clinical effectiveness of the regimen of telephone calls. Information from this study can then be used to inform the design of a full-scale clinical trial of the TELE protocol.

The results of the following hypothesis-testing procedures should be used to guide future research plans rather than to draw definitive conclusions regarding the relative effectiveness of the 2 treatment conditions. In the case of a binary outcome (e.g., abstinence or non-abstinence), tests for differences in proportions will be performed to examine between treatment group differences. A student's *t*-test for independent groups will explore between-group differences on continuous outcome measures. If continuous data violate the assumption of normality, the Wilcoxon rank-sum test will be used to

compare groups. For each of these 2-tailed statistical tests, a *P* value will be presented. However, there will be no predefined level of significance established for the present study due to its exploratory nature.

Outcome measures will be analyzed for the entire study population. Descriptive statistics will be presented for each outcome. The analysis will be conducted to investigate the characteristics of the variables from each site prior to combining data from multiple sites. Comparisons will be between the SCG and TCG performances both within each site and across sites.

Equality of treatment groups at baseline will be evaluated by comparing demographic and drug-use information collected on the CTN ASI-Lite Version 1 and Follow-up forms. Baseline demographic values that potentially affect the responses or are found to be unevenly distributed between groups at baseline despite randomization may be investigated in supplementary analyses. Baseline values are not planned to be covariates in any analyses because sample sizes are expected to be too small. Where possible, treatment effects will be summarized by gender, ethnicity, and age group separately.

A summary will be prepared to show dropouts/retention over time in each treatment group. The number of missing observations will be compared between treatments. In the analysis of the effect of the telephone call regimen on the participant abstinence (objective measure by urinalysis & breathalyzer), participants lost to follow-up at 13 weeks will be handled in 2 different approaches in an attempt to elucidate the influence of missing data on interpretation of the results. In the first analysis, participants lost to follow-up at 13 weeks will be considered “non-abstinent” to account for the possibility that non-abstinent participants may be more likely to be lost at follow-up. In the second approach, participants lost to follow-up at 13 weeks will be considered as missing. We anticipate that the category “missing at follow up” will account for 20% or fewer of randomized participants. Effects of gender and substance use diagnosis will be investigated in a supplementary analysis.

13.4 Serious Adverse Event Listings

At the end of the trial, listings of SAEs will include the relatedness of the event to the study, the outcome of the SAE, gender, age, and ethnicity for the participant. All interim reports will present these events in a blinded manner unless otherwise specified by the DSMB.

13.5 Sample Size Estimate

Because this is a feasibility study, we had 3 major considerations: to complete the study in a timely manner, to keep the costs low, and to recruit as many participants as possible within these constraints. Thus, rather than statistical power guiding the sample size decision, real-life research constraints were invoked. In terms of study timeline, the duration of enrollment is anticipated to be 9–12 months in order to give the CTPs ample time to become familiar and competent with the study protocol, so that in addition to

months reflecting start-up, we would have data for several months that reflect the full potential of the CTPs to recruit participants. Each CTP is expected to randomize about 60 to 120 participants across the recruitment period. Thus, 360 participants are estimated for the total sample size across CTPs.

Not all individuals who agree to participate will complete their residential treatment episode, and an additional number will fail to meet the eligibility criteria for the study. Based upon program experience, we expect approximately 25% of participants to fail to complete their residential treatment, and an additional 15% to fail to meet the eligibility criteria of the study. Thus, if 16 participants per month agree to participate, we would expect 12 to complete their residential treatment, and approximately 10 to meet the eligibility criteria of the study. Based on these numbers, we expect that approximately 4 participants per week will agree to participate at each CTP (at intake to the residential program).

13.6 Post Hoc Analysis

During the course of conducting the primary and secondary summaries, the data may suggest other interesting differences by CTP or treatment group. Post hoc analyses are anticipated to explore these findings. One potential post hoc analysis would be the exploration of factors found to be significantly different between groups at baseline, as they relate to study outcomes. Other potential post hoc analyses would be the exploration of the effects of gender and site on outcomes. Additionally, a comparison of baseline characteristics between participants who are randomized and those contacted for follow-up will be completed for generalization of the conclusions.

13.7 Randomization

Randomization (1:1 treatment allocation) will be performed using a randomized block design, stratified by site. This will enable sites to enroll differing numbers of participants while maintaining a fairly close balance between groups within sites. One of the outcomes of this feasibility study is the measure of whether the CTPs are capable of enrolling the expected numbers. Thus, some of the CTPs may not enroll the expected number, and we will employ blocking in order to preserve our ability to examine existent data at the end of the study. Block size will be determined by the statistical group at the Lead Node who will prepare the randomization scheme.

14.0 DATA MANAGEMENT AND CASE REPORT FORMS

14.1 Data Collection

Database management and quality control for the TELE trial are the responsibility of the Duke Clinical Research Institute (the Lead Node Data Management Center).

