Published in final edited form as:
Clin Trials. 2010 February ; 7(1): 58–68. doi:10.1177/1740774509356575.

Principles for defining adverse events in behavioral intervention research: lessons from a family-focused adolescent drug abuse trial

Viviana E Horigian[a], **Michael S Robbins**[a], **Roberto Dominguez**[a], **Jessica Ucha**[a], and **Carmen L Rosa**[b]

[a]Center for Family Studies, University of Miami, Miami, FL, USA

[b]Center for the Clinical Trials Network, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA

Abstract

Background—Behavioral intervention research has lagged behind biomedical research in developing principles for defining, categorizing, identifying, reporting, and monitoring adverse events and unanticipated problems.

Purpose—In this article we present a set of principles for defining adverse events and how they were applied in a large national multi-site family therapy study for substance-using adolescents, The Brief Strategic Family Therapy (BSFT™) Effectiveness Study.

Methods—The BSFT™ Effectiveness study tested how BSFT™ compares to Treatment as Usual (TAU) for the treatment of drug-abusing adolescents. During protocol development, experts in the BSFT™ intervention, medical safety officers, ethicists and senior investigators defined the procedures for identifying, tracking and reporting adverse events for drug using adolescents as well as their family members. During this process the team identified five key guiding principles.

Results—The five guiding principles that were used for defining adverse events in this behavioral trial were that that the adverse events should be validated and plausible, and that monitoring systems should assess relatedness, be systematic, and are a shared responsibility. The following non-serious adverse events were identified: arrest, school suspension and drop out, runaway, kicked out of home and violence. The serious adverse events in this study for the identified adolescent participant and all other consented family members were physical or sexual abuse, suicidal behavior, homicidal behavior, hospitalization (drug related or psychiatric related only) and death. The methods used in categorizing, identifying and reporting adverse events in the BSFT™ trial are outlined. More than 50% of the adolescent population (277/481 = 57.5 %) experienced an adverse event during the trial. Family members experienced less adverse events, (61/1338 = 4.5%). The most common event for the adolescent group was arrest (164/277= 59.2%), followed by school suspension/dropout (143/277 = 51.6%), and runaway (79/277= 28.5 %). For the family member group, the most common event was violence (25/61 = 40.9%) followed by arrest (13/61 = 21.3%). There was a significant difference in the presence of adverse events in family members that were randomized to BSFT™ 44/721 (6.1%) when compared to Treatment as Usual 17/617 (2.8%) (p = 0.004). A probable explanation for this is that there were more opportunities to identify adverse events for family members assigned to BSFT™ because family

Author for correspondence: Dr. Viviana E. Horigian, Center for Family Studies, University of Miami, 1425 NW 10 Ave, Miami, FL 33155, USA. vhorigian@med.miami.edu.

members attended therapy sessions. This difference may also represent the risk for family members that participate in an evidence-based family intervention like BSFT™.

Limitations—The utility of the principles outside of the BSFT™ trial is unknown.

Conclusions—Based on the events reported in this trial, the efforts for monitoring and categorizing adverse events appeared justified and appropriate. The strategies and principles described in this paper may be useful for those developing safety plans for behavioral intervention research, and to family therapy researchers for assessing the safety of behavioral family interventions.

Introduction

Despite the widespread development and implementation of procedures for protecting human subjects, the process of defining, categorizing, identifying, reporting, and monitoring participant safety lacks consistent guidelines, particularly in behavioral[1] trials [1,2]. The National Institutes of Health (NIH) policies require a safety monitoring plan and the establishment of Data Safety Monitoring Boards (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants [3]. For decades, biomedical research has been the benchmark used by Institutional Review Boards (IRBs) and DSMBs to evaluate safety in behavioral trials. However, behavioral intervention research should not simply borrow models from biomedical research, but should follow general principles that track adverse events in a manner relevant to the clinical populations that are studied and the risks of the behavioral interventions that are delivered.

Behavioral intervention research has lagged behind biomedical research in developing and describing procedures for monitoring and reporting adverse events. Risks envisioned for these interventions may be viewed as ‘minimal’ when compared to complex oncology treatment trials or the development of investigational drugs. In fact, it has been proposed that the magnitude of risks from behavioral interventions is no greater than those encountered in everyday life. Thus, some believe that there is little to be learned from monitoring adverse events in these studies [4,5].

There is a dearth of literature that explores links between behavioral interventions, monitoring of adverse events, and unanticipated problems (such as psychiatric hospitalizations, truancy, criminal acts, and suicide) [6]. Despite the efforts that are expended in reporting safety in clinical trials, it is rarely adequately reported in the literature. Both in medical research and social science research, safety reporting often receives less attention and space than do the authors and their affiliation [7–9]. In part, the lack of reports in the behavioral research literature about adverse events stems from the fact that studies have not systematically defined, tracked, and reported these events [5,9–11]. Even the terms ‘adverse event’ and ‘unanticipated problems’ are somewhat novel to many behavioral researchers who have typically only examined these ‘events’ as deleterious outcomes or isolated incidents [4,12–16].

