Protocol Title: Brief Strategic Family Therapy For Adolescent Drug Abusers

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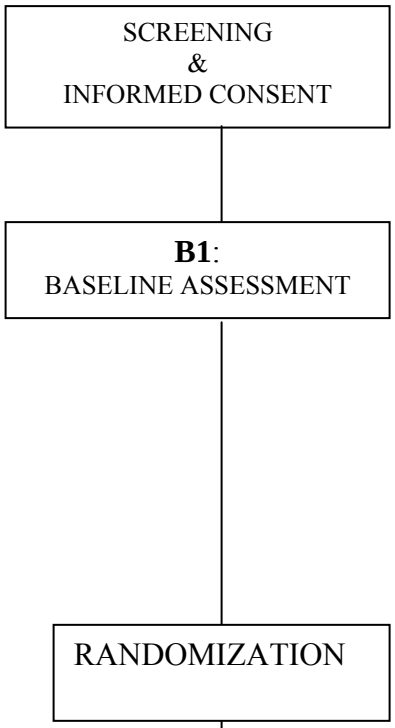
LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BSFT	Brief Strategic Family Therapy
CRF	case report forms
CTN	Clinical Trials Network
CTP	community treatment program
DMC	data management centers
DMAS	Data Management and Analysis Subcommittee
DSM-IV	Diagnostic and Statistical Manual, Fourth Edition
IRB	Institutional Review Board
NIDA	National Institute on Drug Abuse
SAMHSA	Substance Abuse and Mental Health Services Administration
SAE	serious adverse event
SOP	Standard Operating Procedures
TAU	Treatment as Usual

SYNOPSIS AND SCHEMA

This study randomly assigns drug using adolescents to Brief Strategic Family Therapy (BSFT) or Treatment as Usual (TAU). 480 adolescents and their families from approximately 8 community treatment sites will participate. Randomization will be stratified by CTP. Within CTP participants will be stratified using urn randomization. This will be achieved using a standard telephone call-in service provided by the Veteran's Affairs. Drug use will be assessed at baseline and every month for 12 months post-randomization. Adolescents and their parents will be assessed with measures for secondary outcome hypotheses at baseline, at approximately 4-months, 8-months, and 12-months post. Randomization takes place after baseline (B1 for outpatient sites; B2 for post-residential sites). Figure 1 represents the protocol schema.

FIGURE 1. STUDY SCHEMA



	MONTHS POST RANDOMIZATION											
	1	2	3	4	5	6	7	8	9	10	11	12
Intervention Services: BSFT or TAU	X	X	X	X								
Assessments for drug use	X	X	X	X	X	X	X	X	X	X	X	X
Assessment for secondary hypothesis				X				X				X

Figures 1 shows that all participants are screened and complete informed consent procedures prior to inclusion in the study. Following consent, all participants complete the B1 (baseline) assessment. Adolescents are randomized immediately after the baseline assessment. The implementation of BSFT and TAU begins following randomization. All other assessments are completed based on time since randomization: T1 through T12 for drug use assessments, and T4-4 months post-randomization; T8-8 months post-randomization; T12-12 months post-randomization.

1.0 BACKGROUND AND RATIONALE

This section briefly summarizes the background and rationale for this study. Appendix A contains a more thorough review of this information about trends in adolescent drug use.

1.1 Overview of the Problem of Adolescent Drug Abuse

Adolescent drug abuse continues to represent one of the most pressing public health issues in the United States. Although trends over the past decade indicate that individual drug use may vary slightly from year to year, our nation's teenagers continue to use illicit drugs at a stable rate (Monitoring the Future, NIDA, 2001; Drug Abuse Warning Network, SAMHSA, 2001). For example, trends suggest that use of nearly every drug of abuse has remained relatively stable over the past decade, including marijuana, cocaine/crack, amphetamines, heroin, "club drugs," and others (NIDA, 2001). This trend is paralleled by data indicating the perceived availability of illicit substances. Another worrisome trend is that there are increasing numbers of youth mentioned in emergency room treatment for drug related issues (SAMHSA, 2001).

1.2. The Impact of Family Therapy on Adolescent Drug Abuse

Although population-based surveys suggest that adolescent drug use continues at a worrisome stable rate, there is strong evidence that specific interventions can have a dramatic impact on adolescent drug use and related behavior problems. For example, broad reviews of the treatment outcome literature indicate that family interventions in general, and BSFT in particular, are effective with drug using youth (c.f. Kazdin, 1994; Liddle & Dakof, 1995; Stanton & Shadish, 1997). Data on the efficacy of BSFT are briefly reviewed.

1.3 Brief Strategic Family Therapy

Outcome research findings for BSFT are briefly presented below, including the impact of BSFT on: 1) adolescent drug use, 2) engagement and retention, 3) behavior problems, and 4) family functioning. Specific clinical interventions are described in detail in the BSFT Treatment Manual (Appendix C).

1.3.1 Drug Outcomes

The three studies briefly reviewed below were conducted to examine the impact of BSFT or the impact of modules of BSFT on adolescent drug abuse. The first study shows the impact of BSFT compared to group therapy. The second and third studies are not efficacy studies of BSFT as a whole, but rather of techniques or modules of BSFT. The latter two studies are particularly important because the variations tested in these studies have been integrated into the clinical model (i.e., strategies for engaging difficult family members and working with one family member). These studies are limited in that only data on completers were obtained at post-test.

1.3.1.1 Study on Efficacy of BSFT in reducing drug use

Santisteban et al., in press. Drug use outcome was determined for 79 adolescents and their families who were randomly assigned and completed either BSFT or a Group Control condition. Marijuana and Alcohol were the two most commonly reported substances and are

the focus of analyses. Urine analyses were used to confirm drug use self-reports and those participants that were shown to be reporting inaccurately were omitted from the analysis reported here (n = 11; 5 in BSFT and 6 in Group Control condition). However, additional analyses including these participants support the findings reported. Results showed a multivariate Condition X Time interaction was significant, F (2, 66) = 3.04, $p < .04$. The multivariate dependent measures were marihuana and alcohol. Univariate analyses indicated a Condition X Time interaction for marijuana use, F (1, 67) = 5.27, $p < .03$, but not for alcohol use, F (1, 67) = 0.43, ns. Follow-up t tests revealed that marijuana use decreased significantly in the BSFT condition, t (50) = 2.14, $p < .04$, but did not change significantly in the Group Control condition, t (23) = 0.67, ns.

Using analysis of Clinically Meaningful Changes (Jacobson & Traux, 1991) in marijuana use for the BSFT condition, 75% showed reliable improvement, 56% were classified as recovered, while 25% showed reliable deterioration. In the Group Control condition, 14% showed reliable improvement and were classified as recovered, and 43% showed reliable deterioration in marijuana use (see Figure 2).

1.3.1.2 Studies on BSFT specific techniques in reducing drug use

Szapocznik, Perez-Vidal et al., 1988. This study randomly assigned 108 adolescents and young adults (ages 12-21) to BSFT with specialized engagement or BSFT as usual. Youth were included in this study if there was direct evidence of drug use (observation of use or self-report) and/or if there was evidence of problems in four domains of functioning (e.g., school, work, peers, family). Of the 108 families participating in this study, 74 were successfully engaged and were present at an intake interview. Drug use self-reports and parent reports obtained during this interview showed that 93% of these adolescents were using drugs at admission. Marijuana was the drug of choice (82.5%), and cocaine was frequently listed as the youth's secondary drug of choice (80%). The frequency of primary drug use was several times per week for 47.2%. Forty-one percent reported restricting their primary drug use to one time per week or less.

Pre- and post- treatment interviews were conducted by independent assessors to examine the effectiveness of therapy in improving participant functioning. Drug use was assessed using the Psychiatric Status Schedule (Spitzer, Endicott, Fleiss, & Cohen, 1970) and the Client Oriented Data Acquisition Process (developed under the sponsorship of NIDA). The former was administered by an independent assessor, while the latter was completed by the therapist.

Results demonstrated a significant Time effect, $F(1,57)$ =39.83, $p < .0001$, but no significant differences for Condition or Condition X Time. Post hoc paired two-tailed t tests showed a significant pretreatment to post-treatment improvement for youth in both conditions, indicating that BSFT (with or without specialized engagement interventions) was effective in reducing adolescent drug use.

To further analyze the effectiveness of the intervention, participants were classified as either totally drug free or continued drug use according to data obtained through the Client Oriented Data Acquisition Process at intake and termination. The totally drug free classification designated no reported drug use during the period 1 month prior to assessment. Results of the analyses revealed a significant reduction in the number of participants using drugs. Although only 7% of the participants completing treatment had been drug free at admission, 80% were drug free at termination, χ^2 (1, n = 56) = 40.00, p < .0001. There were no differences in drug use status by BSFT treatment condition. These data are limited to self-reports of drug use.

Szapocznik, Kurtines, Foote, Perez-Vidal, & Hervis, 1986. This study randomly assigned 37 Hispanic families with drug abusing adolescents (ages 12-20) to receive either conjoint (full family) or one-person family therapy. The One Person BSFT modality was an adaptation of the original therapeutic model. Results indicated that both the conjoint and one person BSFT treatments were successful in reducing adolescent drug abuse as measured by the Psychiatric Status Schedule (PSS; Spitzer, Endicott, Fleiss, & Cohen, 1970), F [1, 34] = 51.0, $p < .001$). This effect did not differ between the two treatment modalities (i.e., no Time X Treatment interaction). In both BSFT modalities, drug abuse scores were reduced by more than one full standard deviation at posttest, and effects were maintained at 6-month follow-up.

1.3.2 Engagement and Retention of Drug Abusers

Engaging and retaining drug abusers is one of the most important, albeit difficult aspects of drug abuse treatment. This problem is further exacerbated when the drug abuser is an adolescent, though it is just as much a problem with adults (Digiuseppe, Linscott, & Jilton, 1996). BSFT has developed, evaluated, and integrated specific strategies for engaging and retaining drug abusing adolescents and their family members in treatment. In separate studies, the effectiveness of specialized BSFT engagement strategies in engaging and retaining drug abusing adolescents and their families in treatment have been demonstrated.

Szapocznik, Perez-Vidal, et al. (1988). 108 Hispanic drug-abusing adolescents (ages 12-21) and their families were randomly assigned to one of two conditions: (a) BSFT with specialized engagement strategies; and (b) BSFT with engagement as usual. With successful engagement defined as completion of an intake assessment, 92.9% of families in the BSFT+Specialized Engagement condition were successfully engaged, as compared to 42.3% of the families in the BSFT+Engagement as Usual; χ^2 (1, N = 108) = 29.64, $p < .0001$. Continuing to use the same specialized engagement strategies to retain cases in treatment in the experimental conditions, 77% of families in the BSFT+Specialized Engagement condition successfully completed a full dose of therapy (approximately 8 sessions), compared to 25% of families in the BSFT+Engagement as Usual condition; χ^2 (1, N = 108) = 26.93, $p < .0001$.

Santisteban et al., (1996). This study replicated and extended the findings of the initial engagement study. This study included more stringent criteria for successful engagement (i.e., intake assessment plus first therapy session), a second control group (group treatment with engagement as usual), and a more culturally diverse sample (i.e., a larger percentage of non-Cuban Hispanics). 193 Hispanic drug-abusing adolescents and their families were randomly assigned to the three conditions. Results indicated that the BSFT+Specialized Engagement condition was again associated with higher rates of successful engagement (81%) than were the two control groups (60%), χ^2 (1, N = 193) = 7.50, $p < .006$.

1.3.3 Externalizing Behaviors (as measured by the Revised Behavior Problem Checklist and reported by a parent/guardian [Quay and Petersen, 1987; Rio, Quay, Santisteban, & Szapocznik, 1989]).

Santisteban et al., 2003. Seventy-nine adolescents (12-18) and their families who had been randomly assigned to either BSFT or a Group Control Condition and completed treatment were included in an analysis of treatment outcome. Results indicated that participants in BSFT showed significantly greater reduction in behavior problems than Group Controls, F (3, 75) = 3.19, p < .05. Follow-up univariate analyses indicated significant Time X Therapy Condition interactions for both Conduct Disorder, F (1, 77) = 8.37, p < .01; and Socialized Aggression (delinquency in the company of peers) F (1, 77) = 7.22, p < .01. Participants in BSFT showed significant pre-intervention to post-intervention improvements in Conduct Disorder, t (51) = 3.82, $p < .001$; and Socialized Aggression, t (51) = 3.57, $p < .001$, while Group Control participants showed no significant changes on either Conduct Disorder, t (26) = -.74, ns; or

Socialized Aggression, t (26) = -.65, ns. *Analyses of Clinical Significance* in Conduct Disorder showed that in the BSFT condition: 44% showed reliable improvement, 26% were classified as recovered, and 5% showed reliable deterioration (see figure 2). In the Group Control Condition only 11% showed reliable deterioration and no case was classified as reliably improved or recovered. A similar pattern was seen for Socialized Aggression.

Santisteban et al., 1997. In this intervention-only, pre-post design, drug abuse prevention study, 122 adolescents ages 12-14 (103 Hispanic, 19 African American) exhibiting risk factors for later drug abuse (e.g., conduct problems, anxiety or depression, academic problems) received BSFT. Results indicated significant reductions in conduct problems, F (1, 121) = 65.81, $p < .001$; delinquency in the company of peers, F (1, 121) = 11.99, $p < .001$; and anxiety, F (1, 121) = 45.56, $p < .001$. Moreover, reductions in behavior problems were associated with reduced likelihood of substance use initiation nine months post-therapy (conduct problems, $b = .08$, $p < .05$; delinquency in the company of peers, $b = .59$, $p < .01$).

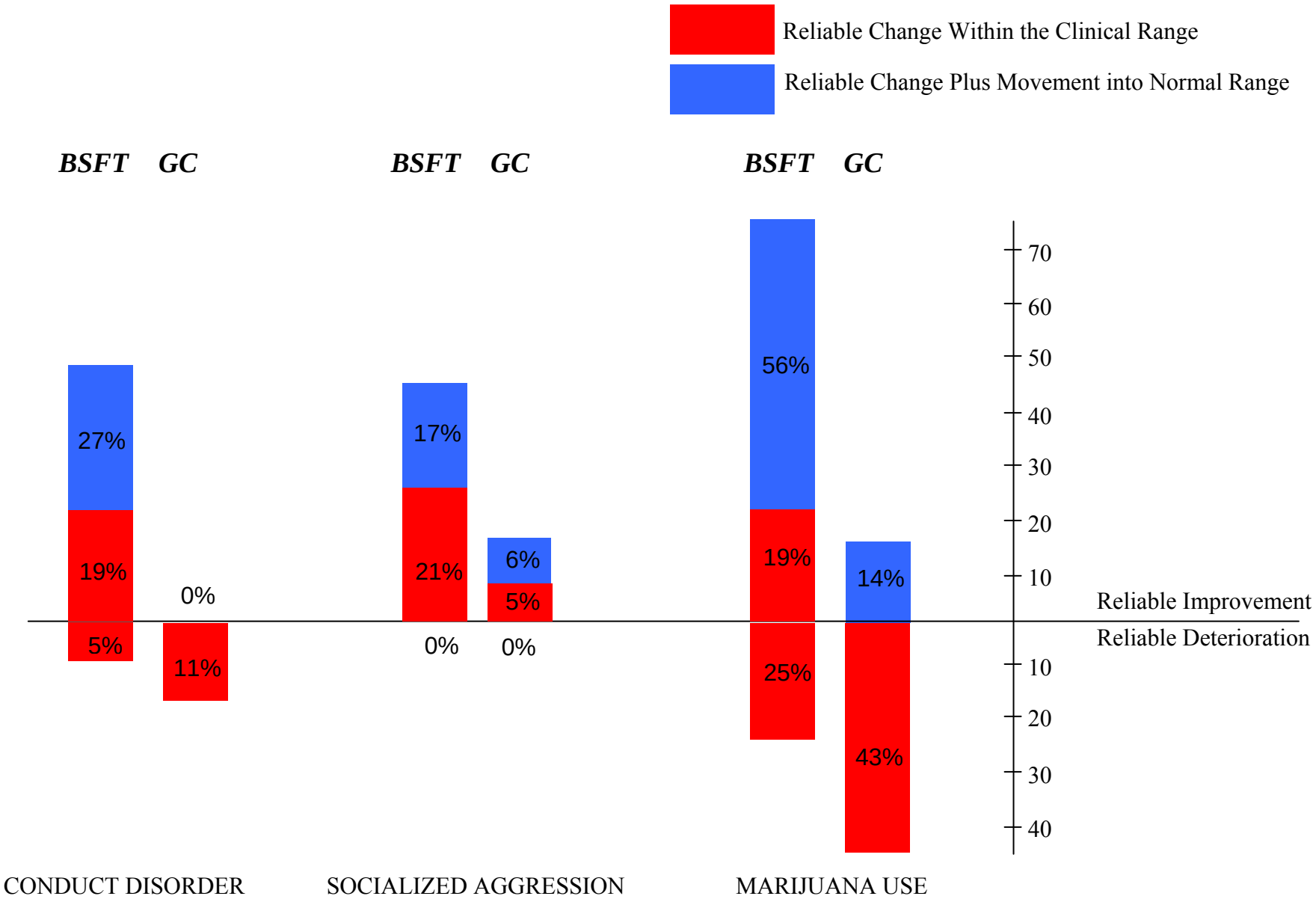
Szapocznik et al., 1986. In the one-person versus conjoint BSFT study reviewed above, both (one-person and conjoint) BSFT modalities produced reductions in the following variables: Conduct disorder, F (1, 34) = 15.6, $p < .001$; Socialized Aggression (delinquency in the company of peers), F (1, 34) = 23.3, $p < .001$; Behavioral disturbance, F (1, 34) = 9.3, $p < .001$; and Impulse control problems, F (1, 34) = 44.1, $p < .001$.

1.3.4 Family Interactions

The primary target of BSFT is family interactions. BSFT theory is based on the assumption that the family is considered to play a critical role in the etiology, maintenance, and treatment of adolescent behavior problems. In the section, studies examining the impact of BSFT on family interactions are presented.

Santisteban et al., 2003. Compared to the group control condition, BSFT produced increases in adolescent-reported family cohesion, F (1, 72) = 6.66, $p < .02$; and improvements in observer-reported family functioning, F (1, 47) = 5.51, $p < .05$. Follow-up paired t tests revealed that improvements in the BSFT condition were responsible for the family cohesion effect, t (49) = 3.41, $p < .02$; and that deterioration in the group control was responsible for the

FIGURE 2. BRIEF STRATEGIC FAMILY THERAPY VS. GROUP CONTROL: RELIABLE "CLINICAL" CHANGE
(Santisteban et al., 2002)



family functioning effect, t (13) = 2.15, $p < .05$. An earlier clinical trial focusing on children with emotional and behavioral problems had similar results (Szapocznik et al., 1989), showing improvement in family functioning for the BSFT condition and deterioration in family functioning for an individual child psychodynamic control.

Santisteban et al., 1997. In the BSFT drug abuse prevention study, both adolescents, F (1, 116) = 21.27, $p < .001$; and parents, F (1, 121) = 41.80, $p < .001$, reported significant improvements in parent-adolescent communication as a result of therapy.

Szapocznik et al., 1983. In the one-person versus conjoint BSFT study, improvements were found in family interactions as measured by an independent observer. The five dimensions of observer reported family functioning assessed demonstrated significant improvements: family structure/organization, F (1, 34) = 32.7, $p < .001$; observer-reported family flexibility, F (1, 34) = 14.4, $p < .001$; family resonance, F (1, 34) = 30.3, $p < .001$; family developmental appropriateness, F (1, 34) = 15.8, $p < .001$; identified patienthood, F (1, 34) = 16.0, $p < .001$; and family conflict, F (1, 34) = 18.2, $p < .001$.

2.0 OBJECTIVES

2.1 Primary Hypothesis

The primary goal of this study is to examine the effectiveness of BSFT in the treatment of adolescent drug abusers. It is hypothesized that:

Hypothesis 1: BSFT will be significantly more effective than TAU in reducing adolescent drug use, defined as the percentage of drug use days in 28-day periods.