The investigators will collect information required by the protocol on case report forms (CRFs). Data on subjects collected on CRFs during the trial will be documented in an

anonymous fashion, and the subject will only be identified by the subject number and by his or her initials. Upon completion, the CRFs will be forwarded to the Lead Node Data Management Center.

All information required by the protocol should be obtained and any omissions should be explained. CRFs should be completed on an ongoing basis during the study according to the instructions provided during training. The investigator is responsible for maintaining accurate, complete and up-to-date records for each participant. The investigator is also responsible for maintaining any source documentation related to the study, including any items such as recordings, computer discs, or tapes.

14.2 Data Accrual, Editing and Control

Completed CRFs will be submitted on a regular basis to the Data Management Center at Duke Clinical Research Institute. Upon receipt of the CRFs, the Data Management Center will process them according to DCRI standard operating procedures. Quality control methods will be utilized throughout the process to maintain the data's integrity (see section 12.3.4).

When data is received at the Data Management Center, it will be reviewed, and if incomplete or inaccurate data are found, a Data Clarification Form (DCF) will be forwarded to the sites for a response. Sites will resolve data inconsistencies and errors prior to returning data to the Data Management Center. All corrections and changes to the data will be reviewed prior to being entered into the study database.

When there are no required or expected outstanding queries, and all expected data has been received, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Lead Node project leader, the Lead Node trial statistician, the Lead Node data manager, and a NIDA representative.

15.0 TRAINING AND FIDELITY MEASUREMENT

15.1 Training

Training of the Node QA monitors will be performed by the Lead Node prior to the commencement of enrollment. This training will consist of the details of implementing and following through with the protocol requirements and the monitoring aspects of the protocol. Periodically during the trial, discussions will occur between the Lead Node and node QA monitors to ensure adherence to the monitoring plan.

Protocol training of CTP research staff will be performed by the Lead Node and as needed by the local node quality assurance monitor.

Training of research assistants and other applicable site study personnel will cover protocol specific measures including screening, locator, breath alcohol, urine collection,

participant contact, continuing care compliance, serious adverse events and study completion. See section 11.0 for details.

Training in Good Research Practices (GRP), the ASI and the RBS will be provided at the node level, with the goal of certifying research assistants to collect study data measures in the manner established by the CTN training committee.

Counselors selected to participate in the protocol will be trained by the Lead Node to conduct the study calls in a standardized manner using the script found in the TELE Counselors Manual. Additionally, TELE counselors and research assistants will be directed to follow the minimal suggested instructions in the Counselors Manual and their local CTP guiding policies in the management of emergency situations such as suicidal threats and other medical emergencies.

On-site clinical supervision for TELE counselors will take place within each of the 4 CTPs, according to CTP supervisory plans acceptable to the Lead Node PI.

15.2 Fidelity Measurement

An interventional fidelity procedure was developed by using the model described by Bond et al. (2000). The fidelity issues to be reviewed include issues surrounding call protocol implementation. The questions to be answered include—

- Are the calls being implemented in the same manner within and between participating sites?
- Are all counselors adhering to the call protocol?

To determine fidelity to the telephone protocol, a comprehensive list of the essential and prohibited call dimensions was generated by the TELE Protocol Development Team, under the guidance of the Betty Ford Center. A list of behaviors considered to be essential elements to the call process was developed and used to create a rating instrument designed to measure counselor fidelity. The rating instrument will be utilized by an independent reviewer from the Lead Node to score the counselors on the key dimensions of the call procedures.

The key dimensions of the call protocol include the content, style, and time allocation of each call. The content component will look at adherence to the TELE Counselors Manual. The style of the call is expected to be consistent with the philosophy of the Betty Ford model, which includes active listening and positive reinforcement. The counselor is expected to express interest in the well-being of the participant, and to allow the participant the opportunity to voice concerns.

The time allocation for each call is estimated to be 15 –30 minutes in duration.

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A portion of calls will be recorded and at least 10% of successful calls at each site will be randomly selected and rated to generate an estimate of fidelity with a reasonable confidence interval.

Participants will be informed during the consent process that their phone calls may be recorded for fidelity purposes only, and if recorded, may then be compared by an independent rater at the Lead Node for reliability purposes only.

This procedure will allow for site and counselor comparisons. All recordings will be destroyed after fidelity is measured.

Other data sources, including the Participant Contact Form, will be reviewed for fidelity purposes. A subset of the contact forms will be reviewed to determine whether the contact protocol was followed, i.e., no more than 3 attempts made to contact the participant at each of the 7 contact points. The contact sheets will also be reviewed to make sure the telephone contacts occurred during the appropriate weeks (1, 2, 4, 6, 8, 10, 12).

16.0 SIGNATURES

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; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse events as defined in section 12.3.3 of this protocol.

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

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