Only more recently has behavioral intervention research begun to identify, track, and report adverse events in a more systematic manner [1,17]. However, there has been considerable variability in how behavioral intervention [1] researchers have defined and monitored adverse events. In light of this variability, as well as the absence of clear general guidelines, we developed a set of general principles that guided us in the definition and categorization

[1]*Behavioral clinical trials* include interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., drug use, smoking, sun exposure) and/or improve coping and quality of life.

of adverse events for the Brief Strategic Family Therapy (BSFT™) Effectiveness study: A multi-site randomized clinical trial of family therapy for drug using adolescents.

The lead team for the BSFT™ effectiveness tailored a safety plan to the population being studied. The literature revealed neither guidelines nor precedent to define and categorize adverse events (AEs) resulting from participation in a randomized clinical trial of a family therapy intervention [18–21]. The purpose of this article is to present the principles that guided the definition, identification, and reporting of adverse events in the BSFT™ Effectiveness Study.

Methods

Multi-site family therapy trial

The BSFT™ for adolescent drug abuse is a multi-site randomized clinical effectiveness trial intended to test how BSFT™ compares to treatment as usual (TAU) for the treatment of drug-using adolescents [22]. This multi-site evaluation of BSFT™ represents one of the largest and most rigorous examinations of the impact of family therapy on adolescent drug use in real life community settings. The primary hypothesis is that BSFT™ will be significantly more effective than TAU in reducing adolescent drug use. Secondary hypotheses examine the relative effectiveness of BSFT™ over TAU in: (a) engaging adolescents and family members in treatment; (b) decreasing adolescent externalizing behaviors; (c) decreasing adolescent sexually risky behaviors; (d) increasing adolescent pro-social activities (e.g., school, work); and (e) improving family functioning (e.g., parenting, parent-adolescent relations). The trial randomized 481 adolescents in age group 12 to 17 and their families. Because target adolescents (youth who were referred for substance abuse treatment) and their family members participated in study activities, approximately 1,800 individuals were included in the final safety population.

Developing the general principles for defining adverse events and serious adverse events

During protocol design and prior to implementation, the protocol development team, which included experts in the (BSFT™) intervention, medical safety officers, ethicists, and senior investigators with expertize in multi site trials, defined the procedures for identifying, tracking, and reporting adverse events (AEs) for drug using adolescents as well as their family members. The first step in this process involved discussions about the fundamental importance of eliciting and examining AEs in clinical research. The team recognized that protection of participant safety is paramount. In these discussions, prior to the initiation of the protocol, several key principles emerged. These general principles were influenced by many factors, including (a) the lessons learned from conducting prior biomedical and behavioral/social intervention research with diverse clinical populations (e.g., minority and non-minority adolescents and adults, depression, anxiety, and substance use), (b) general research about the nature of the clinical population in this study (e.g., adolescent substance users), and (c) clinical and research experience with the interventions studied (e.g., brief strategic family therapy and TAU).

Developing the BSFT™ safety plan

The study team developed a safety plan for the BSFT™ trial based on the agreed principles (discussed below). The plan defined the safety population and the AEs that would be monitored throughout the study. It also provided procedures for assessing, reporting, and tracking the AEs and serious adverse events (SAEs). This safety plan was reviewed and approved by the study DSMB and participating IRBs.

Training

Representatives from the lead team provided training to participating sites in all aspects of the study, including procedures for assessing safety and reporting AEs. The training was offered prior to study implementation at each site, with regular re-training sessions as necessary.

Results

The general principles we devised for developing a safety plan for a behavioral trial are as follows:

(1) AEs should be grounded in previous research on the clinical population— AEs should be defined in the light of previous research on clinical population being studied, including research on natural progression of the disorder and constellation of symptoms [23]. For example, the AEs expected in a study of cognitive therapy for depressed participants may be informed by basic research on the prevalence of suicidal thoughts and behaviors. In this way, knowledge of the clinical disorder and population can help guide decisions on what risks to assess.

(2) AEs queries should include domains plausibly affected by the interventions being tested—A primary question in defining AEs in a behavioral trial should be: 'What are the potential risks or negative events that can occur as a result of a specific intervention, or study procedures?' Behavioral intervention research should also address behavioral, psychological, legal, economic, and social events as these domains could be affected by the interventions being tested. In understanding the adverse events or unexpected problems that can occur as a result of a behavioral intervention, investigators should be clear on what the process of change will entail. These changes could be inherent to the mechanism of action of intervention under study. For example, does confronting or challenging false beliefs (delusions) increase the risk for suicidal thoughts or behavior [24]? Does a family intervention require family conflict to emerge before it can be effectively resolved? Addressing questions of mechanisms of action prior to implementing a trial is not only essential for defining treatment-emergent AEs, but also (as will be discussed below) for timing the assessments for AEs.

(3) Monitoring should attempt to assess relatedness between interventions and AEs—Behavioral trials should be designed to identify proximal links between specific interventions or study procedures and AEs. Although establishing a temporal relationship between the delivery of an intervention and the occurrence of an AE does not imply relatedness to the intervention, this temporal link is a necessary feature in evaluating relatedness. Unfortunately, however, other than a temporal link between interventions and events, there are few guidelines for how to systematically determine a link between a specific AE and a behavioral intervention. For example, Killeen *et al*. [17] defined a related AE as 'any AE that was completely or partially a result of participation in the study or one in which the study could not be ruled out as an implicating factor'

(4) Systematic monitoring is essential for identifying unexpected events—The identification of AEs is limited by the manner in which they are assessed. The behavioral trials implemented by the National Treatment Clinical Trials Network of the National Institute on Drug Abuse demonstrate differences in the classification of AEs, the manner, and timing in which they are assessed (Table 1). Spontaneous self-report and open ended questions may be insufficient to identify events that are in the domains plausibly affected by intervention.