2.2 Secondary Hypotheses

Secondary hypotheses examine the relative effectiveness of BSFT over TAU in:

Hypothesis 2a: Engaging adolescents and family members in treatment
Hypothesis 2b: Decreasing adolescent externalizing problem behaviors
Hypothesis 2c: Decreasing adolescent sexually risky behaviors
Hypothesis 2d: Increasing adolescent prosocial activities (e.g., school, work)
Hypothesis 2e: Improving family functioning (e.g., parenting, parent-adolescent relations).

3.0 STUDY DESIGN

480 participants will be recruited from 8 outpatient CTPs. On average, each CTP will provide 60 participants. Participants will be randomized to BSFT or TAU within each CTP.[1] Potential participants will be screened by a research assistant (or designated staff) for inclusion/exclusion criteria and level of interest. Eligible youth and their families will participate in an informed consent process and a

[1] Several strategies were considered before selecting a design that compared BSFT with TAU. The alternative design that was given the most consideration was to compare BSFT as an add-on intervention. In this second design, the comparison would focus on BSFT plus TAU versus TAU alone. This alternative was considered favorable because it might be the easiest to implement, provided a within site control for TAU, and placed no additional demands on TAU. A second benefit of this design is that therapists would not have to be randomized to condition, and would permit particularly capable therapists to be selected for BSFT. One of the primary problems with this design is the increased treatment costs associated with providing an additional intensive psychotherapy. For example, most CTPs currently provide weekly therapy sessions. Adding another psychotherapy to existing treatment packages substantially increases treatment costs. The increased costs may limit the ability of CTPs to integrate BSFT into current services and would threaten the sustainability of the intervention. Moreover, adolescents and family members may simply be overextended with psychosocial services. A related problem is that a BSFT trial as an add-on, may suffer bleeding between conditions if youths in both conditions participated in the same group therapy sessions. Given these complexities, a design was selected that provided the more rigorous design for testing BSFT across modalities.

baseline assessment. Youths will provide assent, and adults will provide consent. Parent(s) or legal guardian(s) will provide consent for minors under the age of assent.

- The baseline assessment will be conducted approximately three weeks after the adolescent signs assent, followed by randomization into BSFT or TAU.
- Study interventions will be initiated following randomization.
- Assessment of primary outcomes (drug use) will be conducted at baseline and monthly post-randomization (T1-T12). Secondary outcomes will be conducted at four time points: baseline, 4-, 8-, and 12-months post-randomization.

3.1 Design:

- Randomized "intent to treat" design.
- Informed assent will be obtained from adolescents (ages 12 to 17 inclusive) and consent from a parent or legally authorized guardian. Consent from the guardian will include the adult's agreement to participate in research, consent for the adolescent to participate in the research study**,** and consent for any other minors under the age of assent. Additional adults and minors in the family will also be consented/assented prior to participation in any aspect of the study.
- Following consent, participants (adolescent, parents, and family members) will complete a baseline assessment (B1).
- Following the baseline assessment (B1), participants will be randomly assigned to BSFT or TAU.
- Treatment in both conditions will be provided in non-restrictive, community settings (e.g., clinic, home, and school). BSFT consists of 12 to 16 sessions (each approximately 1 to 1.5 hours long) over a 4-month period, plus up to 8 "booster" sessions. TAU will vary depending on the current activities at participating CTPs. For the purpose of this study, it is recommended that TAU in participating CTPs consist of at least 1 therapy session per week and may include participation in ancillary services (e.g., case management, AA, etc.) for a minimum of 3 to 4 months.
- Follow –up assessments of primary outcomes (drug use) will be conducted at monthly intervals following randomization (T1-T12).
- Follow-up assessments for secondary outcomes will be conducted at 4-, 8-, and 12-months following randomization.
- Measures of service utilization (including attendance in study intervention sessions) and adverse events will be conducted at 2-, 4-, 8-, and 12- months post-randomization.
- Alliance with therapist will be assessed 2- and 4- months post-randomization.
- AEs and SAEs will be reported whenever they are identified.

4.0 STUDY POPULATION

4.1 Number of Sites and Subjects

Study Population: Participants will be 480 (or more) adolescents ages 12 to 17 inclusive who have used any illicit drugs (other than alcohol and tobacco) in the 30-day period that preceded the baseline assessment or that were referred from an institution for treatment of drug use. Participants will be recruited from approximately 8 outpatient CTPs (approximately 60 per CTP). Participants' family members will also be included in the study. For the purposes of BSFT, family is defined broadly, and includes the full range of family compositions, extended family members and individuals

outside the family that serve in traditional family roles (e.g. emotional and financial support). [However, for the purpose of consent, only a biological parent or legal guardian will be allowed to provide consent for the minor to participate in the study.] CTPs will be recruited from programs that provide services to adolescent drug users. Among the CTPs recruited, efforts will be made to sample approximately 100 females**,** and at least 100 Hispanic and 100 African American adolescents and families.

8 CTPs, including a site in Puerto Rico, have expressed interest in participating in this protocol. The CTPs vary with respect to number of youth served, type of services provided (outpatient, residential, etc.), and populations served (minority, girls). Thus, the estimated sample size of 480 adolescent from approximately 8 CTPs appears to be a reasonable goal

4.2 Duration/Patient Flow

The length of time to complete research and clinical training, treatment (BSFT, TAU), and data collection (B1-T12) is shown in (see Table 3, section 12.0). Clinical training takes approximately 5 months to complete, whereas protocol-specific research training may be completed in one to two weeks. Research and clinical training may occur simultaneously or may be staggered depending on Node/CTP training resources. Clinical training will occur in the five-month period prior to beginning randomization of participants.

The expected length (months) of the total protocol for a CTP 29 months. This estimated timeframe is based on a rate flow of 60 cases available for randomization of youths per CTP. CTPs with a more substantial case flow may be involved for a shorter period of time, or provide a larger number of youths, if needed. CTPs with a less substantial case flow may take longer to recruit participants. The enrollment period will last approximately twelve months. Therefore, the total duration of the protocol will be approximately 29 month.

Each CTP will provide approximately 60 participants. CTPs with a smaller case flow will be able to participate in the protocol.

4.3 Informed Consent/Human Subjects Safety

Informed consent/assent will be obtained prior to initiating data collection. Prospective participants will receive a copy of the informed consent/assent documents. Consent/assent forms will be read or explained to participants by a research assistant, and participants will also be given ample time to read the informed consent document. Informed consent/assent procedures and forms will be conducted in Spanish or English according to the language prospective participants are most comfortable reading and speaking (a Spanish version will be made available by the Lead Node). Participants will be encouraged to ask questions to clarify any aspect of the study. A brief test (modeled after an instrument utilized in existing research practices, i.e., Joffee, Cook, Cleary, Clark, & Weeks, 2001) will be utilized to assess if eligible participants understand key aspects of the study. An instrument appropriate to each consent/assent form will be developed. Potential participants must correctly understand all questions before they are asked to sign consent/assent forms. Areas assessed include participants' (adolescents and participating family members) understanding that: a) that this is a research study, b) that their participation is voluntary, and c) that they can withdraw at any time. In addition, participants must demonstrate sufficient comprehension of other aspects of the study including its purpose, procedures (including duration, interventions, videotaping, etc.), and risks specific to BSFT. Consent forms will be signed only after it is clear that eligible participants understand all aspects of the study/protocol. Any incorrect responses should be explained and verbally re-asked until the potential participant demonstrates that s/he understands the item.

Any individual that participates in any aspect of the study, including assessments therapy**,** or videotaping must sign informed consent/assent forms. In BSFT, when individuals are added to the family therapy group, they will be consented prior to participation.

4.4 Eligibility Criteria

Participants will be included if they are ages 12 to 17 inclusive and have used illicit drugs, other than alcohol or tobacco, in the 30-day period preceding the baseline assessment. Adolescents referred from an institution (e.g., detention, residential treatment, court etc.) will be included even if they do not report drug use in the 30-day period preceding the baseline assessment). Adolescents must currently live with or be expected to live with formal or informal "family". Family is defined as any individual(s) who serve in the legal or traditional role of family members. However, placements in foster care settings will be excluded from the study. After randomization, adolescents must reside in the same geographical area of a CTP, within an "area" designated by each CTP (see section 4.5 below). Adolescents will be excluded if they are expected to be released to a halfway house, institution, independent or assisted living facility, foster care, or to a location outside of the designated geographical area.

4.5 Inclusion Criteria

1) Adolescent between the ages of 12-17 (inclusive).
2) Adolescent who used any illicit drug (other than alcohol and tobacco) in the 30-day period that preceded the baseline assessment or that is referred from an institution (e.g., detention, residential treatment, court etc.) to the CTP for the treatment of drug use.
3) Adolescent who currently lives with or is expected to live with formal or informal "family." Family member is defined as any individual who serves in the legal or traditional role of family members, except foster family/home.
4) Adolescent and family reside in the same geographical area as their CTP (each CTP will be allowed to set its own radius of operation). This criterion is required because BSFT may involve regular home therapy sessions.
5) Adolescent and other family members under 18 years of age will sign informed assent; parent figure(s) and/or legal guardian(s) will sign informed consent to participate in study and to allow adolescent to participate. Attempts will be made to obtain consent from both guardians if guardianship is shared. Only the consent of a biological parent or a legal guardian will be accepted for consenting participation of a youth into this study.

4.6 Exclusion Criteria

1) Adolescents that are expected to live in a halfway house, institution, independent or assisted living, foster care, or outside of geographical area will be excluded.
2) Adolescents with suicidal or homicidal risk at screening or baseline will be included in the study only after crisis stabilization and consultation with crisis stabilization provider.
3) Adolescents with current/pending legal charges for severe offences will be included in the study. However, adolescents with current/pending severe criminal offenses (e.g., murder, attempted murder, aggravated assault, sexual battery/assault) that may result in short- or long-term incarceration will be excluded[2] to maximize their availability to the protocol. Adolescents who are otherwise court involved will be included.
4) Adolescents from non-restricted settings will be excluded if they are already receiving regular (approximately 1 or more sessions per week) treatment services for drug abuse.

[2] This is done to maximize the likelihood that adolescents will remain available for treatment, and that charges that occurred prior to entry into the study do not affect availability for follow-up assessments.

4.7 Subject Discontinuation Criteria

4.7.1 Required Termination

Participants and family members will be terminated from the study when they state they no longer want to participate, hence, at the participant's request all assessments will be stopped. However, participants that are withdrawn from a treatment condition (i.e., stop attending treatment, or ask to discontinue treatment, or break the agency's rules) will continue to be included in the study, and assessments will still be conducted.

4.7.2 Withdrawal of Participants

Adolescent and family members may be withdrawn from the treatment condition in the event the adolescent: a) attempts suicide with the intent to die, b) reports homicidal ideation with the intent to kill, or, c) dies.

It should be noted that removal from the treatment protocol does not mean removal from analysis. This is an "intent to treat" design. Therefore, every participant that is randomized will be analyzed.

4.7.3 Procedures for Discontinuation

Participants who express a desire to discontinue the study will be asked about the reasons why they wish to stop participating. The research assistant will attempt to address potential concerns, but will not pressure participants to continue their involvement in the project. All premature terminations will be immediately reported (within 48 hours) to the CTP Principal Investigator, the Node Study Coordinator and within 2 weeks to the Project Director at the Lead Node. Participants that withdraw from the study will be treated without prejudice**.** Participants that terminate or drop out of therapeutic services will continue to be approached for research assessments, unless they specifically request to not continue to participate in the assessments.

5.0 STUDY TREATMENTS

5.1 Study Interventions: Participants will be randomly assigned to BSFT or TAU. BSFT is a family therapy approach that consists of 12 to 16 sessions (each approximately 1 to 1.5 hours long) over a 4-month period, and up to 8 "booster" sessions. Interventions are delivered to adolescents and relevant family members in non-restrictive community settings (e.g., clinics, homes, school). The BSFT Treatment Manual is included in Appendix C.

TAU varies depending on the current activities at participating CTPs. To participate in the study, however, CTPs should offer services that include at least 1 therapy session per week (individual or group therapy) as well as participation in ancillary services (e.g., case management, AA, etc.). CTPs that provide intensive manualized family intervention services will be excluded from this study.

5.2 Intervention Conditions

5.2.1 Brief Strategic Family Therapy (BSFT)

This section briefly presents the program parameters of BSFT. For a full description of BSFT, a treatment manual is included in Appendix C.

- BSFT (Szapocznik & Hervis, 2001) systematically targets patterns of interaction in the family system that have been shown to influence adolescent drug abuse. BSFT consists of three distinct but interrelated classes of interventions:
    1) getting all family members joined/engaged into treatment,
    2) diagnosing the family relationships and roles that are strengths or that conversely are contributing to or maintaining maladaptive interactions linked to serious adolescent problems, and;

3) developing and implementing a treatment plan to create new family interactions that builds on family interactional strengths (e.g., supportive interactions), corrects maladaptive family interactions (e.g., improved parenting practices and conflict resolution, decreased parent-adolescent conflict) to protect the adolescent from drug use.

- BSFT is intended to be delivered in 12 to 16 sessions (each approximately 1 to 1.5 hours long) over a 3 to 4-month period. However, the actual number of sessions/length of service is based on the therapist's ability to achieve necessary improvements in specific behavioral criteria (e.g., drug use and family interactions). The amount of time needed to achieve improvements may increase or decrease based on: a) the extent and type of adolescent comorbidity; b) the number of family members with psychiatric disorders, including drug abuse; and c) the level of family disruption.
- Therapists may conduct "booster sessions" after the 12-16 sessions with cases that relapse, present adverse events during follow-up assessments, and/or in response to a family petition. Therapists cannot conduct more than 8 booster sessions after the completion of initial BSFT services.
- When an adolescent is placed in a more restrictive setting during the treatment phase, therapists will contact the family each month to determine when the adolescent is expected to be released back to live with the family. For adolescents that are released back to live with the family prior to 12-months post-randomization, sessions will be conducted with adolescents and family members to facilitate a smooth transition back into the home and to achieve or solidify improvements in family functioning and adolescent behavior problems.
- The majority of therapy sessions should involve multiple family members. If more than 25% of a therapist's clinical contact time involves only one family member, therapists are considered to be failing to adhere to BSFT.
- Services should include psychiatric consultation and medication for the adolescent whenever it is indicated. In BSFT, psychiatric consultation and medication is also made available to other family members.
- Services should include a systematic assessment and plan for involving individuals from other relevant systems in which the adolescent is involved (e.g., school, peer, justice).
- Location of services is flexible and should not be permitted to become an obstacle to the delivery of BSFT interventions. Home/community visits are often prescribed in a substantial percentage of cases to ensure adolescent and family participation.
- BSFT is well suited to be delivered in the context of ongoing services at CTPs. Thus, adolescents may receive ancillary services, such as case management, vocational training, and support groups (e.g., AA/NA) as they would in TAU. However, youth assigned to BSFT will NOT receive the formal counseling (i.e., individual therapy, group therapy) that occurs in TAU, unless this counseling is part of the package of services required by residential or day treatment. Moreover, BSFT therapist will interface with CTP-provided ancillary services to coordinate the direction of services.

5.2.2 Treatment as Usual (TAU)

TAU will vary depending on the current activities at participating CTPs. TAU in CTPs currently include individual, group, and non-manualized family therapy counseling as well as case management. At least 1 intervention session per week is common as well as participation

in ancillary services (e.g., case management, AA, etc.). However, CTPs providing weekly, manualized family therapy sessions will be excluded.

Program Parameters. TAU and BSFT will have similar "dose opportunities," including the possibility of the booster sessions. TAU may involve more frequent contact than BSFT. For example, a TAU may involve an intensive "step down" outpatient program with 3-4 hours of weekly contact with adolescents for the first 3-months post-discharge, with services decreasing gradually over the remainder of the year.

5.2.3 Tracking of Dose

CTPs document clinical contact using a Service Activity Log stored in a database, which may be easily retrieved. CTPs will provide this information to the site RAs for participants in both conditions.

5.3 Selection and Training of Therapists

At each CTP, therapists will consist of 4 (or more) providers selected from the total pool of therapists that provide clinical services, including regular part- and full-time clinical staff as well as contract workers. Therapists must meet the following criteria: 1) Sign consent to provide therapy services as part of a research study (see Appendix D); 2) Be willing to participate in a selection process; 3) Be willing to participate in family therapy training and to provide family therapy services; 4) Be willing to videotape their sessions, and have sessions reviewed, coded, and analyzed for the purpose of adherence ratings, supervision and future studies on therapy process; and 5) Be willing to conduct home-based therapy services. Once selected, therapists will be randomized to condition. The selection and training process is the following:

Step 1 – Consent. CTPs will determine all of the potential therapists that may participate in the study. All potential therapists will be asked to volunteer to participate. Informed consent will be obtained from those therapists who volunteer.

Step 2 – Identifying pool of eligible therapists that meet BSFT and TAU criteria. A CTP PI (or designee) will review the academic training and clinical experience of all potential therapists to determine the total pool of therapists at a CTP that meet criteria for TAU. The BSFT Head Training Supervisor and National Project Coordinator will interview each therapist to ensure that they meet criteria for BSFT. With respect to the individual interviews, the BSFT Head Training Supervisor and National Project Coordinator will focus on the therapist's: 1) general interpersonal skills; 2) openness to learning new information and responding to feedback; 3) openness to recognizing the role of relationships in influencing behavior; and, 4) directness and clarity of communication. The CTP PI (or designee) also considers these qualities before recommending a therapist for participation in the study.

Therapists will also provide a videotape of a therapy session with a family that will be reviewed by two members of the BSFT certification panel, or by one member of the panel and the Trainer/Supervisor that will be assigned to that CTP. Videotapes will be reviewed to evaluate the therapist's ability to join all family members. This evaluation uses items from the Therapist Behavior Checklist to examine the extent to which therapists: 1) convey understanding, acceptance, and respect to all family members; 2) speak with families in a manner that is comfortable and familiar; 3) reflect family members' comments without being challenging or critical; 4) obtain information from each family member; and, 5) stimulate dialogue between family members. In addition, videotapes will also be evaluated for general interpersonal skills, and directness and clarity of communication.

Therapists who meet criteria to conduct TAU as determined by the CTP PI, and meet all criteria for participation in BSFT will be included in the study.

Step 3 – Randomizing therapists to condition. Therapists who meet both BSFT and TAU criteria will be randomly assigned to BSFT or TAU. Therapists from within a CTP are grouped in 2s if there is an even number of therapists or in the case of odd number of therapists a group of 3 is created. The groupings are based on academic training, clinical experience, and ability to conduct therapy with Spanish speaking clients. Therapists within group stratified in this fashion are randomized to BSFT and TAU. The total number of eligible therapists will vary from agency to agency (approximately 4-8 therapists). After the initial randomization of therapists, when an additional therapist is needed for the study, an additional pair of therapists is brought into the study following criteria as outlined above. The therapists are then randomized one to BSFT and one to TAU. However, if there is a full complement of therapists for one of the conditions, for that condition the therapist can be randomized out of the study.

Therapists that have been randomized out of the study can be brought up again to the selection process as member to a new pair. In these circumstances, the therapists will need to be re-consented and will complete a new selection process.

Step 4 – Training BSFT therapists. Therapists assigned to BSFT will receive approximately 46 hours of training over a 5-month period. At the end of training, therapists will be evaluated to determine if they meet criteria for implementing BSFT. It is necessary to randomize to BSFT and train in BSFT more than 2 therapists (if sufficient eligible therapists are available) to increase the probability that at least 2 therapists are certified to provide BSFT services. This filtering process reflects standard practice in BSFT. Therapist filtering for TAU will have occurred in Step 2 above. If more than 2 therapists assigned to BSFT meet criteria, we will work with the Node and Site Principal Investigators to select which therapists (at least 2) will provide BSFT in the implementation phase of the protocol. The certified BSFT therapists not selected for immediate provision of BSFT within the study will be used as back-ups as needed. [Note that CTPs with a large clinical staff, i.e. who can assign 3-4 therapists to each condition**,** can choose to have all 3-4 therapists provide BSFT services instead of using 1-2 therapist(s) as (an) alternate(s).] Please also note that to avoid bleeding across conditions, any therapist who receives any BSFT training will not be allowed to provide services for study cases other than BSFT.

5.3.1 Training and Supervision

BSFT: Procedures for training and supervision in the clinical aspects of BSFT are described in detail in Appendix C (and will be provided by the Florida Node RRTC). Training occurs over a 5-month period and involves approximately 144 hours of training and supervision, which include didactic presentations, live supervision, case review and planning, pilot cases and weekly supervision.

Therapists will complete the *Views of Adolescent Drug Abuse Q-Sort (VADAQ).* The Q -sort is a 56- item questionnarie developed in a collaboration the LI team and the University of Arizona team which is part of the San Francisco-Arizona Node. Therapists will be asked to sort 56 statements of opinion concerning the nature and treatment of adolescent drug abuse (each typed on a separate card) into eight different categories ranging from "least agree: (category 1)

to "most agree" (category 8). This measure will be administered during the therapists selection process, prior randomization to BSFT or TAU. For BSFT therapists only the VADAQ will be administered again the first time the therapists submit a tape for certification in BSFT.

Three times during the course of their BSFT training, therapists will complete a case formulation exercise in which they respond orally to one written clinical vignette depicting a family with adolescents who use illicit drugs. For each vignette, respondents will be asked (a) "What do you see happening in this family, and why does the youth use drugs?"; (b) "What additional information would you want in order to assess this family?"; and, (c) "What would you propose as a preliminary treatment plan?". Therapists' open-ended responses to these questions will be individually (privately) audio taped. This qualitative information will be used by trainers to gauge how training is progressing. This also allows the trainer to better tailor the training to each therapist's progress.

The overall BSFT training includes approximately 96 hours of training delivered in four 3-day workshops – and 48 hours of supervision that occur in weekly supervision sessions. The first workshop includes an extra day to train the therapists on the clinical forms and the identification of therapist' and family AE/SAEs.

The BSFT supervisor delivers weekly supervision sessions in a conference call involving the BSFT therapists at each site. Alternates will also participate in these supervisory sessions, although they will not receive supervision on cases. Prior to the conference call, the BSFT Clinical Supervisor will review: 1) Contact Log and Weekly Case Summary for every case that is assigned to each therapist; 2) One randomly selected videotape from each therapist's current caseload; 3) At least one adherence rating form a session of each therapist caseload rated by an independent observer. Sampling for adherence and videotape supervision will be performed within therapists. The review of this material takes about three hours per supervision session, per site. Using this information, the Clinical Supervisor will meet with all of the therapists at a site (usually 2-3 therapists per CTP) in a telephone conference call of approximately 2-3 hours. During the meeting, the Clinical Supervisor will briefly review this material with each therapist, and will plan activities for the upcoming week. The meeting will also focus on identifying and addressing problem areas or unique clinical issues. At least half of this meeting will be devoted to reviewing 30-minutes of videotape for each therapist.

The BSFT Head Training Supervisor will generally hold weekly meetings with the team of training supervisors at the Lead Node to oversee all clinical supervision activities. Moreover, the BSFT Head Training Supervisor will sit in on supervision conference calls alternating among supervisors to minimize differences in supervision across supervisors.

Research training for therapists on all aspects that are BSFT-specific will be provided by the Lead Node. Participating RRTC and CTP BSFT protocol PIs, participating RRTC BSFT Protocol QA, and RAs will be required to complete the BSFT-specific research training provided by the Lead Node. However, training that is not BSFT-specific will be provided by the participating Node's RRTC. All personnel responsible for completing Case Report Forms (CRFs) will be required to attend common and protocol specific training. All CTP therapists and researchers will also be required to complete GRP training.

TAU: No additional clinical training or supervision of TAU therapists will be provided as part of this protocol, except as required for research purposes, such as GRP, Adverse and Serious Adverse Events notification and completion of research-related CRFs if any.

5.4 Administration of Study Interventions

5.4.1 Randomization

To ensure that participants are balanced with respect to key variables, participants will be assigned to BSFT or TAU using an urn randomization procedure. Urn randomization procedures employ an algorithm that uses information about the composition of treatment groups to maximize the similarity of groups on specific variables (Stout et al., 1994). This procedure maintains random assignment but ensures comparability between the two conditions on key variables. The key variables that will be balanced in this study include:

- Ethnicity/race (African American, Hispanic, or other)
- Level of drug use at baseline (any drug diagnosis other than alcohol or tobacco, no drug diagnosis)

Randomization will be conducted using a standard telephone call-in system created by the Veteran's Affairs.

5.4.2 Study Blind Maintenance

The issue of minimizing awareness of research assistants to condition assignment is very difficult in psychosocial research conducted in a clinic setting. Participants frequently contact assessment staff (i.e., research assistants) in times of crisis or when they are unable to reach their therapist. Also, during assessments it is common for participants to mention their therapist or the type of therapy they are receiving, even when participants are encouraged not to disclose information about their treatment or therapist at the beginning of each contact. To maximize the likelihood of blindness for the primary outcome, an independent research assistant blind to condition will be assessing drug outcome measures (TLFB and biological measures). These research assistants will be trained to understand the importance of study blind maintenance. They will be trained to discourage disclosure of condition by the adolescents. These blind assessors will be asked at each time point to report if she/he knows the participant's condition.

The primary concern is that research assistants conducting the interviews for secondary outcome measures may be biased by knowledge of the participant's intervention condition (BSFT or TAU). This may result in subtle (or overt) differences in their interviewing style. Such differences can dramatically influence the direction of the results.

Several components will be implemented to minimize the potential influence of interviewer bias for all research assistants, including those assessing primary and secondary outcome variables. First, research assistants will undergo intensive training with investigators at the participating (CAB) and the Lead Nodes (protocol specific), and will receive specific instructions on how to administer every instrument in the assessment battery. Clear explanations of the importance of asking questions in a standard manner will be emphasized throughout training. Second, Research Assistants will meet with the BSFT Project Coordinator from the Lead Node once per month (via telephone) and their CTP PI or designee every three months (in person) to review all aspects of the procedures, forms, participant contact (including assessments). Third, all research assistants will receive GRP training.

5.4.3 Quality Control of Therapies Administered

Quality control for BSFT will be achieved and monitored through intensive training, supervision, and rating of adherence from the Lead Node. Initial training will consist of approximately 5-months of didactics, live supervision, case discussion, etc. (see Appendix C). During training, therapists will be trained to complete all necessary study documentation standardized for this protocol (as recommended by the Training Committee). Prior to initiating BSFT with study cases, therapists will be evaluated to certify their competence in delivering BSFT interventions and in completing research forms. The evaluation for BSFT certification will be conducted by members of the Lead Node using a standardized therapist evaluation checklist. Evaluation for BSFT Certification will require videotapes conducted by the therapist

without live supervision. During the treatment phase of the study, therapists will participate in weekly supervision calls with a BSFT supervisor. Supervision will include reviewing videotapes of therapy sessions as well as case discussion and planning. During this phase, therapy sessions will be rated for adherence by trained independent observers at the Florida Node RRTC to identify the therapists' ability to implement prescribed interventions and avoid proscribed interventions. Feedback from these ratings will be given to therapists via their Florida Node RRTC BSFT supervisor during weekly supervision. Note: Videotapes of therapy sessions will be copied at each CTP. Each CTP will keep the original and forward the copy along with the necessary clinical documentation for supervision (i.e., Clinical Contact Logs and Weekly Case Summaries) to the Lead Node directly every week. The Lead Node will be responsible for getting these forms as well as the randomly selected videotapes to the BSFT Clinical Supervisor within approximately ten days of each therapy session. Feedback from the BSFT Clinical Supervisor to the therapist will occur approximately two weeks of the conduct of a case.

To ensure proper BSFT clinical adherence practices, the following procedures will be used. If a therapist falls below 70% on adherence for 3 consecutive sessions: 1) no additional cases will be assigned to that therapist until s/he reaches a minimum of 80% in two consecutive sessions, 2) supervision will be increased, and if needed the therapist will be retrained. In CTPs with at least 3 BSFT therapists, if the therapist does not meet criteria to return to the study after six weeks of intensive supervision and retraining, if necessary, the back-up BSFT Certified therapist will be used for new cases. Training may be extended until the therapist meets criteria. To ensure continuity of care the failing therapist will be allowed to complete all current cases and, if s/he continues to not meet criteria, after the completion of her/his cases will be withdrawn from the study. The BSFT Clinical Supervisor will make the ultimate decision on failure to adhere.

6.0 CONCOMITANT THERAPY

6.1 General considerations

The primary consideration is that participants must have the opportunity to receive treatment to address drug abuse and related psychological and behavioral problems. For youth assigned to TAU, this includes individual and group therapy sessions, or non-manualized family therapy sessions. For youth assigned to BSFT, this includes manualized BSFT sessions. Youth assigned to both conditions will be provided ancillary services such as AA/NA groups, case management. Youth in BSFT will not be provided any group interventions outside of AA/NA.

6.2 Medications Prohibited During the Trial

There are no prohibitions for a specific medication in this protocol.

6.3 Medications Allowed During the Trial

Youth in both conditions may receive medical and/or psychiatric evaluations at any point prior to or during the study. If it is deemed appropriate by medical staff, youth may receive medication for concomitant physical or psychological problems. Youth and family members who are taking medication at baseline will not be excluded from the study. BSFT actively works with families to encourage them to seek medical guidance when it appears to be necessary. Thus, in BSFT, adolescents as well as other family members may receive medications as needed.

7.0 MEASUREMENTS, EVALUATIONS, AND ANALYTICAL METHODS

7.1 Identification and Screening

For parent guardians and adolescents that appear to meet the protocol's inclusion/exclusion criteria, CTP staff members will briefly describe the protocol and ask for permission to make a referral to the research assistant. The research assistant will briefly explain the study to the parent guardian, and ask their permission to ask the screening questions. Parent guardians must also give verbal permission to speak with adolescents, other children under 18, and other family members before any screening of adolescents or informed assent/consent procedures with adolescents or other family members are initiated. Research assistants will query to identify key family members that play an important emotional or instrumental role in the life of the adolescent and family. Eligible participants will be informed about the nature of the study, and will be asked about their level of interest in being part of the protocol.

The research assistant will be trained in relevant aspects of the protocol, including identification of prospective participants and determination of inclusion/exclusion criteria. Ongoing supervision for adherence and retraining if needed of the research assistants on protocol procedures will be conducted by each Node.

7.2 Informed Consent

Informed consent/assent procedures are also described in Section 4.3. After routine screening, the research assistant will explain all aspects of the study to eligible participants, including risks, benefits, randomization, interventions, videotaping sessions, assessments, duration, and reimbursement. Eligible participants will be encouraged to ask questions about any aspect of the study. The research assistant will also ask questions to assess individuals' understanding of the key issues mentioned above. Following clear indications that eligible participants understand the study they will be asked to sign the consent/assent forms.

7.3 Inclusion/Exclusion Criteria Review

Participants will be 480 (or more) adolescents ages 12 to 17 inclusive, who used illicit drugs, other than alcohol or tobacco, in the last month or that is referred from an institution (e.g. detention, residential treatment, court) to the CTP for the treatment of drug use.

Participants' family members will also be included in the study. Recruitment will be focused on including a minimum of 100 female and 200 minority adolescents (100 African American and 100 Hispanic). Participants will be included if they are age 12 to 17 inclusive, and have used any illegal drug in the 30-day period preceding the baseline assessment or if they were referred from an institution (e.g. detention, residential treatment, court) to the CTP for the treatment of drug use. Adolescents must currently live with or be expected to live with formal or informal "family". Adolescents must reside in the same geographical area as the CTP following randomization. Adolescents will be excluded if they are expected to live in a halfway house, institution, independent or assisted living facility, foster care, or in a location outside of the CTP's geographical area.

7.4 Enrollment Procedures

Based on preliminary data from the Adolescent Snapshot Interview, the current flow of cases at interested CTPs indicates that CTPs should have no difficulty meeting the expected number of cases for this study. However, if there are any difficulties recruiting cases, additional advertisements may need to be included. All advertisements will be approved by the appropriate IRBs.

7.5 Prevention of Study Dropouts

As part of their consent/baseline assessment, participants will complete a list of three persons to contact in case the research assistant is unable to find the participants. The participants will be asked for specific consent to contact the individuals on this contact list for tracking purposes only. In the

event that these individuals need to be contacted, research assistants will not reveal any confidential information about the reason for seeking the whereabouts of the participant. The only information research assistants will provide is that the participant listed the individuals name and number in case they were unable to be reached in the future. Moreover, to prevent further attrition from the study, all participants will be reminded of assessments, interviews, and/or appointments by phone the week prior to their scheduled time/day. An SOP with a brief script for research assistants will be developed for these purposes. Also, CTPs are encouraged to send holiday and birthday cards to participants as a way of maintaining participation in both conditions. Finally, the monetary incentives for completing follow-up assessments also serve to increase participation.

7.6 Overview of Assessments

Timing of Assessments

Assessment of primary outcomes will be conducted at baseline (B1) and monthly post-randomization (T1-T12). Secondary outcomes will be conducted at four timepoints: baseline, 4-, 8-, and 12- months following randomization.

- The baseline assessment will be completed within approximately 2 weeks but not more than three weeks from adolescent assent.
- The 4-month assessment will correspond roughly with the end of BSFT, while the 8-month and 12-month assessments will occur at roughly 4-months and 8-months after the completion of BSFT.

Determining Who Participates in the Assessments

Only a biological parent or legal guardian can give consent for participation of the youth in the study. However, other adults may also participate in the study. Research assistants will follow a standard procedure for determining which parent figures (in addition to the target adolescent) to ask to participate in the study. Parent figures may be selected based on one or more or the following criteria. The family member 1) is biologically related to the youth; 2) lives in the same home as the youth; or 3) serves a functional leadership role (i.e., monitoring/supervision, discipline, financial support) with regard to the youth. This selection will be made prior to the informed consent process, so that all potential participants can be included in the informed consent process.

However, it is possible that adolescent participants may experience a change in caregivers during the course of the study (e.g., moves in with grandmother or other parental adult). Consequently, the issue of which family members to include in assessments will be re-evaluated by the research assistant before each follow-up assessment. If there are no changes in caregiving relationships, the same caregiver should complete the follow-up assessments. An SOP will be developed to provide guidance with regard to which family members should be included in each assessment. Parent figures or any family members who are new to the study will be required to provide informed consent before participating in assessment (or treatment). Only the adolescent and her/his primary caregiver will be included in the formal assessments. Therapists in BSFT will consent additional family members that may be included in therapy sessions.

Confidentiality During Assessments

Adolescent and family member reports on assessments will be kept strictly confidential, including confidential from each other. The only exceptions are in cases of imminent danger, including suicidality, homicidality, abuse or neglect. Similarly, self-reports, interviews, and biological data collected from an adolescent as part of the research protocol will not be shared with parents or any outside agency, unless in instances of suicidality, homicidality, abuse or neglect. This requirement applies in particular to protecting the release of research data to outside agencies (such as the juvenile justice system), which is of great importance when working with a “prison” population. The research assistant will remind participants about the confidentiality of reports as well as their limitations. Parent

guardians will be informed that information conveyed by adolescents during the assessments is strictly confidential, and that they will NOT have access to this information (except in the instances of imminent danger mentioned above). Adolescents will also receive the same assurances of confidentiality. Emphasizing confidentiality is particularly important for ensuring accurate reports of adolescent drug use and other problem behaviors. At each assessment time point (B1-T12), once the administration of the measures is finalized, Research Assistants will present the following statement to the adolescent: "I have faith that the information I have provided will be kept confidential". Adolescents will rate this statement using a five-point Likert scale as follows: strongly agree, agree, neutral, disagree, and strongly disagree. This will allow proper monitoring for faith in confidentiality. Sometimes, as treatment progresses, faith in confidentiality of information increases, and adolescents report more drug use.

Baseline Assessments

Baseline assessments will be completed to assess functioning and behaviors prior to entering treatment. Table 1 shows the measures that are administered at baseline. Measures are briefly described below.

Post-randomization Assessments

Primary outcome assessments are conducted monthly and at 4-, 8-, and 12-months following randomization. Secondary outcome measures used in the baseline assessment are also administered at 4-, 8-, and 12-months following randomization as indicated in Table 1.

7.7 Assessment Battery

Measures were selected to examine the study's primary and secondary hypotheses. In addition, measures were selected to provide basic demographic information about family members and the family. Measures are also included to obtain information (e.g., parent drug use) that may be useful in interpreting results. Table 1 summarizes the measures included in this study, providing information about informant, administration time – separately for parent and adolescent, and domain assessed.

As noted in Table 1, some measures were selected from the CTN Common Assessment Battery. The measures are briefly described below. Measures are described within the domain/area that is being assessed. Copies of the actual measures are found in Appendix B.

7.7.1 Demographics

The CAB Demographic measure is used to characterize the participants. In addition, a family demographic form was added to provide information about aspects of the family that is not contained in the CAB and that may be useful in interpreting the results.

- CTN Demographics Form. The CTN Demographics Form (Common Assessment Battery).
- Parent Demographic Form. This 20-item questionnaire identifies who lives in the adolescent's home, serve in important familial roles as well as identifies family composition/type and family household income.
- Family Demographic Form. This measure is an interview for parents/guardians at B1, T4, T8 and T12. The purpose of this measure is to identify who resides in the home with the adolescent as well as family members or other individuals that have regular contact with the adolescent. This form also tracks changes in family constitution along the study.

TABLE 1. MEASURES

INSTRUMENT	ADMIN MODE	PARENT TIME (MIN)	ADOL. TIME (MIN)		TIMEPOINT	DEMO-GRAPHICS	PSYCH FUNC.	DRUG USE	EXTERNALIZING BEHAVIOR	INTERNALIZING BEHAVIOR	FAMILY	PEER
CTN COMMON ASSESSMENT BATTERY												
CTN Baseline Demographics Form	Interview	--	10’		B1	X						
Urine drug screen	Assay	--	5’		Monthly, B1 – T12,			X				
Risk Behavior Survey	Interview	--	10’		B1, T4, T8 & T12				X			
Addiction Severity Index-Lite- Drug Abuse module only	Interview	10’	--		B1 & T12			X				

TABLE 1. (CONTINUED) MEASURES

INSTRUMENT	ADMIN MODE	PARENT TIME (MIN)	ADOL. TIME (MIN)		TIMEPOINT	DEMO-GRAPHICS	PSYCH FUNC.	DRUG USE	EXTERNALIZING BEHAVIOR	INTERNALIZING BEHAVIOR	FAMILY	PEER
PROTOCOL SPECIFIC ASSESSMENTS												
Parent Demographic Form	Interview	10’	--		B1, T4, T8, T12	X						
Family Demographic Form	Interview	5”			B1, T4, T8, T12	X						
DISC Predictive Scales	Interview	15’	15’		B1 & T12		X		X	X		
DISC SA	Interview	--	30’		B1 & T12							
Timeline Follow Back	Interview	--	30’		Monthly, B1 – T12,			X				
National Youth Survey	Interview	--	10’		B1, T4, T8 & T12				X			
Parenting Practices (Chicago Survey)	Self-report	20’	20’		B1, T4, T8 & T12						X	X
Family Environmental Scale	Self -report	5’	5’		B1, T4, T8 & T12						X	
Conventional Activities of friends (Pittsburgh survey)	Self- report	5’	5’		B1, T4, T8 & T12							X
Peer delinquency Scale	Self-report		5’		B1, T4, T8 & T12							X
Youth Self Report	Self-report	--	20’		B1, T4, T8 & T12				X	X		
Adverse Events+	Interview	5’	5’		B1, T4, T8 & T12							

7.7.2 Drug Use (Hypothesis 1)

Hypothesis 1: BSFT will be significantly more effective than TAU in reducing adolescent drug use defined as the percentage of drug use days in 28-day periods. The Time Line Follow Back is used as the measure of outcome. Biological measures are included to improve the veracity of adolescent self-reports.

- Substance Abuse Assays. *Urine drug screens* will be conducted at all assessment points (administered by research assistant). The urine drug screens will be used at each assessment point to improve the veracity of self-reports. Sensitivity of detection of drugs varies greatly with the dose taken. Sensitivity can be affected by the quantity of fluids a person takes in prior to a urine void, whether the urine void is the first of the day after waking or not, whether the individual is a chronic user, and the individual's natural body metabolism. Urine analysis can detect cocaine and opioid use for 2 to 3 days. Marijuana can be detected for 10 days and even up to 30 days for chronic users. Benzodiazepines can be detected up to 14 days. Barbiturates can only be detected for 3 days but Phenobarbital up to 2 weeks. PCP is detected for 3 to 8 days. LSD is detected in urine up to 2 days. Urine assays will monitor the use of marijuana, opioids, cocaine, amphetamines, methamphetamines, benzodiazepines, PCP, and barbiturates. Assessment staff will be trained in appropriate observational methods. Urine drug screens will be conducted using the, SureStep Drug Screen Card 10A and urine cups which includes temperature controlled monitoring. The urine assay used in this protocol will be the same as those included in the Common Assessment Battery.
- Timeline Follow Back (TLFB). The TLFB will be used to measure adolescent drug use. At baseline, the TLFB will be used to identify drug use in the 30-day period that precedes the baseline assessment. At T1, the TLFB will assess daily use for all days between randomization and the T1 assessment. At T2 and through T12 the TLFB will be used to collect data on daily use from the prior assessment to the current assessment. Thus, the TLFB will be used to collect 365 continuous days of data on daily drug use after randomization.