Another reason for systematic monitoring is to identify if there are a disproportionate numbers of AEs in a specific intervention group when compared to another intervention. This difference could identify potential problems associated with a specific intervention approach.

(5) Effective monitoring is a shared responsibility—Safety reporting in all clinical trials is a complex process that involves multiple stakeholders [2,25]. Stakeholders include the investigator, the sponsor, the DSMB, and the IRB. Investigators should develop a clearly written plan that define safety reporting strategies for their protocols; proposing procedures for defining, identifying, evaluating, reporting, and monitoring AEs and unexpected problems [2,25]. The implementation of a safety plan involves the approval by the DSMBs and respective IRBs. In this way, both entities participate in the review and revision of the safety plan while considering its relevance to the intervention and the target clinical population. As protocols are developed and implemented, research investigators are responsible for evaluating the possible relatedness of events to the intervention being studied, and for providing guidance to internal and external review boards, not only about interpretation of safety results, but also by providing information about the clinical population and experimental intervention that monitoring entities do not typically have expertize in evaluating.

Safety plan for BSFT™

AEs and definitions—As shown in Table 2, a list of 10 AEs were characterized for the BSFT™ trial. Events were categorized into non-serious and serious. Non-serious events included: *(a) arrest, (b) runaway, (c) kicked out of home, (d) school suspension and drop out, and (e) violence*. SAEs included *physical or sexual abuse, suicidal behavior, homicidal behavior, hospitalization (drug related or psychiatric related only), and death*. The primary distinction between non-serious and serious was based on whether the incident was life threatening. For example, violence was categorized as non-serious because many violent incidents which drug using adolescents experience are typically not life threatening (such as fighting or witnessing fights). If a violent incident was to become life threatening, then the incident would have been categorized as 'physical abuse' and would have been considered an SAE. We also included an '*other'* category to allow the on-site principal investigator (PI) to report serious or non serious AEs that were not included in our categorizations defined above.

In an effort to only track for the safety concerns, we operationalized each of the definitions of these events. In doing so, we specifically defined not only the event, but also the procedures for tracking and determining when the event was resolved (see last column of Table 2). The operationalization of 'resolution' for each event that posed a safety concern was specifically designed to ensure that intensive oversight of participant safety occurred until the event was resolved (or was deemed unresolvable). For example, in cases in which the adolescent or any consented family member was arrested, we considered the arrest as a distinct one-time event (i.e., start and end date are the same). However, other events were tracked for longer periods of time to ensure participant safety. An example of this is *runaway:* defined as a minor who leaves home and whose parents have no information on his/her whereabouts for at least 24 h. We followed runaways until the parents learned where the adolescent was, and judged this was a safe place. We also tracked to resolution events such as *kicked out of home, suicidal behavior, homicidal behavior, and hospitalization.*

The investigators of the BSFT™ trial used the five principles described above to develop the study safety plan. In the section below, we describe how each of the principles was used in developing this plan.

Principle #1: Grounding events in research on drug using adolescents and their family members—One of the considerations specific to the study population was the usual pattern of drug use and abuse in adolescents. While increased drug use was considered as a potential AE, because the nature of use and abuse among adolescents tends to be erratic-characterized by binges - increase in drug use was not considered an AE in this study. These variations in drug use among adolescents make it difficult to determine if a binge or use of a new drug represents a new pattern or escalation of use. In outpatient treatment settings, the most observable indication that an increase in use has become a significant problem, is, when the adolescent is hospitalized for drug use. In an effort to standardize procedures across all sites, we adopted a concrete strategy to capture clinically significant increases. As such, we included hospitalization as a SAE to capture these clinically significant escalations in patterns of use. Only hospitalization for drug use was considered to be an AE. In the BSFT™ study, patterns of drug use were tracked monthly through the primary outcome measure and were subject to DSMB monitoring.

Other behavioral symptoms that could reflect clinical deterioration were considered for the BSFT™ safety plan. Symptoms included events reported as worsening of symptoms of drug using adolescents such as involvement in violent behavior and delinquency. Substance use, involvement in violent behavior, and delinquency have been found to be clearly interrelated [26]. Research studies suggest that drug use and abuse have been linked to criminal behavior and violence such as arrests, thefts, and aggressive crimes [19,27,28]. School suspension and academic failure have also been related to adolescent drug use and abuse [29,30].

Principle #2: AEs queries should include domains plausibly affected by the interventions being tested—We also considered potential risks associated with the interventions evaluated in this study. Unfortunately, the literature revealed neither guidelines nor precedent as to how to define and categorize AE resulting from participation in a randomized clinical trial of a family therapy intervention [18–21]. AEs resulting from family therapy had to take into account the complex dynamic interplay between the inherent risks of intervention and its contextual factors as well as comorbid disorders related to the disease.