  The TLFB has been adapted for use with adolescents (Bry & Krinsley, 1992; Bry et al., 1986; Liddle et al., 1997). The TLFB method obtains retrospective reports of daily drug use by using a calendar and other memory prompts to stimulate recall. It gathers daily information on specific drugs used and amount of use, (number of drinks, hits, rocks, etc.). The TLFB yields consistently high test-retest correlations over periods of up to 1 year (Carey, 1997; Mason et al., 1994), and has been shown to correlate with other self-reports as well as with collateral reports (Sobell & Sobell, 1992).
- C-Diagnostic Interview Schedule for Children, Substance Abuse /Dependence Module (DISC SA/D). The computerized generic DISC will be used to diagnose substance abuse or dependence. Developed by Shaffer and colleagues (1996), the DISC generic is a highly structured diagnostic interview designed for use by non-clinicians to assess mental health diagnosis. DISC adheres tightly to DSM-IV criteria. A scoring algorithm permits diagnosis to be established based either on symptom criteria alone or symptom criteria and a minimum level of diagnosis–specific impairment. Test-retest reliability and validity of DISC 2.3 have been found moderate to good in multiple samples (Schwab-Stone et al., 1996). The DISC 2.3 has been shown to be in high agreement (ranging from 0.69 to 0.99) with the ICD –10, DSM-III-R, and DSM IV (Hasin et al., 1997).

7.7.3 Engagement in Treatment Sessions (Hypothesis 2a)

Hypothesis 2a: BSFT will be significantly more effective than TAU in engaging adolescents and family members in treatment.

Engagement in treatment will be captured using the service activity logs for clinical services that are completed for sessions in both conditions. Information from agency service activity logs will be captured on the Study Termination CRF.

7.7.4 Adolescent Externalizing Problems (Hypothesis 2b)

Hypothesis 2b: BSFT will be significantly more effective than TAU in decreasing externalizing behavior problems.

- National Youth Survey. The *Self-Report Delinquency Scale* (Elliot et al., 1983) will be used in testing Hypothesis 2b. This Scale consists of 23 items from the National Youth Survey (Huizinga & Elliot, 1983). Items assess adolescent criminal behavior on five subscales: 1) *Total Delinquency*, 2) General Theft, 3) Crimes Against Persons, 4) Index Offenses, and 5) Drug Scales. The instrument is well validated and has been used extensively in prior research. The *Total Delinquency* scale will be used as an indicator of externalizing in Hypothesis 2b.
- Youth Self Report. The YSR is a self-report instrument (Achenbach & Rescorla, 2001) administered to children ages 11 – 18 to describe their own functioning. This instrument is designed to assess the severity of 105 problem behaviors along two scales of social competence: 1) Activities Scale: Includes scores for the number of sports, recreational activities, jobs and chores, plus ratings on the amount and quality of participation in the child's various activities; 2) Social Scale: Includes scores for participation in organizations, number of close friends, number of weekly contacts with friends, how well the child gets along with others, and how well the child plays and works alone. The YSR is designed to provide standardized descriptions of the child's functioning (Achenbach & Rescorla, 2001). Problem behaviors can be scored along the dimensions of the super-ordinate domains of "internalizing" and "externalizing" behaviors, or along smaller syndromes of behavior problems (e.g., delinquent, aggressive anxious/depressed). The "externalizing" domain will be used as an indicator of externalizing behaviors in Hypothesis 2b.
- Diagnostic Interview Schedule for Children-Predictive Scales. *Externalizing disorders (Oppositional Defiant Disorder and Conduct Disorder)* will be identified using both parent and adolescent report, and will be used as indicators in testing Hypothesis 2b (measure described in 7.7.8).

7.7.5 HIV/Sex Risk Behaviors (Hypothesis 2c)

Hypothesis 2c: BSFT will be significantly more effective than TAU in decreasing adolescent sexually risky behaviors.

- Risk Behavior Survey. *HIV risk* will be assessed using this 9-item questionnaire (CTN Common Assessment Battery; NIDA, 1991). The Risk Behavior Survey (RBS), an abbreviated version of the Risk Behavior Assessment (RBA) developed for a NIDA Cooperative Agreement (NIDA, 1991), will be used to measure HIV and HCV risk behaviors. HIV 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 (Needle et al., 1995; Weatherby et al., 1994).

Most CTPs that have expressed interest in our protocol have a standardized procedure for screening HIV risky behaviors at intake. In case Risk is determined (i.e., non barrier use) patients will be counseled to seek HIV testing.

7.7.6 Prosocial Activities (Hypothesis 2d)

Hypothesis 2d: BSFT will be more effective than TAU in increasing prosocial behaviors.

- Pittsburgh Youth Survey. (Loeber et al., 1998). The *Conventional Activities of Friends Scale* will be used to measure prosocial activities of friends. This scale includes 8 questions concerning the number of friends that engaged in prosocial activities. These behaviors range from obeying school rules to participating in religious activities. High scores indicate that most friends engage in these conventional behaviors, and the lowest scores reflect the complete absence of any friends involved in these prosocial and traditional activities. Scale scores are summed for each subject, thereby reflecting the overall degree of exposure to peers engaged in these conventional behaviors. This scale will be used as an indicator of prosocial activities in testing Hypothesis 2d.
- Pittsburgh Youth Survey. (Loeber, 1989). The *Peer Delinquency Scale* will be used to measure affiliation with deviant and delinquent peers. This scale consists of 15 questions that the adolescent rates on a 5-point scale based on the number of friends that have engaged in a variety of antisocial and delinquent behaviors. Behaviors rated range in severity from minor infractions to serious and violent crimes against others. This scale will be used as a negative indicator of prosocial activities in testing Hypothesis 2d.

7.7.7 Family Functioning (Hypothesis 2e)

Hypothesis 2e: BSFT will be significantly more effective than TAU in improving family functioning.

- Parenting Practices Questionnaire of The Chicago Youth Development Study. *Parenting practices* will be measured through 47 questions on parent and adolescent reports (Gorman-Smith, Tolan, Zelli, & Huesmann, 1996). The Parenting Practices Measure, was derived from the parental supervision and discipline interview used in the Oregon Youth Study and Pittsburg Youth Study (Thornberry, Huizinga, & Loeber, 1995). Factor analyses have identified four factors 1) Positive Parenting, 2) Discipline Effectiveness, 3) Avoidance of Discipline, and 4) Monitoring. Positive parenting refers to the use of positive rewards and encouragement of appropriate behavior. Discipline effectiveness is a measure of how effective parental discipline is in controlling the youth's behavior. Avoidance of discipline refers to the parent's avoidance of providing consequences or disciplining for fear of the youth's behavior escalating. Monitoring is a measure of monitoring and involvement in daily activity and routines and knowledge of youth's whereabouts throughout the day. Reports of discipline effectiveness and avoidance of discipline are gathered from parents only. Estimates of positive parenting and extent of monitoring are gathered from both parent and child. Internal consistency reliabilities of each of the subscales ranged from .68 to .81. Confirmatory factor analyses have consistently identified two latent constructs of Discipline and Monitoring which will be the two indicators of parenting used in the family functioning composite (Gorman-Smith et al., 1996). All four factors in this inventory will be used as indicators of parenting practices.
- Family Environmental Scale. The Family Environmental Scale (FES; Moos & Moos, 1986) is a widely used measure that was developed to measure social and

environmental characteristics of families. This measure has been used in thousands of studies to capture critical aspects of family functioning. In this study, we will be using the cohesion and conflict subscales of the FES, administered to both parents and adolescents. Internal consistency reliability estimates for the subscales range from 0.61 to 0.78. Conflict and cohesiveness subscales will be administered to measure family functioning.

7.7.8 Adolescent and Parent Psychiatric Functioning (Planned Post-Hoc Analyses)

Measures of adolescent and parent psychiatric functioning are included to provide information that is useful in interpreting and reporting results. These variables may be used as potential covariates in the analyses.

- Diagnostic Interview Schedule for Children-Predictive Scales. This measure will be used at baseline to identify the probability of the *presence or absence of 13 psychiatric disorders—Simple Phobia, Social Phobia, Agoraphobia, Panic Disorder, Avoidant Disorder, Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Major Depressive Disorder, Mania, Psychotic Disorder, ADHD, Oppositional Defiant Disorder, and Conduct Disorder.* This measure is administered to both youth (98 items) and parents (92 items) to assess the adolescent's psychological functioning. This instrument has demonstrated excellent sensitivity and specificity compared to the full Diagnostic Interview Schedule for Children (Lucas et al., 2001). Research Assistants will be trained to refer cases to the Clinical Supervisor in the event that adolescents and parents answer positively for psychotic symptoms or threshold Major Depressive Disorder. In these cases, further assessment will be offered in accordance with standard CTP practice. However, for this protocol these symptoms will not be considered AEs.

7.7.9 Adolescent Internalizing Problems (Planned Post-Hoc Analyses)

Internalizing problem measures were selected to provide information that is useful for interpreting and reporting results.

- Youth Self Report (Achenbach & Edelbrock, 1991). The broad – band *Internalizing factor* from this measure will be used as an indicator of internalizing problems (measure describe above). In the event adolescents answer positively to the question: I deliberatively try to hurt or kill myself, the Research assistant will refer the adolescent to the Clinical supervisor for further evaluation for suicide risk
- Diagnostic Interview Schedule for Children-Predictive Scales. *Internalizing disorders (Phobia, Panic, Avoidant Disorder, GAD, OCD, and MDD)* will be identified using both parent and adolescent report (measure described in 7.7.3).

7.7.10 Parent Functioning (Planned Post-Hoc Analyses)

The ASI-Lite is included in this battery because it provides information about parents' functioning that is useful for interpreting and reporting results.

- Addiction Severity Index-Lite. The Alcohol and Drug Use items from the Addiction Severity Index-Lite (Common Assessment Battery) will be administered to participating primary parent or caregiving figure to assess parent alcohol and drug use.

7.7.11 **Adverse Events**

- Adverse Events/Serious Adverse Events. A general inquiry method will be employed to identify AEs/SAEs (Jacobson, Goldstein, Dominguez, & Steinbook, 1987; Levine & Schooler, 1986) by the Research Assistants. Scheduled inquiries by the non-blind

research assistant will occur at each B1, ~~T2,~~ T4, T8, and T12. However, identification of AEs/SAEs may occur at any point in the project. Often, AEs/SAEs will be identified by therapists if the participant or family members bring them up in the sessions. The Research Assistant blind to condition and who performs drug use outcomes will also identify SAEs and AEs during the monthly assessments with adolescents. Research assistants and therapists in both conditions will be trained to identify adverse events and serious adverse events as defined in this protocol. All AEs/SAEs will be documented by project staff (research assistants responsible for secondary outcomes and other appropriate site research staff) using the Adverse Events CRF designed for this protocol (see Appendix B).

7.7.12 Clinical Forms for BSFT (see Appendix B)

- Clinical Contact Log. A contact log will be completed to document every therapist-participant contact, including telephone calls and therapy sessions. This form identifies the type of contact (e.g., individual therapy, family therapy, group therapy, telephone call) as well as general information about the contact (e.g., who participated, length, location, date). A sample of this form is included in Appendix B. A copy of this form will be sent to the Florida Node at the end of each week for the purpose of supervision.
- Weekly Case Summary. *BSFT* therapists will complete a Weekly Case Summary Form (Appendix B), which will be updated every week. This form documents the level of severity of specific family problems that are targeted for treatment as well as the amount of focus directed to each problem every week. This form is used for the purpose of supervision, and as such, for each participant/family, a copy will be sent to the Lead Node at the end of each week.

7.8 Administration Time

The baseline assessment takes approximately 3 hours to complete for the adolescent, and approximately 1.25 hours for parent(s)/guardian(s). Follow-up assessments take approximately 2.5 hours for the adolescent and 1 hours for parent(s)/guardians(s).

7.9 Reimbursement

Participants will be reimbursed for their completion of scheduled secondary outcome assessments. All payments will be made to parent(s)/guardian(s) at the completion of each assessment. For the completion of secondary outcome measures the parent /guardian will receive $25 at B1, $35 at T4, $45 at T8, $55 at T12. The total payment recommended for a participant family is $160. All payments will be made directly to the parent figures/guardians participating in the assessment. Adolescents will receive approximately $10 in movie tickets or a similarly valued incentive for the primary outcome assessments (B1, T1 T12)

Sites may include additional compensation to reimburse participants for transportation costs to and from the assessment location. The amount of additional compensation will be determined by each CTP and must be approved by the corresponding IRB. Participants will not be compensated for therapy sessions.

7.10 Pilot Cases

Pilot participants will be recruited to participate in testing the procedures for all aspects of the study. Pilot participants may participate in all or a specific aspect of the study. For example, a pilot participant may only be involved in piloting one of the baseline measures.

With respect to pilot cases, the only requirements for enrollment and consent are that the adolescent be between 12-17 years of age (inclusive) and that they live with an adult (over 21 years old) parent figure. These requirements apply for piloting any aspect of the study (BSFT or assessment measures). However every effort should be made to pilot participants as close as possible to the study inclusion-exclusion criteria. All pilot participants should be consented to participate in the pilot phase.

Pilot participants will also be tracked for AE/SAEs.

8.0 ASSESSMENT AND REPORTING OF ADVERSE EVENTS

Adolescent and family member responses on assessments will be kept strictly confidential. The only exceptions are in cases of imminent danger, including suicidality, homicidality, abuse or neglect.

8.1 Assessment of Adverse Event Severity and Relationship to Treatment

Based on our experience implementing BSFT, we have identified common AEs and SAEs for this population; these will be reported during protocol. The events are defined in Table 2.

Table 2. Family Participants

Adverse Events	Serious Adverse Events
1. Arrest	6. Physical/Sexual Abuse
2. Runaway	7. Suicidal Behavior
3. Kicked out of Home	8. Homicidal Behavior
4. School Suspension/Expulsion/Dropout	9. Hospitalization (psychiatric, drug related)
5. Violence (Victim/Exposure)	10. Death

Unexpected Adverse event
11. Other (indicate if serious)

Adverse events for this study may be identified during regularly scheduled intervals or may be reported at any other times during the study. For adolescents and their parent /guardians that are participating in assessments, the ten adverse events listed above (see Table 2) will be queried specifically at T4,T8,T12 time points. An "other" category has been included to allow sites to capture unexpected adverse events reported by participants which do not fall within the scope of any of the ten defined AEs/SAEs for this protocol. All 13 assessments conducted by the blind research assistant are opportunities for identifying adverse events if reported by the participant. All research assistants conducting primary and/or secondary outcome assessments, will be trained to identify AEs and SAEs at each of these time points. Additionally, anytime during the study, a participant or his/her family member may report an AE. These events will be identified, classified as serious or not**,** and notified by the therapists or RA- blind to the RA –non blind and will be handled in the same manner like AEs during the formal assessments. In the event that any other person reports an adverse event for the adolescent, the research team must find out with the legal guardian or the adolescent about the occurrence of the event.

Both, TAU and BSFT therapists will be trained to identify adverse events, and categorize serious adverse events, based on direct reporting during sessions. Upon identification of an adverse event, all research team (blind RA, non-blind RA, and therapists) should categorize the event for seriousness to guarantee that appropriate care and reporting occurs within approximately 24 hours. As soon as any adverse event is identified, either by querying or direct report, the event will be recorded in the AE CRF by the non-blind research assistant. In addition, the Clinical Supervisor at the site will be notified of any and all AEs. All non-serious AEs will be handled based on standardized operation procedures at the site. In both treatment conditions, action may be taken by the therapist to respond to

non-serious events (e.g., booster sessions, or increase in the frequency of sessions). If therapists or blind research assistant were the ones to identify the events, after notifying the Clinical Supervisor, they are to notify and inform the non-blind research assistant, who is then responsible for conducting further evaluations and completion of the AE CRF. All non-serious adverse events require no further reporting. All AE CRFs will be reviewed by the CTP PI weekly to evaluate relatedness to the intervention and resolution.

If the event is categorized as serious, the reporting procedures for SAEs experienced by any participant in the BSFT trial will be in accordance with the CTN Medical Safety Monitoring Policy. In the occurrence of a SAE, the Clinical Supervisor and the CTP PI must be notified when possible within 2 hours of identification. The non-blind research assistant will be responsible for recording the event in the AE CRF. The Clinical Supervisor will be responsible for ensuring care of participants, based on standardized operating procedures at the site. The CTP PI will then be responsible for assessing the event's "relatedness to the intervention".

For SAEs, an initial telephone report will be made to NIDA/CCTN Medical Monitor for BSFT**,** the Node PI, the Lead Node Project Director (Mike Robbins) and the Lead Investigator (José Szapocznik) at the University of Miami Center for Family Studies. The CTP PI will be responsible for completing and faxing the SAE form report within 24-hours of identification to the to NIDA/CCTN Medical Monitor for BSFT, the Node Study PI, the Lead Node Project Director (Mike Robbins) and the Lead Investigator (Jose Szapocznik) at the University of Miami Center for Family Studies. The research staff will also contact the same parties listed above, to ensure that paperwork is received and proper notifications are made.

The Lead Investigator (Jose Szapocznik) in collaboration with the BSFT Medical Officer (Roberto Dominguez) will then be responsible for completing a final written SAE summary report. Completions and submission of the Summary Report to the NIDA medical office will be done within 2 weeks of notification. The NIDA/CCTN Medical Monitor for BSFT will then inform the DSMB. The BSFT Project Director (Michael Robbins) will forward the LI Summary Report to the Lead Node IRB (UM IRB) as well as to other CTPs and Nodes, with a request that they report to the respective IRBs involved. The CTP PI, the NODE PI, and the Lead Investigator will track all SAEs until resolution has been achieved. Follow-up reports will be sent by the CTP PI to the LI on a monthly basis. However, if any relevant follow-up information is learned about the SAE this must be reported to the LI as soon as the CTP PI becomes aware. SAE summary reports on follow-ups will be submitted to NIDA on a quarterly basis.

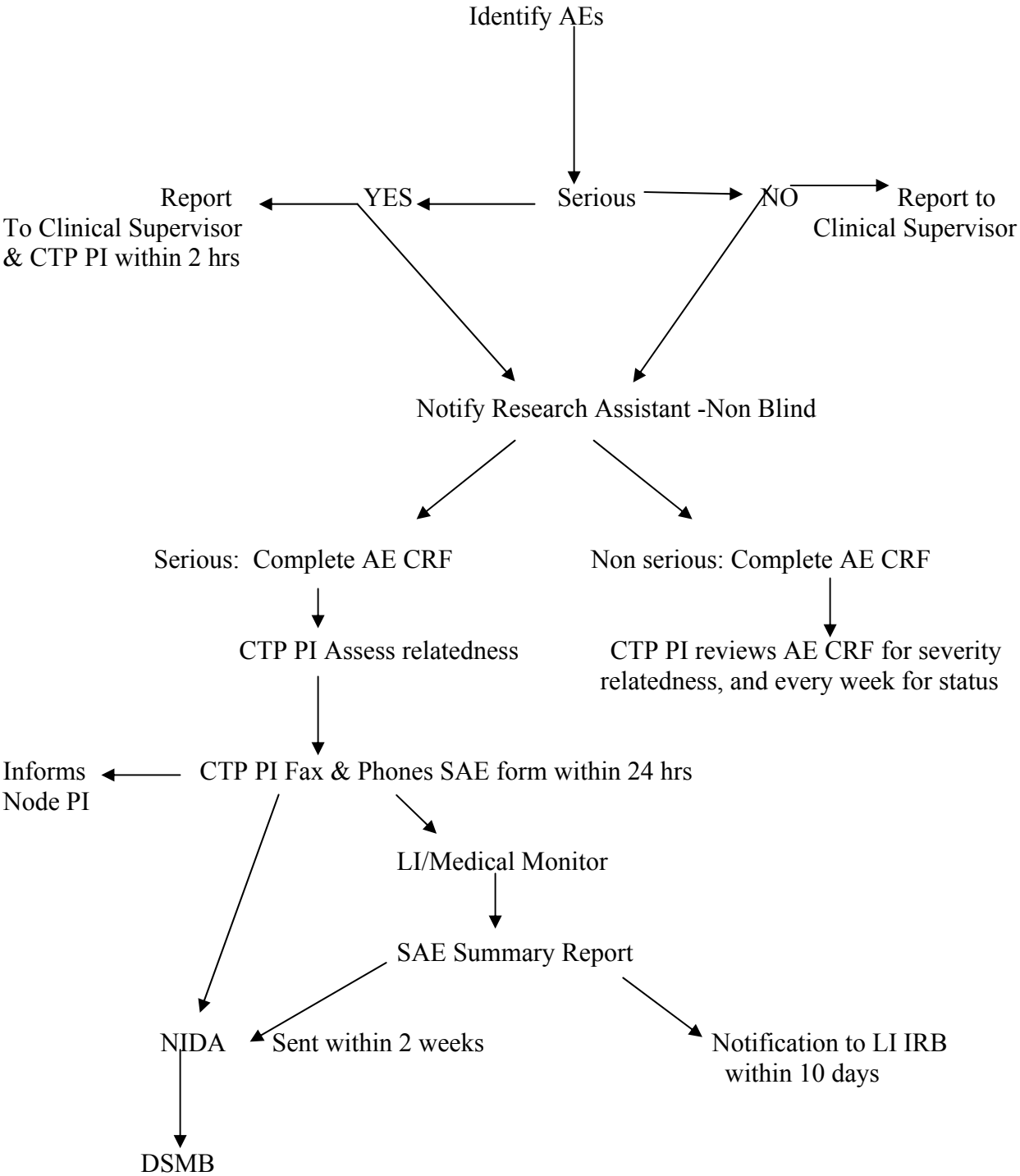
In this study, therapists are also considered research participants. However, therapists are not the target of the intervention. As such, therapists are not directly influenced by the intervention. Nonetheless, there may be negative consequences for therapist participants in this protocol. All of these consequences are job-related. Three AE/SAEs for therapists will be identified, recorded and reported. These include 1) any injury that is sustained on the way to, during, or on the way back from a therapy session, 2) death, and 3) other event identified by the Site Principal Investigator or Site Clinical Supervisor. These risks as well as confidentiality issues are included in the consent forms and procedures**.** Reporting of adverse events for therapists will follow the same guidelines as for participants in the study.

8.2 Monitoring Adverse Events

As depicted in Figure 2, AEs may be tracked and identified in three ways: 1) the research assistant will inquire and document the occurrence of the listed events during the assessment at B1, T4, T8, T12; 2) the blind research assistant will identify upon self report at all 13 monthly primary outcome assessment points, and/or 3) the adolescent and/or family may report the listed events during scheduled or unscheduled contacts. If an AE is identified, the adolescent will be referred to the

research assistant- non blind for further assessment of AEs. The assessment and logging of the AE CRFs will be performed by the research assistant responsible for the secondary outcomes assessments. This is to ensure blindness to condition by the blind research assistant. Likewise, if the therapist identifies the adverse event, the participant will be referred to the non-blind research assistant for further assessment. Therapists (both BSFT and TAU) and research assistants will notify the Clinical Supervisor of all AEs. For SAEs, therapists and research assistants will notify CTP PI and Clinical Supervisor within approximately two hours of identification. For all events identified in either the assessment or through therapy contacts, the non-blind Research Assistant is responsible for completing the AE CRF except for evaluation on severity, relatedness to the intervention and resolution status. The latter are the responsibility of the CTP PI. For SAEs, the CTP PI is responsible for completing the SAE Form and notifying the NIDA representative and the LI within 24 hours (via fax or phone). The LI (or Study MD) will complete an SAE Reporting Form and a summary report for every SAE. SAE Summary Reports must be submitted to NIDA within 2 weeks of notification.

Figure 2: AEs & SAEs Identification, Assessment and Report
Research Assistant- Non Blind (T0, T2**,** T4, T8, T12)



Note: * Research Assistant blind to condition will be trained to identify AEs in the event they are communicated during drug use assessments by the adolescent. In this event, they will refer the adolescent to the Research Assistant responsible of the assessment of secondary outcomes.

Each week the CTP PI must review all of the AE CRFs completed during that week – 1) to determine the study-relatedness of all AEs/SAEs, and 2) to track the current status of all unresolved SAEs. All SAEs will be tracked by the CTP PI and the LI (or protocol Medical Officer) monthly until a satisfactory resolution is achieved. Tracking and resolution parameters for each SAE are described below. It should be noted that non-serious AEs will not be tracked to resolution.

8.3 Serious Adverse Events

SAEs include 1) Physical/Sexual Abuse, 2), Suicidal Behavior, 3) Homicidal Behavior, 4) Hospitalization (psychiatric or drug related), and 5) Death.

All of these problems may involve imminent danger to self or other. In cases of current suicidal, homicidal, and abusive behaviors, participants in both BSFT and TAU will be immediately referred to the clinical supervisor to ensure that appropriate crisis intervention services are provided. Each of the CTPs that have expressed interest in this protocol has a procedure in place for managing these emergencies. Serious adverse events listed in this study will also be reported for any family participant. However, these cases will not be withdrawn from the study. Adequate medical care of family members, like with the adolescents, will be provided following the SOPs at each CTP.

1) Physical /Sexual Abuse

Any injury inflicted by hitting, kicking, burning, shaking or throwing (etc.) that result in bruises, marks or injuries, that require medical attention should be considered physical abuse. The CTP Clinical Supervisor is responsible for the ultimate safety of adolescents and family members in the case of family therapy, in both conditions. As such, the CTP Clinical Supervisor will oversee the implementation of the CTP procedures for handling physical abuse. These procedures will be handled identically in both conditions. However, in BSFT, our experience with drug abusing adolescents is that for the vast majority of cases, an intensification of intervention dosage is sufficient to overcome the crisis. BSFT therapists will work with the BSFT Clinical Supervisor and the CTP Clinical Supervisor to ensure that both CTP and BSFT implementation parameters are applied appropriately. In those cases in which the situation is exceptionally intense / dangerous, a strategy we have used successfully is to arrange a respite for the family members. One step in achieving such a respite is to work with extended family to arrange for the potentially violent individual to stay with extended family for a few days, although all members continue to be active in therapy and work through the critical family issues. In extreme cases in which no family members or kin are available as resources for the family, we have successfully used community shelters where the adolescent can stay in a non-therapeutic but safe environment. Conjoint therapy sessions continue during this period of respite providing continuity to the treatment. CTPs have considerable experience negotiating difficult situations such as potential violence. Although CTPs are less likely to utilize the solution of placing adolescents with extended family members, CTPs may link family members to community shelters or seek other mechanisms to protect individuals from harmful situations. This does not require the adolescent's withdrawal from the study because in many cases it is the caregiver/parent figure who is asked to leave the home in which the adolescent resides—or the adolescent may be placed temporarily in a shelter where they are not at immediate risk. Adolescent will be withdrawn from the study only in cases in which contact with any potential caregivers is proscribed.

Any reports of sexual abuse by adolescents or family members will require a legal report. As noted above, the CTP Clinical Supervisor is responsible for the ultimate safety of adolescents in both conditions. As such, the CTP Clinical Supervisor will oversee the implementation of the CTP procedures for managing and reporting sexual abuse. This is likely to include additional interviewing, scheduling pediatric consultations, as well as the potential placement of the alleged perpetrator or

victim outside of the home. Again, the CTPs procedures for managing such events will be maintained in both conditions. However, BSFT therapists will also implement family-focused interventions. Like in cases of physical abuse, an intensification of intervention dosage is often required. During this type of crisis, BSFT therapists may work with family members to process anger and shame that family members may feel after the disclosure of abuse. This anger is often directed toward the individual that "betrayed" the family by sharing this secret. The BSFT therapist attempts to gather information about the short- and long-term consequences (e.g., legal, home composition) of this report, and design and implement interventions that facilitate adaptive family coping responses and minimize the negative impact on the target adolescent.

2) Suicidal Behavior

Suicidal behaviors include any risk or attempt to inflict serious bodily harm to self that may result in death. The typical procedure at CTPs in cases of adolescent suicidal behaviors is to refer the adolescents for an evaluation by a licensed mental health provider, preferably a psychiatrist. However, based on the services available within the CTP and in the community, the specific nature of services that adolescents may receive for the treatment or stabilization of suicidal behaviors may vary. All suicidal behaviors will be referred to the CTP Clinical Supervisor who will conduct an evaluation to determine the need for additional emergency psychiatric consultation and/or hospitalization. In our discussions with CTP representatives on the Protocol Development Team, we have identified that the following examples are common in the CTPs responses to and evaluation of suicidality. Evaluation should be made of: a) the circumstances (emotional and social) preceding or following the suicidal behavior, b) history of impulsive behavior, c) wishes to die or to influence others at the time of the attempt, and d) whether a friend or a family member has committed suicide. The nature of the behavior should be considered as an indicator of intent: accidental discovery versus attempt in the views of others or telling others immediately, careful plans to avoid discovery, hanging or gunshot. Hopelessness, regret at being rescued, belief that things would get better for self or others if dead, wish to rejoin a loved one, belief that death is temporary and pleasant and unwillingness to call before attempting suicide are considered indicators of intent to die. Due to high clinical risk in these patients it is expected that clinical consultation by a psychiatrist will result in hospitalization for attempts and for ideation with a plan and intent to die.

3) Homicidal Behavior

Homicidal behaviors include any attempts to seriously injure or kill another person. Homicidal behaviors also include any ideations (e.g., thoughts/intentions) that are considered to represent a legitimate threat to another person. All homicidal behaviors will be referred to the CTP Clinical Supervisor who will conduct an evaluation to determine the nature of the behaviors, including the legitimacy of the threat. When necessary, the CTP Clinical Supervisor is responsible for notifying the appropriate authorities as well as the potential victim that is identified by a legitimate threat. Adolescent participants with homicidal behaviors will be withdrawn from BSFT**.** BSFT services may be reinstated when the homicidal behaviors are no longer present. Adolescents and family members will continue to receive study assessments.

4) Hospitalization (psychiatric or drug-related)

Given the chronic nature of drug abuse as well as the high incidence of psychiatric comorbidity among adolescent drug users, we expect that some youth may require hospitalization for psychiatric or drug-related reasons during the protocol. All hospitalizations for psychiatric or drug-related reasons will be reported to the CTP Clinical Supervisor.

When an adolescent is placed in a more restricted environment during the treatment phase of BSFT, therapists will contact the family each month to determine when the adolescent is expected to be released back to live with the family. When appropriate and permitted, family sessions will continue. For adolescents that are released back to live with the family prior to 12-months post-randomization, treatment (in the first 6 months) or "booster" sessions will be conducted with adolescents and family members to facilitate a smooth transition back into the home and to achieve or solidify improvements in family functioning and adolescent behavior problems.

5) Death

For adolescents in BSFT, deaths of primary caregivers and immediate family members (e.g., brother, sisters) that are participating in the intervention will be reported. As with all other SAEs, the CTP Clinical Supervisor is responsible for ensuring that therapists in both conditions follow standard CTP procedures for handling deaths. In BSFT, therapists are expected to conduct sessions with surviving family members to facilitate the family members' adjustment and to make referrals to appropriate mental health services if necessary.

8.4 Unexpected events

The eleventh category ("other") has been included to allow sites to capture unexpected adverse events reported by participants which do not fall within the scope of any of the ten defined AEs/SAEs for this protocol. Any other adverse event serious or non serious for which the specificity is not consistent with the described events in the protocol should be considered under this category. It is up to the judgment of the CTP PI to determine which unexpected events qualify under this category.

8.5 Immediate Report of Serious Adverse Events

Independent of causality, any SAEs that occur during the course of this study must be reported to the Clinical Supervisor and CTP PI when possible within 2 hours of notification. The CTP PI will be responsible for assessing relatedness to the intervention and forwarding the report within 24-hours of identification to the NIDA/CCTN Medical Monitor, the Project Director and Lead Investigator at the University of Miami Center for Family Studies and the Node Study PI. The Lead Investigator is responsible for completing a final written SAE summary report and seeking medical consultation from the BSFT Medical Monitor. Completions and submission of the Summary Report to the NIDA medical office should be done within 2 weeks of notification. The NIDA/CCTN Medical Monitor will then inform the DSMB. The BSFT Project Director will then forward the LI summary report to the Lead Node IRB as well as to other CTPs and Nodes, with a request that they report to all IRBs involved. The CTP PI, the Node Study PI and the Lead Investigator will follow up all SAEs until resolution has been achieved. SAE summary reports will be submitted to NIDA on a quarterly basis.

Reports submitted via telephone or fax to NIDA and to the Lead Investigator and the Protocol Medical Monitor should go to the numbers or electronic addresses listed below.

NIDA Medical Officer	(Voice)	301-443-2246
	(Fax)	301-443-2599
José Szapocznik, Ph.D.:	(Work)	305-243-8217
BSFT Lead Investigator	(Home)	305-443-4408
	(Cell)	305-610-5723
	(Fax)	305-243-7680
	(Email)	jszapocz@med.miami.edu
Michael Robbins, Ph.D.:	(Work)	305-243-4324

BSFT Co-Lead Investigator/ Project Director	(Home)	954-430-0815
	(Cell)	305-331-5600
	(Email)	mrobbins@med.miami.edu
Roberto Dominguez, M.D.: BSFT Medical Monitor	(Work)	859-296-4121
	(Home)	859-296-4121
	(Pager)	305-287-1093
	(Email)	rdomingu@med.miami.edu

Table 2. AEs and SAEs Summary Table

EVENT	IDENTIFICATION By therapists at sessions or RAs blind to condition (B1-T12)	ASSESSMENT PROCEDURES By RA Non-Blind RA (B1, T4, T8, T12	SERIOUSNESS	CLINICAL ACTION Ensured by the Clinical Supervisor	REPORTING & MONITORING FOR SAFETY Ensured by the CTP PI
1. Arrest	Report	Structured QUESTIONING	NO	Increase frequency/dose of sessions, or booster sessions if therapy completed or other	None
2. Runaway	Report	Structured QUESTIONING	NO	Increase frequency/dose of sessions, or booster sessions if therapy completed or other	None
3. Kicked out of Home	Report	Structured QUESTIONING	NO	Increase frequency/dose of sessions, or booster sessions if therapy completed or other	None
4. School Suspension/Expulsion/Dropout	Report	Structured QUESTIONING	NO	Increase frequency/dose of sessions, or booster sessions if therapy completed or other	None
5. Violence (Victim/Exposure)	Report	Structured QUESTIONING	NO	Increase frequency/dose of sessions, or booster sessions if therapy completed or other	None
6. Physical/Sexual Abuse by family member	Report	Structured QUESTIONING	YES	Mandatory reporting to authority; Increase frequency/dose of sessions, or booster sessions if therapy completed or other	Report to LI and NIDA within 24 hrs
7. Suicidal Behavior	Report	Structured QUESTIONING	YES	Referral to psychiatrist or other	Report to LI and NIDA within 24 hrs
8. Homicidal Behavior	Report	Structured QUESTIONING	YES	Report to police, inform the victim. Referral to a psychiatrist or other. Withdrawal from the intervention	Report to LI and NIDA within 24 hrs
9. Hospitalization (psychiatric, drug related)	Report	Structured QUESTIONING	YES	None or other	Report to LI and NIDA within 24 hrs
10. Death	Report	Structured QUESTIONING	YES	Intensify work with Family in BSFT or other	Report to LI and NIDA within 24 hrs

8.6 Data Safety Monitoring Board

The Node Quality Assurance Coordinator will perform on site review of 100% of the informed consent forms, inclusion/exclusion criteria, randomization assignments, and serious adverse events.

Study Procedures

The initial quality assurance monitoring visit should, whenever possible, take place no later than two weeks after the 3rd participant is enrolled at a CTP. A full on site review of 100% of the following should occur for the first ten participants.

- Review all procedures and forms for screening, informed consent forms, baseline assessments and randomization.
- Review all procedures and documentation of urine drug screens.
- Review adverse events.
- Review all other case report forms.

The Node Quality Assurance Coordinator will randomly review 10% of the remaining participants. Moreover, to monitor the quality of data for our primary outcome measure at least 50% of the remaining timeline follow back data will be randomly reviewed throughout the course of the study. This creates an expectation for all professional staff that more than 1 out of every 2 assessments will be thoroughly reviewed encouraging a context where research assistants are highly motivated to do thorough assessments of drug use**.**

Quality Control of BSFT Administration

The clinical forms and procedures will also be monitored by the Node Quality Assurance Coordinator. The Coordinator will review the query reports from the Lead Node for accuracy and timeliness. The first 10 queries for each BSFT therapist will be reviewed and 25% of the remaining queries for each BSFT therapist will be reviewed.

In addition, the Node PI and NIDA monitors will perform schedule reviews as deemed necessary.

Depending on how data are collected at each site, either the Node Quality Assurance Coordinator will examine data forms on site or it will be done at Node's Data Management Center. Missing, incomplete, or out of range data will be identified. The CTP PI and Research Assistant will be notified as soon as possible about potential errors. The Node Quality Assurance Coordinator and Node Data Management Center will verify that corrections have been made.

9.0 VARIATIONS IN PROTOCOL IMPLEMENTATION

Based on the characteristics of adolescents at CTPs it may be necessary to expand inclusion criteria to ensure an adequate sample for the current study. This should be limited however to avoid creating variability in the sample across CTPs. One area that will not threaten the ability to interpret cross-site findings is the radius where adolescents and family members reside which will be established by each CTP separately.

10.0 STATISTICAL ANALYSIS

10.1 Objectives of Analysis

The primary goal of this study is to examine the effectiveness of BSFT with adolescent drug-abusers. Specifically, it is hypothesized that:

Hypothesis 1: BSFT will be significantly more effective than TAU in reducing adolescent drug use, defined as the percentage of drug use days in 28-day periods.

Secondary hypotheses examine the relative effectiveness of BSFT over TAU in:

Hypothesis 2a: Engaging adolescents and family members in treatment
Hypothesis 2b: Decreasing adolescent delinquent behaviors and conduct problems
Hypothesis 2c: Decreasing adolescent sexually risky behaviors
Hypothesis 2d: Increasing adolescent prosocial activities (e.g., school, employment)
Hypothesis 2e: Improving family functioning (e.g., parenting, parent-adolescent relations).

10.1.1 Overview of Analysis

Testing of Distributional Assumptions. Statistical tests for univariate and multivariate normality (tests of skew & kurtosis) as well as visual inspections of the empirical distributions will be conducted. For all hypotheses residuals from the statistical analysis will be examined to determine that distributional assumptions are met. If these analyses show significant deviations non-parametric, or non-normal based versions of the proposed hypothesis tests will be devised. For example, for count data of small range, Poisson regression is indicated (Koch, Atkinson & Stokes, 1986).

Sampling and Generalizability. To establish comparability for subsequent analyses, comparisons of demographic characteristics between the following groups of participants will be conducted: participants who agree to participate (sign consent), and participants who are randomized. Analyses will also document the reasons for non-eligibility and reasons for non-participation of those eligible. Further comparisons will be made to the groups that remain in the study through various assessment times as described below in Missing Data and Attrition.

Urn Randomization. Randomization will be conducted separately by the CTP using a telephone call-in procedure developed by the Veteran's Affairs. This procedure uses an urn randomization program to increase the likelihood that treatment groups are balanced on two characteristics: Ethnicity/ race (Hispanic, African–American, other) and Level of Drug Use (any drug diagnosis other than alcohol or tobacco, no drug diagnosis) at baseline. This will ensure balance across the two treatment conditions.

All variables included as factors in the urn program will be included as covariates in the primary test of the intervention effectiveness. In addition, age, gender, baseline levels of psychiatric co-morbidity status (no comorbidity, externalizing disorder/s, internalizing disorder/s, internalizing and externalizing disorders), primary drug of abuse, family type and family-peer functioning will be controlled due to their anticipated relationship to most of the outcomes.