Given that the experimental intervention specifically targeted families that are typically characterized by a history of conflict and other problems (such as physical or sexual abuse, neglect, parental drug use), we considered the possibility that family interventions may increase conflict within the family, which may in turn increase risk within family violence or other problems, such as adolescent runaway or being kicked out of the home.

Principle #3: Monitoring should attempt to assess relatedness between interventions and AEs—A challenge that behavioral interventions present is in how to measure AEs in a way that causal links between specific interventions and AEs can be identified. Some studies have chosen monitoring events that happen during a session or as a result of pursuing the goals determined by the experimental condition [3]. Based on our experience in previous studies, and following the principle of monitoring for causal relationships between the intervention and AEs, it was clear that we should elicit and follow events that emerged at any time during a subject's participation in the study. Also, in this effectiveness study, BSFT™ is typically delivered during an active treatment period in the first 4 to 6 months post-randomization, but booster sessions can occur at any time during the 12 month post-randomization and follow-up period. AEs related to family therapy do not necessarily occur only during a session or when treatment is active.

In the BSFT™ trial, the PI at each site was asked to make the determination about relatedness. In doing so, the PI was encouraged to (a) review the event, (b) review the participants full treatment episode at the agency (e.g., number of sessions, date of last

session), (c) interview the treating therapist to identify potential proximal links between an intervention and an event, and (d) compare the information gathered in (a) through (c) with their experiences of working with clients at their respective agencies. From this evaluation, the PI made the determination whether the event was related or not related to the specific study interventions. It should be noted that, irrespective of relatedness, it is critical that investigators define, assess, and report all AEs that occur during the course of a trial.

The application of these steps provided consistency in how PIs made determinations across sites. However, the final decisions still required judgment by the PI, which was not always an easy process. For example, relatedness was easier to determine when a fight broke out between family members during the session versus when an adolescent ran away from the home several days after a therapy session.

Principle #4: Systematic monitoring is essential for identifying unexpected events—The safety plan specifically included numerous planned assessments for identifying AEs. Moreover, due to the frequency of contact with participants (in both assessment and treatment), there were numerous opportunities to identify unexpected events in both treatment conditions. AEs were identified and tracked in the same manner for both BSFT™ and TAU. It should be noted, however, that because BSFT™ involved therapy sessions with multiple family members and TAU typically included individual or group therapy sessions, we expected that there would be more frequent opportunities for identifying AEs for family members in the BSFT™ condition.

During the study, adolescents and parents (in both conditions) were assessed in a structured manner for the occurrence of AEs at baseline (post-consent) and at 4, 8, and 12 months post-randomization. AEs were also assessed during the monthly interviews of drug use with adolescents. At all assessments, the research assistants queried for events by asking a general opening question, for example ‘Did anything uncomfortable happen to you since our last contact?’ The interview followed with specific questions targeted to each of the events identified for the study, for example: ‘Since the last time we met were you hospitalized for drug overdose or psychiatric reasons?’ The research assistants were trained on the operational definitions of study targeted events as well as how to assess the adolescent and the parent in this structured interview. By following this structured model, the relationship between time and occurrence of events as well as potential mechanisms of action of study treatments could be evaluated. This systematic monitoring is also essential for identifying unexpected events.

Principle #5: Effective monitoring is a shared responsibility—The safety of participants is the responsibility of the PI. In practice, however, the PI must rely on all research staff to ensure that events are identified and resolved in an appropriate and timely manner. Thus, safety is a shared responsibility. In the BSFT™ trial, this responsibility extended to research assistants, research coordinators, and therapists. Given that the trial included intensive and multiple contacts with adolescents and family members, there were numerous opportunities for assessing the participant safety. In fact, we expected that AEs could be reported spontaneously through self-report during the active intervention phase as well as at any time during the 12 month follow-up period. That is, members of the research team could learn about events from any family member about any other family member. As such, it was critical that every member of the research team, including therapists, be trained in identifying AEs. It should be noted, however, that irrespective of how an event was identified, participants that reported AEs were assessed by the site PI.

Summary of safety data

More than 50% of the adolescent population (277/481 = 57.5%) experienced an AE during the trial. Family members experienced less AEs, (61/1338 = 4.5%). The most common event for the adolescent group was arrest (164/277 = 59.2%), followed by school suspension/dropout (143/277 = 51.6%), and runaway (79/277 = 28.5%). For the family member group, the most common event was violence (25/61 = 40.9%) followed by arrest (13/61 = 21.3%). When comparing AEs between BSFT™ and TAU, there was a significant difference in the presence of AEs in family members that were randomized to BSFT™ ($\chi^2(1) = 8.56$, $p < 0.004$). A probable explanation for this is that there were more opportunities to identify AEs for family members assigned to BSFT™ because family members attended therapy sessions. This difference may also represent the risk for family members that participate in an evidence-based family intervention, such as BSFT™. For example, two violent incidents occurred during the family therapy sessions. BSFT™ (or family interventions in general) may thus be associated with an increase in risk of exposure/victimization of violence.

Only 1% of the randomized adolescents (5/481) experienced an AE that was judged to be related to the study therapy; and only 0.4% (6/1338) of the randomized families experienced AEs that were assessed as related to the study therapy. A total of 10 study related AEs occurred among BSFT™ participants. As noted above, the most common related adverse event for adolescent and family members was violence. Two incidents of violence with two separate families accounted for eight of these events. For the first family, the father and adolescent had a physical altercation in a session. This event accounted for six AEs because other family members were present and witnessed the fight. For the second family, there was also a fight between the father and adolescent. However, because they were the only two who attended the session, this incident accounted for only two AEs. The other two related events were categorized as adolescent runaway. These events were deemed related because the adolescent ran away when the family therapist arrived to the home for a session. Thus, all 10 events occurred immediately prior (runaway) or during (violence) a BSFT™ session. Table 3 illustrates a summary of AEs by event and by subject population, adolescent and family members, by treatment and overall.

Thirty two randomized adolescents and 14 randomized family members experienced a serious adverse event (32/481 = 6.6%; 14/1338 = 1%). None were assessed to be related to the study therapy. The most common SAE for the adolescent group was hospitalization (16/277 = 5.7%) followed by suicidal behavior (13/277 = 4.6%) and homicidal behavior (7/277 = 2.5%). The most common SAE on the family member group were hospitalization (7/61 = 11.4%) followed by suicidal behavior and death (5/61 = 8.1%).

In the trial, 30% of the events (295/954) were spontaneously self reported to research assistants or therapist and 70 percent were identified during structured interviews. Even the opportunities for identification through structured questions was less frequent.

Conclusion

Monitoring AEs in behavioral trials is at an important crossroads. To date, these trials have not employed systematic standards for addressing the issue of monitoring AEs to ensure participant safety. In part, this lapse in focus seems to be because the risks associated with behavioral interventions have been presumed to be minimal; which, in turn, has raised questions about the utility and cost effectiveness of tracking adverse events in behavioral trials. In our review of the literature, the lack of findings on relatedness of AEs to behavioral interventions result from the absence of relevant safety plans that have been included in prior research [1,2]. It is our belief that investigators should provide safety plans to monitor

participant safety in all clinical trials, regardless if a medication is involved or not. As such, we agree with Papanikolau *et al*. [9] that unless we assess AEs in behavioral interventions we would not know if these interventions could cause potential harm.

The experience in designing and implementing the safety plan in this trial provides a framework that can be useful for developing safety plans for similar (behavioral interventions) studies in the future. The principles described above are more than ideas, they provide a structure for investigators to follow when designing and implementing safety plans in future behavioral studies. The principles challenge investigators to carefully review the research literature on the specific clinical populations and interventions that they are interested in studying to tailor their safety plan in a manner that is appropriate. For example, investigations of the impact of individual cognitive behavioral treatment for depression among elderly populations should include safety plans that are different than research on family-based interventions for enhancing adherence to HIV medication.

The safety plan of the BSFT™ study has important implications for future studies with drug using adolescents and with family-based interventions. For example, other investigators may choose to track similar events that are common among adolescent drug users (e.g., arrest, runaway) and families that are frequently characterized by high conflict (e.g., physical abuse). Moreover, the safety plan provides guidance about how and when to assess for AEs, and provides useful guidelines about determining relatedness and resolution of events.

The principles that were developed and implemented in this study were specific to the issues and challenges we faced in designing a multi-site family therapy study with drug using adolescents, and could reflect a subset of a larger set of principles that may be relevant for behavioral research. As such, the application of these principles in designing procedures for defining and tracking AEs in research on other behavioral interventions (such as individual or group therapy) or clinical populations (e.g. depressed or anxious) may be limited.

In retrospect, we also believe that our definitions of AEs may have been too narrow. We would recommend that future marital and family therapy studies measure other social adverse events, such as marital separation and divorce.

Finally, safety data in the BSFT™ trial support the principles that founded the BSFT™ safety plan and illustrate the importance of safety monitoring in behavioral intervention research.

Acknowledgments

This work is supported by the National Institute on Drug Abuse (Grant No. U10-DA13720, José Szapocznik, Principal Investigator).

References

1. Czaja SJ, Schulz R, Belle SH, et al. Data and safety monitoring in social behavioral intervention trials: the REACH II experience. Clin Trials. 2006; 3:107–118. [PubMed: 16773953]
2. Califf RM, Morse MA, Wittes J, et al. Toward protecting the safety of participants in clinical trials. Control Clin Trials. 2003; 24:256–271. [PubMed: 12757992]
3. [accessed 14 February 2008] NIH Guide: Further guidance on a data and safety monitoring for phase I and phase II trials. Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
4. Petry NM, Roll JM, Rounsaville BJ, et al. Serious adverse events in randomized psychosocial treatment studies: safety or arbitrary edicts? J Consult Clin Psychol. 2008; 76(6):1076–82. [PubMed: 19045975]