Missing Data and Attrition. Analyses will be conducted to identify patterns of attrition and to determine if there is differential attrition by treatment condition. Attrition between conditions will be captured with the use of contact logs, and termination forms. To minimize any impact of attrition on the test of hypotheses, intent-to-treat analyses will be conducted for all hypotheses. Note that individuals that are placed in more restrictive settings for brief periods of time may continue to be included in subsequent assessments. Data will be collected for these individuals at all scheduled timepoints (if possible). The primary outcome measure will be used to identify days that the adolescent was placed in a restrictive environment.

Missing items from multi-item scales will be imputed using the Expectations Maximization (EM) algorithm (Little & Rubin, 1987); however, missing outcome measures (e.g. caused by missing an assessment) will not be imputed. Rather, the hypotheses will be modeled in an intent-to-treat fashion with a maximum likelihood algorithm, which allows the inclusion of cases with missing data (this is possible with the assumption that data are missing

at random). Note that the protocol calls for continued assessment of cases that drop out of intervention in the hope of minimizing all forms of missing data.

Reliability. When appropriate, reliability of all measures and outcomes will be assessed using confirmatory factor analysis. To confirm internal consistency reliability, estimates of Cronbach's alpha for each of the outcome variables (e.g., drug use, externalizing problem behaviors, family functioning) will be determined with a confirmatory factor analysis (Fornell & Larker, 1981). The indicators of the outcomes in this protocol are scales of established reliability and validity. For any indicator/scale with an alpha < .70 (in this sample), items with low item-total correlations will be trimmed from the scale and the scale re-assessed for reliability. In the confirmatory factor analyses of the outcome variables based on these indicator/scales, should the overall fit of these models prove inadequate (Comparative Fit Index < .95 or standardized root mean squared residual >.06 (Hu & Bentler, 1999; Kline, 1998), additional modifications of the measurement model will be made to achieve an adequate fit. Specifics of the measurement models are described below under "Outcomes and Hypotheses".

Baseline and Other Planned Interim Analyses. The logistical plans for this protocol include the introduction of sites in waves, thus we plan to examine baseline data in waves. Once baseline data has been collected from a particular site, a "soft-lock" of the data from that site will be performed in accordance with the Data Management and Analysis Committee's SOP on Baseline Analyses. Once all necessary quality control is done on this data a series of analyses will be done to examine the issues described above: distributional assumptions, sampling and generalizability, balance of the randomization, and reliability of the proposed measurement scales within this site. Once data from all sites in the study have been 'locked,' similarities across sites will be described and differences across sites on the baseline assessment measures will be tested. In addition, confirmatory factor analysis of all constructs (described below in the hypotheses) will be performed. Once each follow-up time point is completed at each site, a similar procedure will be done each of the follow-up time points. Note that all of the follow-up descriptive analyses will be done blind to condition and that these analyses will not require a penalty for interim efficacy analyses, because efficacy of the intervention will not be examined.

10.2 Primary Outcome and Hypothesis

Hypothesis 1. BSFT will be significantly more effective than TAU in reducing adolescent drug abuse, *defined as the percentage of drug use days in 28-day periods.*

Outcome Variable. The outcome variable for this hypothesis is the percentage of days of drug use within a 28-day period. This variable will be constructed from the Timeline-Follow-back instrument and will be measured as the sum of the number of days with positive use in 28-day increments (there are thirteen 28-day periods in this design, B1 and T1-T12). Periods in which the participant is in a restricted environment will be flagged in the database, but will be included in the primary analysis. If there is missing information on the time-line follow-back within a 28-day period, the percentage will be calculated as the percentage of available days in that period, as long as not more than 14 days are missing**.** There is a chance that data collected at the same assessment point are more related than data collected across assessment points. Our data analysis strategy exploits the nested structure of our data. Thus, in this protocol, 28-day measures of drug use are nested within 13 assessment points, these assessment points are nested within individuals, individuals are nested within community treatment providers. The statistical model, as defined below, accommodates these different nesting factors. From our experience, in models with many levels of nesting, it is not uncommon for some of the random effects associated with these levels to have close to zero variance. Thus, our strategy will be to first examine the trajectories (blind to the condition assignment), and to

estimate the random effects associated with each level of nesting. If any of these are statistically not significantly different from zero, we will drop these from the specification, prior to testing of the hypotheses. Note further, that as described below, the Hierarchical Linear Model (HLM) to be used to test our hypotheses is described with only a linear term in time. During our examination of the levels of nesting we will also examine the trajectories (again blind to condition) to ascertain any higher order polynomial trends in the data. For example, if a quadratic term in time is found to have significant variance over individuals, we will include the quadratic term in the HLM. The model as presented below does not show the nesting of 28-day periods within assessments and only shows the linear term of the growth model in an effort to keep the notational clutter to a minimum.

Analysis. Hypothesis 1 will be tested using hierarchical linear models (HLM) (Bryk & Raudenbush, l992) to estimate the growth curve of drug use post-randomization. The trajectory of change in drug use will be compared between BSFT and TAU. HLM controls for the nesting of both repeated observations within the same adolescent over time and the nesting of adolescents within a CTP and further allows for a single test of the effect of the intervention across multiple times and sites (see planned post-hoc tests, below). HLM allows for the flexible inclusion of adolescents who may have missed assessments, and allows for non-linearity of the trajectory of change in the dependent measure. Finally, HLM allows us to consider treatment site as a random effect and to examine variability in treatment effects across sites. The treatment of site as a random effect is in keeping with the mission of the CTN to test the general applicability of proven treatments in real world settings. Thus, it is a goal of this protocol to show that BSFT will be efficacious in the population of community treatment providers, not just the community treatment providers in the sample (which a fixed effect specification would imply). This specification of the test actually compares the effectiveness of BSFT relative to the average effectiveness of TAU in the sites in the protocol. The analysis will include as a covariate referral from an institution for the treatment of drug.

HLM conceptualizes the growth curve as separate equations for the intercept and another equation or other equations (if more than linear change is examined) for the slope, though both (all) are estimated jointly. With the addition of treatment site as a random effect, this model is a three level HLM model. These three levels are associated with 1) time, 2) individual and 3) site. There is an additional level, or random effect associated with the nesting of 28-day periods within an assessment. As noted above, prior to testing hypotheses, in an analysis blind to condition, we will fit these 4 different levels (and additional polynomial terms). If any of the random components, or polynomial terms are not significantly different from zero, we will drop them from the model. Note that in the presentation that follows, we just present the substantive levels of the individual and omit the higher order polynomial terms to focus the exposition on the substantive issues (the growth curve and site variation). To facilitate interpretation of the growth curve, time will be centered on the 4-month post-randomization assessment (T4). Thus, the intercept term represents the difference between the two conditions immediately post intervention. If the expected ordinal nature of the outcome measure results in sufficient deviation from normality a Poisson link function will be used.

10.2.1 Level 1

For Hypothesis 1, the time path of percentage of days having used drugs in 28-day periods will be estimated and the growth trajectory will be parameterized to be a function of BSFT intervention status. Additional predictors will be the stratification variables specified in the urn randomization and the other variables, described under the heading randomization (see section 10.1.1) and any baseline variables found to predict the occurrence of missing data. The growth curve analysis will include the times after baseline only, and baseline value of the dependent measure will be included as a covariate (i.e. an analysis of covariance parameterization). The presentation below does not include the baseline value of drug use or

these other additional covariates, to ease the exposition. As mentioned this is a three-level HLM model. Level 1 describes the trajectory over time for an individual participant:

Level 1

$$y_{ijt} = \pi_{ij0} + \pi_{ij1} \cdot a_{ijt} + \varepsilon_{ijt},$$

where y_{ijt}, a_{ijt}, and ε_{ijt}, are % of drug use days, time, and a random (or error) term, respectively, for person i, in CTP j, at observation occasion t. The variable a_{ijt} will be measured as time from assessment point (T4), which occurs four months post randomization. The variables π_{ij0} and π_{ij1} are the intercept and slope of drug use, respectively for person i, in CTP j.

10.2.2 Level 2

The Level 2 model describes the individual intercept, π_{ij0}, and the individual slope term, π_{ij1} as a function of *BSFT*:

Level 2

$$\pi_{ij0} = \beta_{0j0} + \beta_{1j0} BSFT + r_{ij0},$$

$$\pi_{ij1} = \beta_{0j1} + \beta_{1j1} BSFT + r_{ij1}.$$

The *BSFT* variable is a 0-1 or dummy-coded variable that is coded 1 if the participant is receiving BSFT, and 0 otherwise. Given this coding of the *BSFT* variables, β_{0j0} and β_{0j1} are the intercept and slope, respectively, for participants who are in the TAU condition. The parameters, β_{1j0} and β_{1j1}, are the increments to the intercept and slope of the TAU participants, (β_{0j0} and β_{0j1}, respectively), for participants receiving *BSFT* at treatment site j (i.e. intercept for *BSFT*= $\beta_{0j0} + \beta_{1j0}$ and slope for *BSFT*= $\beta_{0j1} + \beta_{1j1}$). Finally, r_{ij0} and r_{ij1} are person-specific random terms for the intercept and slope.

10.2.3 Level 3

The Level 3 model incorporates the variability across treatment sites into the coefficients of the Level 2 model.

Level 3

$$\beta_{0j0} = \gamma_{000} + u_{0j0},$$

$$\beta_{1j0} = \gamma_{100} + u_{1j0},$$

$$\beta_{0j1} = \gamma_{001} + u_{0j1},$$

$$\beta_{1j1} = \gamma_{101} + u_{1j1},$$

At level 3, the *u* terms are site-specific error terms. In the absence of covariates, γ_{000} is the grand mean of TAU at T4 (immediately post intervention) and $\gamma_{000} + \gamma_{100}$ is the mean of BSFT at T4 and γ_{100} is the treatment effect of BSFT at T4. Again, in the absence of covariates, γ_{001} is the rate of change from T4 to T12 for TAU and $\gamma_{001} + \gamma_{101}$ is the rate of change of BSFT from T4 to T12 and γ_{101} is the treatment effect of BSFT at T4.

Whereas the model to be tested is conceptualized in 3 distinct levels, it is actually estimated as one single equation with multiple fixed and random effects. Substituting in the various equations gives:

$$y_{ijt} = [(\gamma_{000} + u_{0j0}) + (\gamma_{100} + u_{1j0})BSFT + r_{ij0}] + [(\gamma_{001} + u_{0j1}) + (\gamma_{101} + u_{1j1})BSFT + r_{ij1}] \cdot a_{ijt} + \varepsilon_{ijt}$$

or,

$$y_{ijt} = [(\gamma_{000} + \gamma_{100}BSFT) + (\gamma_{001}a_{ijt} + \gamma_{101}BSFT * a_{ijt})$$
$$+(\varepsilon_{ijt} + u_{0j0} + u_{1j0} * BSFT + u_{0j1} * a_{ijt} + u_{1j1} * BSFT * a_{ijt} + r_{ij0} + r_{ij1} * a_{ijt})$$

This model will be estimated using either SAS Proc Mixed (or Proc NLMixed if a non-linear link function is necessary).

10.2.4 Test of Hypothesis

The primary test of hypothesis 1 is a test of the significance on the coefficients on the BSFT term alone from the intercept equation--γ_{000}, and the term that includes BSFT interacted with a_{ijt} from the equation for the slope of the growth curve--γ_{001}. If γ_{000} is significantly less than zero, then BSFT participants (on average across all the treatment sites) will have achieved lower drug use immediately post intervention than did the TAU participants. If γ_{001} is significantly less than zero, then BSFT participants (on average across all treatment sites) will have had a decrease in drug use relative to the TAU participants from immediately post-intervention to 12months post intervention. Conversely if γ_{000} and γ_{001} are significantly greater than zero, then BSFT participants will have, respectively, greater drug use immediately post-intervention and greater increase in drug use relative to TAU participants. To simplify the presentation and interpretation of results, planned contrasts will also test if there are differences between BSFT and TAU at each follow-up time point (T4 to T12).

10.2.5 Advantages of Statistical Model

There are several advantages to this approach. First, in the test here, a_{ijt} is the time (in 28-day "months") since T4 (approximately 4 months post-randomization). Thus, assessments are not required to be at the same or at equally spaced intervals across individuals. Second, these equations, as presented, assume a linear growth curve, if there is evidence of quadratic trends in the outcome, these will also be modeled, but they are omitted here for ease of exposition.

10.2.6 Planned Post Hoc Analysis

In most hypotheses, HLM has been used to minimize the number of statistical tests per hypothesis. In the case of a significant effect of BSFT in any of these hypotheses, planned post-hoc tests will look at the time path of this difference and document when the simple differences are statistically significant.

An additional sequence of analyses will be done to address variability in the effect of BSFT. This will be accomplished by adding explanatory variables associated with the sites in the equations at Level 3 for the intercept and slope. For example, because TAU services are not standardized**,** additional planned analyses will be conducted to examine the effectiveness of BSFT compared to various types of TAU services (e.g., individual therapy, group therapy, day treatment, recreational treatment). These analyses will include full exploration of the planned characterization of TAU services at each CTP**.** These analyses will also examine if there are differential attrition rates in different types of TAU services, and if BSFT is more effective than TAU when controlling for different engagement and retention rates across TAU services. As such, these analyses will help to address the possibility that TAU is just as effective as BSFT for those cases that remain in treatment. In all of these analyses, referral from an institution for the treatment of drug use will be entered as a covariate.

Companion analyses will examine whether patient characteristics, after controlling for TAU differences, are related to effectiveness of the BSFT intervention. These will be accomplished by adding explanatory variables in the equations for Level 2 for the intercept and slope. Variables to be considered include: age, gender, ethnicity/race, level of drug use, primary drug of abuse, family type, and baseline levels of internalizing/externalizing problems, family and peer functioning. This will answer the question of for whom the intervention worked.

Therapist differences might also be an important source of variability in outcomes. In fact, the effect of participants being nested within therapist might be modeled similarly to the site effect in the planned primary analysis. In planned post-hoc analyses we will explore the effect of adding therapist as a fourth nesting factor (between participants and sites). We will also see if there are particular therapist characteristics (e.g., training, experience) or therapeutic processes (e.g., alliance) that explain this source of variance.

Further analyses will establish the effect-sizes within each of the sites and examine whether patient characteristics differed by site, and thus might explain any observed variability in effect size across sites. As stated above, the primary test of the effectiveness of BSFT is an average of the effectiveness across sites. Whereas it is not expected, it is possible that a site or sites might have TAU results that are more effective than BSFT (a negative effect) but still on average across sites show BSFT to be more effective. This planned post-hoc analysis will document that this is or is not the case.

Analyses of alternative formulations of the drug use outcome variable will be explored to provide evidence for planning of future drug abuse trials with adolescents. Specifically we will look at various ways of weighing drug use days by the number of drugs used in the day. This variable may be more sensitive to poly-drug use, however standard psychometrics including reliability and validity are not presently available.

Finally, whereas the primary outcome in this proposal is related to the functioning of the participating adolescent, family therapy modalities also are likely to affect all family members. Thus a post-hoc analysis will be done examining the changes in parent alcohol and drug use using the ASI done on the parent.

10.3 Secondary Outcomes and Hypothesis

There are five categories of secondary outcomes: a) engaging adolescents and family members in treatment, b) decreasing externalizing problem behaviors, c) decreasing adolescent sexually risky behaviors, d) increasing adolescent prosocial activities (e.g., school, employment), and e) improving family functioning (e.g., parenting, parent-adolescent relations). Please note that these secondary outcomes are only measured at B1, T4, T8 and T12.

Hypothesis 2a: BSFT will be significantly more effective in engaging participants in treatment than will TAU.

Outcome Variable. Engagement is defined as attendance by adolescent and/or family members at a minimum of two therapy (treatment) sessions. For BSFT, these will be BSFT sessions, for TAU, these will be defined in a manner that is consistent with the services provided (e.g., individual, group or non-manualized family therapy, day treatment).

Analysis. Hypothesis 2 will be analyzed as in Hypothesis 1 using hierarchical linear models (HLM) (Bryk & Raudenbush, l992). However, in this analysis a logistic link function will be used due to the 0-1 nature of the outcome. Note that because this outcome is not a time-related value, that trajectories are not involved, however all other levels of nesting described in the primary analysis are still in effect and therefore HLM is still the method of analysis. In planned post-hoc analysis

engagement of adolescents and family members (i.e., attendance in therapy sessions), specifically will be examined.

Hypothesis 2b. BSFT will be significantly more effective than TAU in decreasing externalizing problem behaviors.

Outcome Variable. For Hypothesis 2b, a composite of the following scales will be used: 'Total Delinquency' from the National Youth Survey; 'Oppositional Defiant Disorder' and 'Conduct Problems' from the Diagnostic Interview Schedule for Children-Predictive Scales, and the 'Externalizing Scale' from the Youth Self-Report. A confirmatory factor analysis will be conducted to determine that these scales measure a single construct. Reliability of this construct when loadings are constrained to be 1 will be calculated and if sufficient, equally weighted composite scores will be constructed. Otherwise, factor scores will be created using the estimated loadings and the resulting composite will be used to examine hypothesis 2b.

Analysis. The analyses for Hypothesis 2b is identical to the hierarchical linear models (HLM) (Bryk & Raudenbush, l992) used to test Hypothesis 1. It is anticipated that no link function will be necessary.

Hypothesis 2c: BSFT will be significantly more effective than TAU in decreasing sexually risky behaviors

Outcome variable. For Hypothesis 2c, the total score of the 'HIV/Sex Risk Behaviors' measure will be used as the outcome.

Analysis. The analyses for Hypothesis 2c is identical to the hierarchical linear models (HLM) (Bryk & Raudenbush, l992) used to test Hypothesis 1. It is anticipated that no link function will be necessary. The composite measure will be constructed using the methodology described in hypothesis 2b applied to the items of the Risk Behavior Survey from the Common Assessments Battery.

Hypothesis 2d. BSFT will be significantly more effective than TAU in increasing prosocial activities.

Outcome Variable. A composite measure will be verified using confirmatory factor analysis. Scales to be included in the composite and confirmatory analysis are the 'Conventional Activities of Friends' scale of the Pittsburgh Youth Survey, and the (negatively weighted) 'Peer Delinquency' scale from the Pittsburgh Youth Survey.

Analysis. Hypothesis 2d will be analyzed as in Primary Hypothesis 1 using hierarchical linear models (HLM) (Bryk & Raudenbush, l992). Again, the composite measure will be constructed using the methodology described in 2b.

Planned Post-hoc Analyses. Planned post-hoc analyses for the secondary hypotheses are identical to those explained above under the primary hypotheses. These analyses will attempt to explain the variability in the treatment effect.

Hypothesis 2e. BSFT will be significantly more effective than TAU in improving family functioning.

Outcome Variable**.** The four components of the 'Parenting Practices Inventory' will be used to create a composite for use in this analysis. The four component scales from the Parenting Practices Inventory are 'Positive Parenting', 'Discipline Effectiveness,' 'Avoidance of Discipline' and 'Monitoring' scales from the Pittsburgh Youth Survey (see Gorman-Smith et al., 1996).

Analysis. Hypothesis 4 will be analyzed as in Hypothesis 1 using hierarchical linear models (HLM) (Bryk & Raudenbush, l992). Again, the composite measure will be constructed using the methods described in 2b, above.

10.4 Sample Size and Statistical Power

Prior research on BSFT has shown simple (standardized difference) effect sizes in the range of .56 to .68 for drug use, problem behaviors and family functioning (See Appendix A for review of research findings). For engagement into treatment the difference in percentage engagement has varied from 21% to 51% depending on the study. Because power for uncovering significantly differing percentages depends on the base percentage, the effect size is frequently measured as the difference in arcsine square root transformations of the probabilities, which is invariant to the base. Cohen, 1988, calls this effect size index, h. The range of observed h values for BSFT is .23 to .59.

Power analysis for our planned hypotheses are based on the work of Raudenbush and Liu (2000), which describes a model for use with a simple effect in a multi-site clinical trial where the treatment site is treated as a random effect and there is variability in the effect-size across treatment sites. This model assumes equal numbers of participants at each site. Because we prefer not to exclude sites with smaller potential caseloads, it is likely that we will have varying numbers per site. In addition, if smaller samples are balanced with equal numbers of proportionately larger samples, it will be possible to examine these larger sites separately, in a post-hoc analysis. Because variable site size is the limiting case for power, we present the case of variable numbers per site.

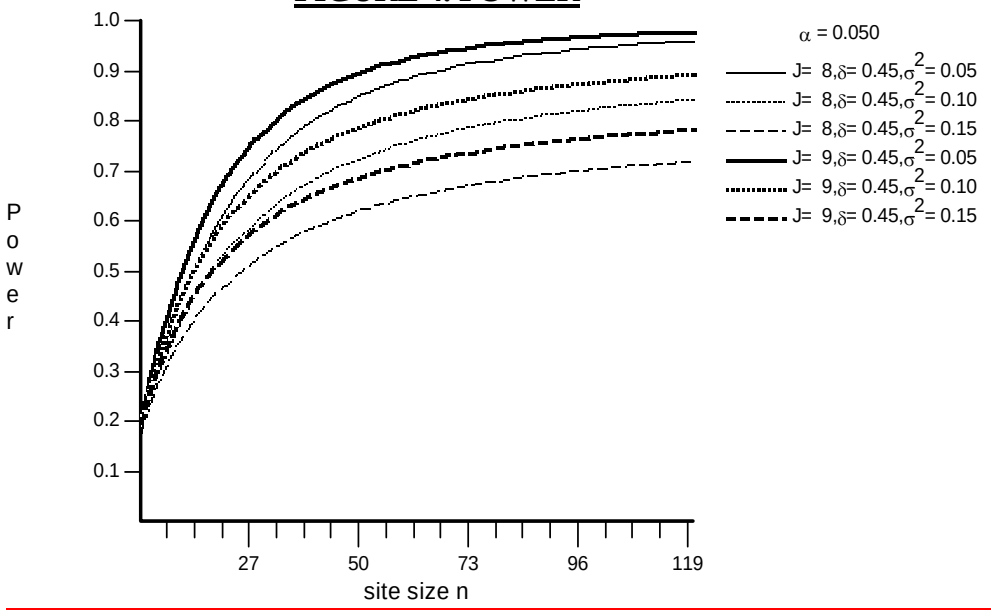
In both cases we use the same methodology to estimate power; however, in the case of varying numbers per site, we use an adjusted n per site. Following the recommendations of Cohen (1988), when there is variability in sample sizes across conditions, a harmonic mean of the individual sample sizes is computed. The harmonic mean weights the mean more to the smaller sample sizes. Once the harmonic mean is calculated then power estimation continues in the normal fashion. This is clearly an approximation, but should be sufficient for our trial planning.

From examining multiple configurations, we propose that we need 8 sites with approximately 60 participants per site, on average. This results in a total sample size of 480. Because we believe that recruitment rates are relatively consistent across the 8 outpatient sites, we estimate an effective n of 57. Thus, there is a 3 subject per site penalty for allowing the sites to vary in size. With our proposed sample configuration (n=60, J=8, effective n=57), there is nearly 75% power to uncover main effects of treatment with an effect-size of .45 and relatively small site by treatment variability.

10.4.1 Main Effect of Treatment (Treatment X Time interaction)

Figure 4 (prepared using software provided by Dr. Raudenbush) shows the expected power to uncover a significant overall treatment effect when there are 8 sites (J=8), the average treatment effect is .45 (δ=.45) and the variability in this effect size is either small, moderate or large (σ_δ^2=.10, and .15; as coined by Raudenbush & Liu, 2000). As can be seen in the graph, at the point of 57 subjects per site, power is 87% with small site variability, 75% with moderate site variability, and 64**%** with high site variability.

FIGURE 4. POWER

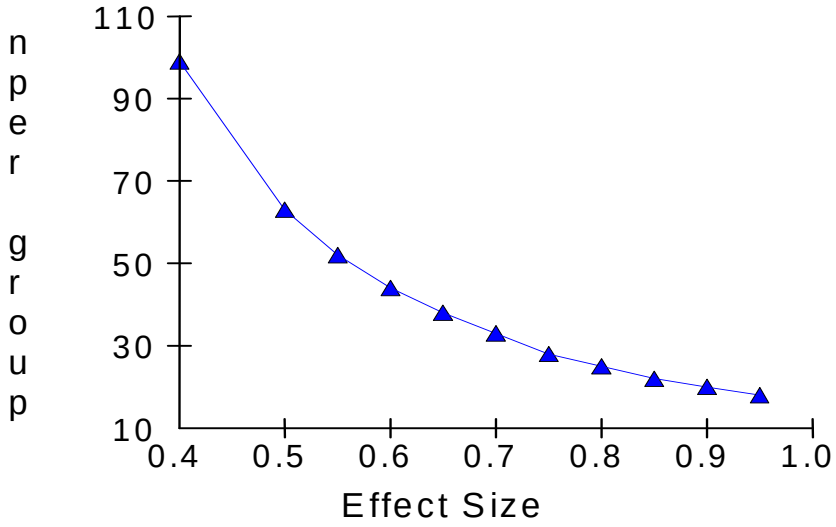


As can be seen in the graph, site variability in effect-sizes may have a substantial effect on power. If we compare the power calculations above with a simple repeated measures power analysis, we see that if there is no variability in effect-sizes across sites, that we have over 80% power to uncover a considerably smaller standardized effect size. We have used the program described in Hedeker, Gibbons, & Waternaux (1999) to calculate power in the case with no variability of effect-size across sites. In this case, there is over 90% power to uncover a Condition X Time interaction with an effect-size of .25 at the last time of assessment. This estimate assumes 28% attrition over the 12-month post-randomization period, a linear growth curve and minimal residual correlation across time (p= .1). Power actually increases as the correlation of measures across time increases. It is not uncommon for measures such as those used to test the hypotheses in the trial to show correlations across time in the range of .2 to .4, so power may be better than described here. Clearly, if site variability is smaller than the estimates in the graph above, there is substantially more power. On the other hand, if site variability is higher than the estimates in the graph above, there is substantially less power.

10.4.2 Post Hoc Analysis of Individual CTPs

When examining the distribution of effect sizes across sites, it may be useful to examine the hypotheses within sub-samples. The smallest planned sub-sample is the site (or CTP). For simple comparisons between BSFT and TAU within a CTP, the following graph (Figure 5) shows the relationship between effect size and the sample per group (treatment and TAU) necessary to have at least 80% power within a CTP. Note that this effect size is measured as the simple standardized difference. For CTPs with 60 (or 30 per group, there is 80% power to uncover a standardized effect size of .72.

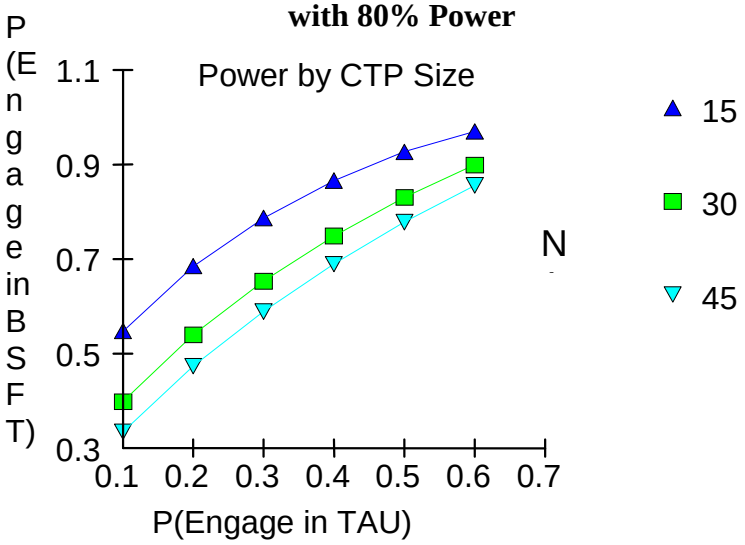
FIGURE 5. REQUIRED CTP N BY EFFECT SIZE



10.4.3 Probability of Engagement within CTPs

Finally, if we look at the power to uncover differential rates of engagement by condition within a CTP, Figure 6 gives the boundaries for 80% power at the 3 representative CTP sizes, 30, 60, & 90. From examining the graph we can see that at a base rate of engagement in TAU of 40% (for example), that a CTP which had 45 participants per condition (n=90) would need to have an engagement rate in BSFT greater than or equal to 69% to have at least 80% power. The equivalent rates in BSFT for CTPs with 30 and 15 participants per condition are .75 and .86, respectively.

FIGURE 6. P(ENGAGEMENT) PAIRS with 80% Power



11.0 DATA MANAGEMENT AND PROCEDURES

11.1 Data Management

In general, data management centers (DMC) of participating nodes will ensure that design, development, validation and implementation of data acquisition systems, independent of the data-model, are in compliance with guidelines and SOPs set forth by the Data Management and Analysis subcommittee (DMAS) of the CTN.

11.2 Design and Development

The lead node will generate and distribute the data-dictionary and sample case report forms (CRFs) to each of the DMCs.

This includes screening and assessment measures, process measures, and tracking measures developed for the study.

The design will incorporate elements of normalized database-design, data-integrity, data-validation, change control, accountability, electronic security and report-generation in each of the acquisition systems.

This includes logical consistency checks, range checks, and handling of missing data.

Each DMC will be responsible for reliability and consistency of their systems and will ensure thorough developer- and user-level testing for completeness and accuracy. Test-data sets shall be provided by the lead-node. The systems need to have adequate backup, recovery and contingency measures for handling of electronic data. As per Federal regulations, the DMC will ensure that any identifying information, if acquired, is stored, both physically and logically, independent of study data. Adequate security measures will be adopted in each Node to only allow authorized access to data-systems.

11.3 Data Acquisition and Entry

Each DMC will ensure timely collection and entry of paper or electronic data in accordance with the requirement of various CRFs. Adequate quality control procedures will be adopted to ensure completeness and accuracy of hardcopies and electronic data. The DMC will establish a regular feedback loop with the study sites (CTPs), via reports and other modes of communication, to ensure quality assurance. In addition, procedures need to be laid out for reconciliation and clean up of collected data. Paper and/or electronic audit-trails with date/time stamps will be maintained to account for any subsequent changes.

11.4 Data Transfer

The DMC will periodically transfer study data to NIDA in a timely and secure manner as per the DMAS guidelines. Corrections based on feedback from the agency will be promptly implemented and will be reflected in subsequent downloads. Periodic summary and detailed study-data reports as specified by the lead-node will be provided by each of the DMCs.

The data-acquisition system for clinical data will be largely in compliance with the DMAS SOPs. DMAS approval will be sought on any divergence from the SOPs.

11.5 Documentation

Adequate documentation pertaining to the conduct of the trial will be maintained by the DMC and/or the CTPs of all stages of the data-cycle for a period specified by government agency regulations. This includes all case-report forms, source documents, recruitment and enrollment logs, consent forms, data-correction forms, error reports, data-transfer documents, data-security, regulatory documents and SOPs. Software documentation for source-code, change-control, data-extraction, report-generation should be maintained by the DMC. Requirements for physical security of study-data and other paper-documents have been specified elsewhere in this document.

11.6 Training

Nodes will provide sufficient training to research and data staff at the DMC and CTPs to ensure

their ability to meet their respective objectives for the study. This includes, but is not limited to, training in security measures, system administration, data-collection, data-entry, data-backup, documentation, and quality assurance and control, as applicable to the data model adopted by the node.

12.0 STUDY TIMETABLE

Table 4 shows the length of research and clinical training, recruitment/randomization and follow-up assessments. Numbers in the table refer to expected rates per month/per CTP. If the case flow at a CTP is less than or greater than the rate shown in Table 4 the overall length of the study at a CTP will also be influenced.

TABLE 4. STUDY TIMETABLE

MONTHS:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Outpatient																																			
Training -- Research				x																															
Training -- Clinical	X	X	X	X	X																														
B1& Randomization						**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**																		
T4										**5**	**5**	**5**	**5**	**5**	**5**	**5**	5	**5**	**5**	**5**	**5**														
T8														**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**										
T12																		**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**						
TOTAL						**5**	**5**	**5**	**5**	**10**	**10**	**10**	**10**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**10**	**10**	**10**	**10**	**5**	**5**	**5**	**5**						

13.0 DISCONTINUATION OF STUDY

Interim Analyses

This trial does not meet any of the conditions listed in the Data Safety Monitoring Boards SOP that would require a planned interim analysis for efficacy:

1) the trial does not involve over 1000 participants

2) treatment is under 6 months in duration

3) death or other serious adverse events are not included as efficacy endpoints

4) published information supports the efficacy of the experimental treatment

5) pharmacological treatment is NOT included in the protocol

There are other factors related to this effectiveness trial's design that lessen the need for an a-priori planned interim analysis. First, this is not a blinded study. Second, the experimental treatment is being compared to the treatment as usual at each site and these sites are established drug treatment centers using established treatment approaches. It is thus highly unlikely that there will be such large effect-sizes that the trial would be stopped early due to the overwhelming efficacy of the proposed experimental treatment. On the other hand, the established research on the proposed experimental treatment does provide substantial evidence of its efficacy in treatment of adolescent problem behavior and drug abuse, making it unlikely that there would be overwhelming efficacy of the treatment as usual, over the experimental treatment. Third, the proposed estimation strategy for this trial directly accounts for the expected variability in effect size across sites by including a random effect for the treatment effect. Note that this variability is expected to be higher than might be seen in efficacy trials due to the variability in treatment as usual across sites. The stability of the statistical model is directly affected by this estimate of variability. It is generally felt that at least 5 sites are necessary to achieve a stable estimate of variability (Brown & Prescott, 1999). Because the primary test includes an interaction by modality (residential vs. outpatient), this would require at least 5 sites in each modality to generate stable estimates of the treatment effect.

For these eight reasons, and, in accordance with the Data Safety Monitoring Board's SOP, presentation of primary and secondary effectiveness outcome data and other data not intended to evaluate safety will be presented for all treatment groups combined, further broken down by study node and by CTP (when more than one CTP per node). No statistical penalty will be taken for these blinded interim analyses of efficacy data that will be conducted for the sole purpose of assessing the acceptability of safety results.

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

Although an interim analysis of effectiveness data is not planned, the DSMB may feel that such analysis is necessary to permit proper evaluation of safety data. Should an unscheduled interim analysis of efficacy be necessary, the Board will specify the question, the analysis required, the critical

values for a decision and the statistical procedures necessary to control the overall type 1 error at $p<0.05$. A protocol amendment will be included in the DSMB report of the analysis describing necessary changes in the statistical plan that result from the analysis.

Should the DSMB desire that an interim analysis plan be established prior to implementation of the trial, we would recommend a single interim analysis to take place after both 1) ½ of the subjects have completed the 8 month follow-up and 2) at least 5 sites from have enrolled some number of subjects (to ensure stability in the estimates of treatment effect variability). The trial will enroll sites "waves."

We would further recommend, due to the lack of a compelling reason to expect overwhelming efficacy in this trial, that should an a-priori interim analysis be desired that an O'Brien-Fleming stopping boundary be used (Jennison & Turnbull, 2000). This type of boundary has the least penalty in the final test and involves the lowest inflation factor to sample size necessary to maintain power (Jennison & Turnbull, 2000; Scharfstein, Tsiatis & Robins, 1997). The critical value for the interim analysis would be 2.7959 (corresponding to a p-value of .0052), whereas the critical value for the final test would be 1.977 (corresponding to a p-value of .048). To maintain power levels the sample would need to be increased from 840 to 848.

14.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

14.1 IRB Approval

Written IRB approval will be obtained from the University of Miami Institutional Review Board (IRB) and from each IRB with jurisdiction over the participating Nodes as well as the individual CTPs when indicated. Approval will be obtained for all aspects of the study, including the assessment of the risk/benefit ratio, informed consent process and document, procedures and rating instruments, randomization, clinical services, and videotaping. Informed consent will also be obtained from the therapists to permit analyses of data by therapist characteristics and therapy process. Any changes that impact the risk/benefit ratio of the study as well as changes to the protocol or to the consent process will be submitted and approved by each IRB prior to implementation. No advertising or direct soliciting of participants will be initiated without IRB approval of all written flyers/brochures/ documents.

14.2 Informed Consent Process

As a part of the informed consent process the research assistant will explain all aspects of the study to the participants in language that is readily understandable. Participants will understand that this is a research study, that their participation is voluntary, and that they can withdraw from the study at any time. Full disclosure will be provided during the informed consent process and through the informed consent document. In addition, risks will be identified. Participating adolescents and family members will sign informed assent /consent documents prior to their participation in any aspect of the study. When the legal guardian is not the primary caretaker of the adolescent participant, the adolescent's primary caretaker is also consented and is the person who participates in the research (in the role of parent figure). For the participation of a minor in the study, the consent of a biological parent or legal guardian will be required. In particular, the consent of a biological parent or legal guardian is required both for minors old enough to assent as well as for minors that are under the age of assent. Adolescents and family members will be given copies of all written consent/assent forms. Written forms will be presented in the language (limited to English or Spanish) the potential participant is most comfortable reading. Research assistants will be trained to encourage dialogue during the explanation of the study, including actively prompting potential participants to ask questions about the study. A brief test (that will be modeled after an instrument utilized in existing research

practices, i.e., Joffee, Cook, Cleary, Clark, & Weeks, 2001) will be implemented to determine if eligible participants understand key aspects of the study when they understand all aspects of the research study. Research assistants will specifically highlight sections about randomization, assessments, the nature of clinical services and any potential negative effects associated with the study. The phone contact number of the Principal Investigator and the appropriate IRB representative will be included on the written forms. If eligible participants have any questions they will be encouraged to contact these individuals. At the time of randomization, if different from the time of first baseline (as in post-residential services), the consent will be re-reviewed with the participants.

Individuals that refuse to participate will be treated without prejudice. Reasons for refusal or withdrawal will be documented, but any identifying information will not be included in the database.

14.3 Confidentiality

Procedures will be established to ensure participant confidentiality. A signed assurance of confidentiality will be obtained from all project staff that will be responsible for meeting with participants and/or handling study data (including videotapes) and will be kept in the regulatory binder. During the initial screening contact, potential participants' names will not be included on referral forms until the potential participant has expressed interest in the study and has agreed to be referred to the recruiter. No identifying information of individuals that are not interested in entering the trial will be collected (e.g., name, date of birth, address, phone number, etc.). All participant forms including referral, informed consent, and assessment and screening measures will be stored in a locked file in a locked room at each CTP. Note that CTPs will keep all original forms, Nodes will have CRFs faxed or web-entered, and the Center for Family Studies will only have electronic data, and copies of the clinical CRFs. Identifying information, however, will not be entered into the electronic database. Assessment and screening measures will be identified in the database using a unique identifier number. This number will be cross-referenced with the participants identifying information in a separate file that may only be accessed by CTPs.

All BSFT therapy sessions during the project will be videotaped for the purpose of providing clinical supervision to participating therapists, as well as determining adherence to the parameters and techniques of the intervention. Videotapes of therapy sessions must be handled with extreme attention to confidentiality because they contain personal and sensitive information about the participants and their family members. Videotape cartons and cassettes are labeled with the participants' unique identifier code number; the date of services, therapist initials, and session number and the roles of the participants in the sessions. No identifying information is stored with a videotape at any time. Videotapes are labeled with ids that are generated by the Lead Node. The labels include the therapist ID, the site and node ID, length and number of session. The same label is to be applied to the carton. No identifying information is contained on this label.

Participants and therapists are asked to sign consent forms for videotaping sessions (Appendix D). The consent forms include specific information about using videotapes for future research purposes. If participants and therapists agree to permit these videotapes to be used in future research, the videotapes will be stored for an indefinite period of time (as described in the next paragraph). If participants or therapists refuse to permit these tapes to be used for future research purposes, the videotapes will be kept for seven years and then erased.

Videotapes will be stored in two locations: 1) the participating CTP, and 2) the Florida RRTC. At the participating CTP, videotapes will be stored in a separate locked file cabinet in a locked room. Videotapes are considered research materials, but will not be stored at CTPs in the same location as research forms because participants on the videotapes may be linked to information contained in the research records. For example, because videotapes contain pictures of individuals it is possible to link a participant to their research record even though both records are stored using only an identifying

code. Copies of videotapes will be sent to Florida Node so that Data Management can randomly select tapes within each therapist for adherence ratings and for review by BSFT clinical supervisors. The University of Miami Center for Family Studies has a storage system that is set up for the express purpose of handling videotaped material. Tapes are stored in a separate room on a separate floor from research records. Dr. Michael Robbins, Co-Lead Investigator/Project Director is responsible for the day-to-day oversight of this system. Dr. Robbins oversees all transfer of videotape data into and out of this system. For the purpose of this study, videotapes will be entered into a separate database. Data may be linked to research records via unique identifier. Adherence raters, BSFT clinical supervisors, study investigators, and clinicians from the CTPs will have access to videotapes. Tapes will be returned to the video storage room at the end of each working day. Adherence raters will undergo training and will sign a confidentiality statement prior to working with study tapes.