5. Project MATCH Research Group. Matching alcoholism treatments to client heterogeneity: Project MATCH three-year drinking outcomes. Alcohol Clin Exp Res. 1998; 22:1300–1311. [PubMed: 9756046]
6. Pollick A. Talking with your IRBs about risk: show them the data. APS Obs. 2008:21.
7. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. JAMA. 2001; 285:437–443. [PubMed: 11242428]
8. Ioannidis JP, Lau J. Improving safety reporting from randomised trials. Drug Saf. 2002; 25:77–84. [PubMed: 11888350]
9. Papanikolaou PN, Churchill R, Wahlbeck K, Ioannidis JP. Safety reporting in randomized trials of mental health interventions. Am J Psychiatry. 2004; 161:1692–1697. [PubMed: 15337661]
10. Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity). Rationale and methods for a multisite clinical trial matching patients to alcoholism treatment. Alcohol Clin Exp Res. 1993; 17:1130–1145. [PubMed: 8116822]
11. Dennis M, Godley SH, Diamond G, et al. The cannabis youth treatment (CYT) study: main findings from two randomized trials. J Subst Abuse Treat. 2004; 27:197–213. [PubMed: 15501373]
12. Dishion TJ, McCord J, Poulin F. When interventions harm: Peer groups and problem behavior. Am Psychol. 1999; 54:755–764. [PubMed: 10510665]
13. Handwerk ML, Field CE, Friman PC. The iatrogenic effects of group intervention for antisocial youth: premature extrapolations? J Behav Educ. 2000; 10:223–238.
14. Moos RH. Iatrogenic effects of psychosocial interventions for substance use disorders: prevalence, predictors, prevention. Addiction. 2005; 100:595–604. [PubMed: 15847616]
15. Poulin F, Dishion TJ, Burraston B. 3-Year iatrogenic effects associated with aggregating high-risk adolescents in cognitive-behavioral preventive interventions. Appl Dev Sci. 2001; 5:214–224.
16. Werch CE, Owen DM. Iatrogenic effects of alcohol and drug prevention programs. J Stud Alcohol. 2002; 63:581–590. [PubMed: 12380855]
17. Killeen T, Hien D, Campbell A, et al. Adverse events in an integrated trauma-focused intervention for women in community substance abuse treatment. J Subst Abuse Treat. 2008; 35:304–311. [PubMed: 18294804]
18. Henggeler SW, Pickrel SG, Brondino MJ. Multisystemic treatment of substance-abusing and dependent delinquents: outcomes, treatment fidelity, and transportability. Ment Health Serv Res. 1999; 1:171–184. [PubMed: 11258740]
19. Henggeler SW, Clingempeel WG, Brondino MJ, Pickrel SG. Four-year follow-up of multisystemic therapy with substance-abusing and substance-dependent juvenile offenders. J Am Acad Child Adolesc Psychiatry. 2002; 41:868–874. [PubMed: 12108813]
20. Liddle HA, Dakof GA, Parker K, et al. Multidimensional family therapy for adolescent drug abuse: results of a randomized clinical trial. Am J Drug Alcohol Abuse. 2001; 27:651–688. [PubMed: 11727882]
21. Sexton, TL.; Alexander, JF. Functional family therapy. In: Sexton, TL.; Weeks, GR.; Robbins, MS., editors. Handbook of Family Therapy. Brunner-Routledge; New York: 2003. p. 323-347.
22. Robbins MS, Szapocznik J, Horigian VE, et al. Brief strategic family therapy for adolescent dDrug abusers: Aa multi-site effectiveness study. Contemp Clin Trials. 2009; 30:269–278. [PubMed: 19470315]
23. Schroeder JR, Schmittner JP, Epstein DH, Preston KL. Adverse events among patients in a behavioral treatment trial for heroin and cocaine dependence: effects of age, race, and gender. Drug Alcohol Depend. 2005; 80:45–51. [PubMed: 16157230]
24. Gould MS, Marrocco FA, Kleinman M, et al. Evaluating iatrogenic risk of youth suicide screening programs: a randomized controlled trial. JAMA. 2005; 293:1635–1643. [PubMed: 15811983]
25. Morse MA, Califf RM, Sugarman J. Monitoring and ensuring safety during clinical research. JAMA. 2001; 285:1201–1205. [PubMed: 11231751]
26. White, HR. Alcohol, illicit drugs, and violence. In: Stoff, DM.; Breiling, J.; Maser, JD., editors. Handbook of Antisocial Behavier. John Wiley & Sons Inc; Hoboken, NJ, US: 1997. p. 511-523.

27. White HR, Loeber R, Stouthamer-Loeber M, Farrington DP. Developmental associations between substance use and violence. Dev Psychopathol. 1999; 11:785–803. [PubMed: 10624726]

28. Brook JS, Whiteman M, Finch SJ, Cohen P. Young adult drug use and delinquency: childhood antecedents and adolescent mediators. J Am Acad Child Adolesc Psychiatry. 1996; 35:1584–1592. [PubMed: 8973064]

29. Dewey JD. Reviewing the relationship between school factors and substance use for elementary, middle, and high school students. J Prim Prev. 1999; 19:177–225.

30. Bergen HA, Martin G, Roeger L, Allison S. Perceived academic performance and alcohol, tobacco and marijuana use: longitudinal relationships in young community adolescents. Addict Behav. 2005; 30:1563–1573. [PubMed: 16122617]

Table 1

Clinical trials with a behavioral component or intervention in the Clinical Trials Network

Protocol	Intervention	Assessment	AEs	SAEs
Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Individuals Seeking Treatment for Substance Abuse	Motivational Enhancement Therapy	Participant self report	None specified	Hospitalization for any reason; death
Motivational Interviewing	Motivational Interviewing	Participant self report	None specified	Hospitalization for any reason; death
Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free Clinics	Motivational Incentive Program	Structured questions	Increased gambling; hospitalization; drug overdose requiring medial intervention	Hospitalization; increased gambling; death
Motivational Incentives: Methadone Clinic	Incentive group	Structured questions	Increased gambling; hospitalization; drug overdose requiring medial intervention	Hospitalization; increased gambling; death
Smoking Cessation Treatment with Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs	Smoking Cessation Counseling with Nicotine Patches	Open ended question	Any reaction, side effect, or untoward event; side effect of the patch; symptom of nicotine overdose; new illness, symptom, sign or worsening of a pre-existing condition or abnormality	Death; life-threatening event; disabling event; hospitalization; congenital anomaly; event that requires intervention to prevent permanent impairment/damage
A Feasibility Study of a Telephone Enhancement Procedure to Improve Participation in Continuing Care Activities	Telephone Enhancement Procedure	Open ended question	New illness, symptom, sign, or worsening of pre-existing condition or abnormality	Death; life-threatening event; disabling event; hospitalization; birth defect
Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Users	Motivational Enhancement Therapy	Open ended question	Vaginal bleeding; abdominal pain; leaking fluid or uterine contractions before week 37 of pregnancy; vision changes; headaches; swelling of face or hands; decreased fetal movement; suicidal or homicidal ideation	Death; life-threatening event; disabling event; hospitalization; birth defect; intervention to prevent any of above listed serious events
Brief Strategic Family Therapy For Adolescent Drug Abusers	Brief Strategic Family Therapy	Structured questions	Arrest; runaway; kicked out of home; school suspension/ expulsion/dropout; violence	Physical/sexual abuse; suicidal behavior; homicidal behavior; hospitalization; death; other
Women's Treatment for Trauma and Substance Use Disorders	Seeking Safety	Open ended question	Worsening of PTDS, SUD or depressive symptoms	Life threatening (drug over-dose, suicidal ideation/ attempt, inpatient hospitalization)
HIV and HCV Risk Reduction Interventions in Drug Detoxification and Treatment Settings	Pretest and post test counseling; Therapeutic alliance	Open ended question	Reaction, side effect, or untoward event that occurs during the course of the clinical trial	Death; life-threatening event; disabling event; hospitalization (drug overdose, suicidality); birth defect; intervention to prevent any of

Protocol	Intervention	Assessment	AEs	SAEs
				above listed serious events emotional distress due to HIV or HCV infection
Reducing HIV/STD Risk Behaviors: A Research Study for Men in Drug Abuse Treatment	HIV/AIDS group therapy	Open ended question	Reaction, side effect or untoward event that occurs during course of trial	Death; life-threatening event; disabling event; hospitalization; birth defect; intervention to prevent any of above listed serious events
Reducing HIV/STD Risk Behaviors: A Research Study for Women in Drug Abuse Treatment	HIV/AIDS group therapy	Open ended question	Abusive partner behavior; marked increase in emotional distress	Death; life-threatening event; disabling event; hospitalization; birth defect; intervention to prevent any of above listed serious events
Job Seekers Training for Patients with Drug Dependence	Basic job training program	Open ended question	Psychological distress due to assessment or training procedures, or physical injuries related to the job search process or to the employment situation	Death; life-threatening event; disabling event; hospitalization (drug overdose, suicidality); birth defect; intervention to prevent any of above listed serious events
Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish Speaking Individuals Seeking Treatments for Substance Abuse	Motivational Enhancement Therapy	Open ended question	Hospitalizations for normal child birth, planned surgical procedures, pre-existing or non threatening medical conditions	Death; life-threatening event; disabling event; requires or prolongs hospitalization and a congenital anomaly/ birth defect
Stimulant Abuser Groups to Engage in 12 Step	Combined group and individual 12 step facilitation	Not specified	New illness, symptom, sign, or disease or a worsening of a preexisting condition; admission to a hospital/ residential facility for drug detox; hospitalization for preplanned surgery, labor, and delivery	Death; life-threatening event; disabling event; hospitalization; birth defect; intervention to prevent any of above listed serious events.