Copies of videotapes will be transported from participating CTPs to the Florida RRTC using express mailing services. Although this creates additional risk to participant confidentiality, the payoff for this is to have higher quality supervision and the ability to monitor therapist adherence. Moreover, videotapes are important data that can be used in future analyses. Again, risk is addressed by transporting tapes with no identifying information about participants on the video carton and the Videotape Label. All tapes are labeled with unique identifiers and no personal information. The Investigators at the Florida RRTC have extensive experience in the transportation and storage of videotapes of therapy sessions, including ongoing experience with sites across the country that are currently receiving supervision by members of the Training Clinic, and the mailing of tapes from the Center for Family Studies to other research sites. The University of Miami Institutional Review Board has approved this system of transportation between sites.

As noted below, section 14.3.1, Confidentiality Certificate, research records will be protected by a Federal Certificate of Confidentiality. Participants and family members will be informed about all of the risks and safeguards that are part of this study, including instances that require reporting, including homicide, suicide, and child and elder abuse. Participants will also be informed that appropriate Federal, as well as Institutional representatives and their agents, can review their records for audit purposes.

14.3.1 Confidentiality Certificate

To protect participant confidentiality the Lead Investigator will apply for a Federal Certificate of Confidentiality. This certificate protects the investigators from releasing information about participants where the participant is identified by name even under court order or subpoena. This protection applies to all situations except mandatory State reporting requirements which are intended to protect the well being of participants.

14.4 Monitoring

NIDA, Node, and Florida Node monitors will conduct a site initiation visit prior to the start of the study. At this visit they will assure that proper study-related documentation exists, and assist in training investigators and other site personnel in study procedures and good clinical practice guidelines.

All investigators will allow representatives of participating Nodes' PI to audit all CRFs and corresponding source documents for each participant at mutually convenient times during and after the study. These monitoring visits provide the CTP PI and study staff with the opportunity to evaluate the progress of the study, collect data for fidelity measures and to inform the Node PI and Lead Node LI of potential problems at the study sites. The Node monitors will assure that submitted data are accurate and in agreement with source documentation. Additionally, Node monitors will verify that participants' consent for study participation has been properly obtained and documented, confirm that research participants entered into the study meet all inclusion and no exclusion criteria, and assure that

all essential documentation required by good clinical practices guidelines are appropriately filed. Prior to leaving the CTP, the study monitor(s) will conduct an exit interview with the CTP PI and study personnel to review and clarify preliminary findings.

At the end of the study, CTP PIs and Node PIs will advise on the disposition and storage of study records. All sites should store their study records in the anticipation of visits by NIDA monitors, the coordinating site Principal Investigator or his designees, the Node PIs or his/her representatives.

14.5 Records Retention

Documentation includes the following:

- Pre enrollment forms
- Informed consent/assent forms
- Randomization Forms (for stratification in urn program)
- Assessment measures (B1-T12) and assessment monitoring and scheduling logs
- Adverse events CRFs
- Clinical forms (contact logs, weekly case progress forms)
- Videotapes of therapy sessions
- Data codebooks
- Data correction forms
- Correspondence
- IRB approval forms and correspondence

Original forms will be kept by the CTP for a minimum period of 5 years following the submission of a final study report to the IRB. When originals are not available, copies of forms are acceptable when these are clean and legible. All documentation will be stored in a locked cabinet in a locked room (under two separate locks) at a location specified by the CTP PI. Copies of videotapes sent to the Florida Node will be stored in the Center for Family Studies (University of Miami, Center for Family Studies) videotape storage system under the supervision of Michael Robbins, Ph.D. Nodes that use teleforms will have a hard copy to store.

14.6 Publications and Other Rights

The planning, preparation, and submission of publications will follow the SOP of the Publications Committee of the CTN.

15.0 REFERENCES

Achenbach, T.M., & Rescorla, L.A. (2001). *Manual for the ASEBA School-Age Forms & Profiles.* Burlington, VT: University of Vermont , Research Center for Children, Youth & Families.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders (DSM-IV).* (4th ed.). Washington, DC.

Angrist, J. D. (1995). Conditioning on the probability of selection to control selection bias (Technical Working Paper No.181). Cambridge MA: National Bureau of Economic Research.

Angrist J. D. (1997). Conditional independence in sample selection models. *Economic Letters, 54,* 103-112.

Bry, B.H., Conboy, C., & Bisgay, K. (1986). Decreasing adolescent drug use and school failure: Long-term effects of targeted family problem-solving training. *Child and Family Behavior Therapy, 8*(1), 43-59.

Bry, B.H. & Krinsley, K.E. (1992). Booster sessions and long-term effects of behavioral family therapy on adolescent substance use and school performances. *Journal of Behavior Therapy and Experimental Psychiatry, 23*(3), 183-189.

Brown, H. & Prescott, R. (1999). *Applied Mixed Models in Medicine*. London: John Wiley & Sons.

Bryk, A.S. & Raudenbush, S.W. (l992). Hierarchical linear models: Applications and data analysis methods. *Advanced Qualitative Techniques In The Social Sciences*. Thousand Oaks, CA: Sage Publications.

Carey, K.B. (1997). Reliability and validity of the time-line follow-back interview among psychiatric outpatients: A preliminary report. *Psychology of Addictive Behaviors, 11*(1), 26-33.

Carroll, K.M., Rounsaville, B.J., Gordon, L.T., Nich, C., Jatlow, P., Bisighini, R.M., & Gawin, F.H. (1994a). Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Archives of General Psychiatry, 51*, 177-187.

Carroll, K.M., Rounsaville, B.J., Nich, C., gordon, L.T., Wirtz, P.W., & Gawin, F.H. (1994b). One-year follow-up of psychotherapy and pharmacotherapy for cocaine dependence. *Archives of General Psychiatry, 51*, 989-997.

Chassin, L., Pitts, S.C., & DeLucia, C. (1999). The relation of adolescent substance abuse to young adult autonomy, positive activity involvement, and perceived competence. *Development and Psychopathology, 11*(4), 915-932.

Cohen, J. (1988). *Statistical Power Analyses for the Behavioral Sciences.* Hillsdale, NJ: Lawerence Erlbaum Associates.

Derogatis, L. R. (1993). *Brief Symptom Inventory: Administration, Scoring, and Procedures Manual.* Minneapolis, MN: National Computer Systems.

Digiuseppe, R., Linscott, J., & Jilton, R. (1996). Developing the therapeutic alliance in child-adolescent psychotherapy. *Applied and Preventive Psychology, 5*(2), 85-100.

Elliot, D.S., Ageton, S.S., Huizinga, D., Knowles, B.A., & Cantor, R.J. (1983). *The prevalence and incidence of delinquent behavior: 1976-1980*. (The National Youth Survey Rep. No. 26). Boulder, CO: Behavioral Research Institute.

Fornell, C. & Larker, D.F. (1981). Evaluating structural equation models with unobservable variables and measurement error. *Journal of Marketing Research, 18*(1), 39-50.

Gorman-Smith, D., Tolan, P.H., Zelli, A., & Huesmann, L.R. (1996). The relation of family functioning to violence among inner-city minority youths. *Journal of Family Psychology, 10*, 115-129.

Hasin, D., Grant, B. F., Cottler, L., Blaine, J., Towle, L., Uestuen, B. & Sartorious, N. (1997). Nosological comparisons of alcohol and drug diagnosis: a multi-site, multi-instrument international study. *Drug and Alcohol Dependence, 47*(3), 217-226.

Hatcher, R.L., Barends, A., Hansell, J.M., & Gutfreund, M.J. (1995). Patients' and therapists' shared and unique views of the therapeutic alliance: An investigation using confirmatory factor analysis in a nested design. *Journal of Consulting and Clinical Psychology, 63*(4), 636-643.

Heckman, J. J. (1979). Sample selection bias as a specification error. *Econometrica, 47,*153-161.

Hedecker, D., & Gibbons, R. D. (1997). Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychological Methods, 2,* 64-78.

Hedeker, D., Gibbons, R.D., & Waternaux, C. (1999). Sample size estimation for longitudinal designs with attrition: Comparing time-related contrasts between two groups. *Journal of Educational and Behavioral Statistics, 24*, 70-93.

Horvath, A.O., & Greenberg, L.S. (1989). Development and validation of the Working Alliance Inventory. *Journal of Counseling Psychology, 36(*2), 223-233.

Horvath, A.O., & Symonds, B.D. (1991). Relation between working alliance and outcome in psychotherapy: A meta-analysis. *Journal of Counseling Psychology, 38*(2), 139-149.

Hu, L.& Bentler, P.M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling, 6*(1), 1-55.

Huizinga, D. & Elliot, D.S. (1983). *Self-report measures of delinquency and crime: Methodological issues and comparative findings*. Report No. 30, National Youth Survey, Boulder, CO: Behavior Research Institute.

Idson, T. L. & Feaster, D. J. (1990). A selectivity model of employer-size wage differentials. *Journal of Labor Economics, 8*(1), 99-122.

Jacobson, A.F., Goldstein, B.J., Dominguez, R.A. & Steinbook, R.M. (1987). Interrater agreement and reliability measures of SAFTEE: General Inquiry vs. Systematic Inquiry. *Psychopharmacology Bulletin, 23,* 97-101.

Jacobson, N.S., & Traux, T. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology, 54,* 106-110.

Jennison, C. & Turnbull, B. W. (2000). *Group Sequential Methods with Applications to Clinical Trials*. Boca Raton, FL: Chapman Hall/CRC.

Joffe, S., Cook, E.F., Cleary P.D., Clark, J.W. & Weeks, J.C. (2001). Quality of informed consent: A new measure of understanding among research subjects. *Journal of the National Cancer Institute, 93*(2), 47-139.

Kazdin, A.E. (1994). Psychotherapy for children and adolescents. In A.E. Bergin & S.L. Garfield (Eds.), *Handbook of psychotherapy and behavior change*, (pp. 543-594). New York: Wiley & Sons.

Kivlighan, D.M., & Shaughnessy, P. (1995) Analysis of the development of the working alliance using hierarchical linear modeling. *Journal of Counseling Psychology, 42*(3), 338-349.

Kline, R. B. (1998). *Principles and Practice of Structural Equation Modeling*. New York: Guilford Press**.**

Koch, G.G., Atkinson, S.S. & Stokes, M.E. (1986). Poisson regression. In Kotz, S. and Johnson, N.L. (Eds.). *Encyclopedia of Statistical Sciences, 7*, 32-41. New York: John Wiley & Sons, Inc.

Levine, J., & Schooler, N.R. (1986). SAFTEE: A technique for the systematic assessment of side effects in clinical trials. *Psychopharmacology Bulletin, 22,* 343-381.

Liddle, H.A., & Dakof, G.A. (1995). Family based treatment for adolescent drug use: State of the science. In E. Rahdert, et al. (Ed.), *Adolescent drug abuse: Clinical assessment and therapeutic interventions* [NIDA Research Monograph #156, NIH Publication 95-3908]. Rockville, MD: National Institute on Drug Abuse.

Liddle, H.A., Dakof, G.A., Turner, R.T., & Tejeda, M. (1997). Family vs. individual therapy for adolescent drug abuse: Results of a controlled trial. Manuscript in preparation, University of Miami, Miami, FL.

Little, R. J. A. & Rubin, D. B. (1987). *Statistical Analysis with Missing Data.* New York: John Wiley & Sons.

Loeber R, Farrington, D. P., Stouthamer-Loeber, M., & Van Kammen, W. B. (1998). *Antisocial behavior and mental health problems: Explanatory factors in childhood and adolescence.* Mawhaw, NJ: Lawrence Erlbaum.

Lucas, C.P., Zhang, H., Fisher, P., Shaffer, D., Regier, D., Narrow, W., Bourdon, K., Dulcan, M., Canino, G., Rubio-Stipec, M., Lahey, B., Friman, P. (2001). The DISC Predictive Scales (DPS): Efficiently Predicting Diagnoses. *Journal of American Academy of Child and Adolescent Psychiatry, 40*(4), 443-449.

Mason, C. A., Cauce, A. M., Gonzales, N., Hiraga, Y., & Grove, K. (1994). An ecological model of externalizing behaviors in african american adolescents: No family is an island. *Journal of Research on Adolescence, 4*(4), 639-655.

McLellan, A.T., Alterman, A.I., Woddy, G.E., & Metzger, D. (1992). A quantitative measure of substance abuse treatments: The Treatment Services Review. *Journal of Nervous and Mental Disease, 180*, 100-109.

Meyers, K., McKellan, A.T., Jaeger, J., & Pettinati, H.M. (1995). The development of the Comprehensive Addiction Severity Index for Adolescents: An interview for addressing the multiple problems of adolescents. *Journal of Substance Abuse Treatment, 12,* 181-193.

Meyers, K., Hagan, T.A., Zanis, D., Webb, A., Frantz, J., Ring-Kurtz, S., Rutherford, M., & McLellan, A.T. (1999). Critical Issues in adolescent substance use assessment. *Drug and Alcohol Dependence, 55,* 235-246.

Myers, W. R. Handling missing data in clinical trials: an overview. *Drug Information Journal, 34,* 525-533.

National Institutes of Health. (2001). Monitoring the future: National results on adolescent drug use. Overview of key findings. (NIDA: NIH Publication No. 01-4923). Washington, DC: Johnston, L.D., O'Malley, P.M., & Bachman, J.G.

Needle, R., Fisher, D. G., Weatherby, N., Chitwood, D., Brown, B., Cesari, H., Booth, R., Williams, M., Watters, J., Andersen, M., and Braunstein, M. (1995). Reliability of self-reported HIV risk behaviors of drug users. *Psychology of Addictive Behaviors*, *9*(4), 242-250.

Raudenbush, S. W. & Liu, X. (2000). Statistical Power and Optimal Design for Multisite Randomized Trials. *Psychological Methods, 5,*199-213.

Santisteban, D.A., Szapocznik, J., Perez-Vidal, A., Kurtines, W.M., Murray, E.J. & LaPerriere, A. (1996). Efficacy of intervention for engaging youth and their families into treatment and some variables that may contribute differential effectiveness. *Journal of Family Psychology, 10*(1), 35-44.

Santisteban, D.A., Coatsworth, J.D., Perez-Vidal, A., Mitrani, V., Jean-Gilles, M. & Szapocznik, J. (1997). Brief structural strategic family therapy with African American and Hispanic High Risk Youth: A report of outcome. *Journal of Community Psychology, 25*(5), 453-471.

Santisteban, D.A., Muir-Malcolm, J.A., Mitrani, V.B., & Szapocznik, J. (2001). Integrating the study of ethnic culture and family psychology intervention science. In H. Liddle, R. Levant, D.A. Santisteban & J. Bray (Eds.). *Family Psychology Intervention Science*, Washington, D.C.: American Psychological Association Press.

Santisteban, D.A., Muir-Malcolm, J.A., Mitrani, V.B., & Szapocznik, J. (2002) Integrating the study of ethnic culture and family psychology intervention science. In H.A. Liddle, D.A. Santisteban, R.F. Levant, & J.H. Bray (Eds.) *Family Psychology: Science-based Interventions*. (pp. 331-351). Washington, D.C.: American Psychological Association.

Scharfstein, D. O., Tsiatis, A.A., & Robins, J. M. (1997). Semiparametric efficiency and its implication on the design and analysis of group-sequential studies. *Journal of the American Statistical Association, 92*, 1342-1350

Shaffer, D., Fisher, P., Dulcan, M.K., et al. (1996).Criterion validity of the NIMH Diagnostic Interview Schedule for Children, version 2.3 (DISC- 2.3). *Journal of the American Academy of Children and Adolescent Psychiatry, 35*, 865-877.

Schwab-Stone, M.E., Schaffer, D., Dulcan, M.K., Jensen, P.S., Fischer, P., Bird, H.R., Goodman, S.H., Lahey, B.B., Litchman, J.H., Canino, G., Rubio-Stipec, M. & Rae, D.S. (1996). Criterion validity of the NIMH Diagnostic Interview Schedule for Children version 2.3 (DISC 2.3) . *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 878-888.

Sobell, L.C., & Sobell, M.B. (1992). Timeline follow-back: A technique for assessing self-reported alcohol consumption. In R.Z. Litten & J.P. Allen (Eds.), *Measuring alcohol consumption* (pp. 41-72). Totowa, NJ: Humana Press.

Sobell, L.C. & Sobell, M.B. (In press). Timeline follow-back: A technique for assessing self-reported ethanol consumption. In J. Allen & R. Litten (Eds.), *Techniques to Assess Alcohol Consumption.* New Jersey: Humana Press Inc.

Spitzer, R.L., Endicott, J., Fleiss, J. & Cohen, J. (1970). The psychiatric status schedule: A technique for evaluating psychopathology impairment in role functioning. *Archives of General Psychiatry, 23*(1), 41-55.

Stanton, M.D., & Shadish, W.R. (1997). Outcome, attrition, and family-couples treatment for drug abuse: A meta-analysis and review of the controlled, comparative studies. *Psychological Bulletin, 122*(2), 170-191.

Stout, R.L., Wirtz, P., Carbonari, J.P. & Del Boca, F. (1994). Ensuring balanced distribution of prognostic factors in treatment outcome research. *Journal of Studies on Alcohol, 12,* 70-75.

Substance Abuse and Mental Health Services Administration SAMHSA (2001). *Mid-year 200 preliminary emergency department data from the drug abuse warning network*. (DHHS Publication No. 01-3502). Washington, DC: U.S. Government Printing Office.

Swadi, H. (1999). Individual risk factors for adolescent substance use. *Drug and Alcohol Dependence, 55*, 209-224. Ireland Ltd. Elsevier.

Szapocznik, J. & Hervis, O. (in press). *Brief strategic family therapy*. [NIDA Treatment Manual Series]. Rockville, MD: National Institute on Drug Abuse.

Szapocznik, J., Kurtines, W.M., Foote, F.H., Perez-Vidal, A., & Hervis, O. (1983). Conjoint versus one-person family therapy: Some evidence for the effectiveness of conducting family therapy through one person. *Journal of Consulting and Clinical Psychology, 51,* 889-899.

Szapocznik, J., Kurtines, W.M., Foote, F., Perez-Vidal, A., & Hervis, O. (1986). Conjoint versus one person family therapy: Further evidence for the effectiveness of conducting family therapy through one person with drug abusing adolescents. *Journal of Consulting and Clinical Psychology, 54*(3), 395-397.

Szapocznik, J., Perez-Vidal, A., Brickman, A.L., Foote, F.H., Santisteban, D., Hervis, O. & Kurtines, W.M. (1988). Engaging adolescent drug abusers and their families in treatment: A strategic structural systems approach. *Journal of Consulting & Clinical Psychology, 56,* 552-557.

Szapocznik, J., Rio, A., Murray, E., Cohen, R., Scopetta, M.A., Rivas-Vasquez, A., Hervis, O.E. & Posada, V. (1989). Structural family versus psychodynamic child therapy for problematic Hispanic boys. *Journal of Consulting & Clinical Psychology, 57* (5), 571-578.

Weatherby, N. L., Needle, R., and Cesari, C. (1994). Validity of self-reported drug use among injection drug users and crack cocaine users recruited through street outreach. *Journal of Education and Program Planning, 17,* 347-355

SPONSOR
NIDA will ensure that the trial will be conducted in compliance with the protocol and all necessary regulatory guidelines

Betty Tai, Ph.D., Director, CCTN (or designee) Date

LEAD INVESTIGATOR
The Lead Investigator will supervise the overall conduct of the trial to ensure compliance with the protocol and all necessary regulatory guidelines

Name/Signature Date

NODE PRINCIPAL INVESTIGATOR
The Node Principal Investigator will supervise the conduct of the trial within the Node to ensure compliance with the protocol and all necessary regulatory authorities.

Name/Signature Date

INVESTIGATOR (S)

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

Protocol Principal Investigator Name/Signature Date

Investigator #1 Name/Signature Date

Investigator #2 Name/Signature Date