Table 2

AEs for participants

Event	Severity	Operational definition	Resolution
Arrest	Non serious	Participant arrested	Arrest is a clear-cut event that starts and ends with the arrest itself. Therefore, date of onset and date of resolution are the same.
Runaway	Non serious	Minor leaves home without notice, does not come back, and does not report his/her whereabouts for 24 h	The event is resolved when the minor's parent/guardian knows the child's whereabouts.
Kicked out of home	Non serious	Participant who gets thrown out by their family does not have a safe place to go. If minor, the parent/guardian needs to know where the child is	The event is resolved when the participant who has been thrown out is in a safe place. For a minor, there is an additional requirement. The minor's parent/guardian must know where the child is.
School suspension/expulsion/dropout	Non serious	Minor is suspended (not allowed to go to school for a limited time), expelled (thrown out of their school without the right to return for an indefinite time) or drops out (decides to leave school)	These events are clear-cut incidents that start and end with the occurrence of the event. Therefore, the date of onset and the date of resolution are the same
Violence (victim/exposure)	Non serious	Participant is subjected or exposed to rough or injurious physical force or abuse, action or treatment but does not require medical attention; witness to a violent event, that involve death, serious injury or a real threat to the physical integrity	The event is resolved when the violent event or exposure to a violent event ends. Therefore, the date of onset and the date of resolution are the same.
Physical/sexual abuse	Serious	Injury inflicted by hitting, kicking, burning, shaking or throwing that result in bruises, marks or injuries, that require medical attention; sexual abuse for minors includes any sexual touching and fondling, exposing a child to pornographic materials and or adult sexual activity, having a child pose, undress or perform in a sexual fashion, peeping into bedrooms or bathrooms, rape or attempted rape; sexual abuse for adults is defined as any unwelcome sexual physical contact	This AE refers to a physical or sexual abuse incident. Repeated incidents should be reported as separate events. The event is resolved when the physical or sexual abuse incident ends.
Suicidal behavior	Serious	Suicidal behaviors include any risk or attempt to inflict serious bodily harm to self that may result in death	The event is resolved when the Clinical Supervisor or other qualified mental health practitioner determines that there is no further risk.
Homicidal behavior	Serious	Any attempts to seriously injure or kill another person; ideations that represent a realistic threat to another person	Resolution for this serious event will be the remission of homicidality as determined by the Clinical Supervisor or qualified mental health practitioner.
Hospitalization	Serious	Hospitalization for psychiatric or drug-related reasons	Resolution of this event is the discharge from hospital.
Death	Serious	Deaths of participants	This event is a clear-cut incident that starts and ends with the occurrence of the event. Therefore, the date of onset and the date of resolution are the same
Other unexpected adverse event	Serious or non serious	Any other adverse event serious or non serious	Resolution is determined by the Principle Investigator and Clinical Supervisor.

Table 3

Summary of all adverse events for adolescents and family members by subject and safety population

	TAU		BSFT™		All	
	Adolescent (*N* = 235)	**Family member (*N* = 617)**	**Adolescent (*N* = 246)**	**Family member (*N* = 721)**	**Adolescent (*N* = 481)**	**Family member (*N* = 1338)**
Any AEs	133/235 (56.6%)	17/617 (2.8%)	144/246 (58.5%)	44/721 (6.1%)	277/481 (57.5%)	61/1338 (4.5%)
Any related AEs	1/235 (0.4%)	0/617 (0.0%)	4/246 (1.6%)	6/721 (0.8%)	5/481 (1.0%)	6/1338 (0.4%)
Any SAEs	16/235 (6.8%)	4/617 (0.6%)	16/246 (6.5%)	10/721 (1.4%)	32/481 (6.6%)	14/1338 (1.0%)
Any related SAEs	0/235 (0.0%)	0/617 (0.0%)	0/246 (0.0%)	0/721 (0.0%)	0/481 (0.0%)	0/1338 (0.0%)
Non serious adverse events[*]						
Arrest	79/133 (59.4%)	4/17 (23.5%)	85/144 (59.0%)	9/44 (20.5%)	164/277 (59.2%)	13/61 (21.3%)
Runaway	45/133 (33.8%)	2/17 (11.8%)	34/144 (23.6%)	5/44 (11.4%)	79/277 (28.5%)	7/61 (11.4%)
Kicked out of home	4/133 (3.0%)	0/17 (0.0%)	6/144 (4.2%)	5/44 (11.4%)	10/277 (3.6%)	5/61 (8.1%)
School suspension	71/133 (53.4%)	1/17 (5.9%)	72/144 (50.0%)	4/44 (9.1%)	143/277 (51.6%)	5/61 (8.1%)
Violence	23/133 (17.3%)	11/17 (64.7%)	31/144 (21.5%)	14/44 (31.8%)	54/277 (19.4%)	25/61 (40.9%)
Unexpected AE other	3/133 (2.3%)	0/17 (0.0%)	12/144 (8.3%)	4/44 (9.1%)	15/277 (5.4%)	4/61 (6.5%)
Serious adverse events[*]						
Physical/sexual abuse	2/133 (1.5%)	0/17 (0.0%)	2/144 (1.4%)	0/44 (0.0%)	4/277 (1.4%)	0/61 (0.0%)
Suicidal behavior	5/133 (3.8%)	1/17 (5.9%)	8/144 (5.6%)	4/44 (9.1%)	13/277 (4.6%)	5/61 (8.1%)
Homicidal behavior	4/133 (3.0%)	1/17 (5.9%)	3/144 (2.1%)	0/44 (0.0%)	7/277 (2.5%)	1/61 (1.6%)
Hospitalization	8/133 (6.0%)	2/17 (11.8%)	8/144 (5.6%)	5/44 (11.4%)	16/277 (5.7%)	7/61 (11.4%)
Death	1/133 (0.8%)	2/17 (11.8%)	0/144 (0.0%)	3/44 (6.8%)	1/277 (0.3%)	5/61 (8.1%)
Unexpected SAE other	1/133 (0.8%)	0/17 (0.0%)	0/144 (0.0%)	0/44 (0.0%)	1/277 (0.3%)	0/61 (0.0%)

[*] A participant could be represented in more than one category.