

**JHSPH Institutional Review Board
RESEARCH PLAN**

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Study Title: Randomized Controlled trial of Trauma Focused Cognitive Behavioral Therapy (TF-CBT) among traumatized children and adolescents in Lusaka, Zambia

IRB No.: IRB00004157

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- 1. Aims/objectives/research question/hypotheses:** Describe the primary and secondary aims/objectives of the research, or the project's research questions or hypotheses.

Research Aims:

1. To determine the effectiveness of an evidence-based mental health intervention – Trauma Focused Cognitive Behavioral Therapy (TF-CBT) – in reducing the severity of mental health symptoms experienced by traumatized children and adolescents in Lusaka, Zambia.
2. To determine the effectiveness of TF-CBT in reducing HIV risk taking behaviors and increasing coping strategies and health promotion activities of traumatized children and youth in Lusaka, Zambia.

2. Background and rationale:

Many children in sub-Saharan Africa experience traumatic events such as loss of family members, severe poverty, and chronic illness. These events frequently affect mental health and ability to function, including the ability to learn and engage in healthy practices and to avoid HIV risky or otherwise negative behaviors.

In 2009-10 the Applied Mental Health Research Group at Johns Hopkins University (AMHR) pilot tested an evidence-based treatment, Trauma Focused Cognitive Behavioral Therapy (TF-CBT) in Zambia to address the mental health effects of trauma among children. Pilot testing included evaluation of the assessment team and the TF-CBT providers, and comparison of the pre and post intervention assessment scores. The conclusions were: 1) Home based caregivers were able to conduct accurate assessments using validated assessment tools; 2) Counselors learned and provided TF-CBT correctly; 3) Mean scores on symptom and function measures significantly improved between pre and post intervention assessment, and 4) Counselors and clients (both children and caregivers) reported that TF-CBT was acceptable and feasible to implement. Since the pilot study, it has been recommended and supported by the Ministry of Health, that the effectiveness of TF-CBT in a randomized controlled trial needed to be completed prior to further capacity building and national scale up of the validated assessment measures and treatment.

Serenity Harm Reduction Programme Zambia (SHARPZ) is a registered community service and faith based organization. SHARPZ has adopted a Public Health Approach to drug and alcohol issues and is under the umbrella of the Capuchin Franciscan Friars in Zambia. SHARPZ was involved in an initial feasibility study, and has maintained a core staff of counselors trained in TF-CBT and is the only organization in Zambia that continues to treat children using this treatment model. SHARPZ will provide the field logistic support and several of their staff will act as counselors and/or supervisors to counselors in the current study. Their specialist center for the treatment of substance abuse issues and mental health, which includes a psychologist, will act as the referral point throughout the study

As a first step, in February and March of 2012, a US-based clinical psychologist and expert trainer in TF-CBT (Dr. Dorsey) will travel to Lusaka Zambia and train 20 counselors in TF-CBT. In addition, Dr. Dorsey will supplement the training of the already established and trained national TF-CBT supervisors

from SHARPZ and the University of Zambia (UNZA). Dr. Dorsey and Dr. Murray will work together to develop all training materials. In March, counselors will take on 1 practice case each in TF-CBT. Local supervisors will meet with the counselors in groups on a weekly basis to monitor the intervention and will be in regular phone and email contact to assist with the initiation of cases. The US-based TF-CBT experts (Drs. Murray and Dorsey) will be in contact with the supervisors on a weekly basis (via skype) to assist with the supervision and provide ongoing support to the supervisors and the counselors. This therapy is already an existing part of SHARPZ treatment program and will be provided to clients who receive services from the new counselors who will have been trained in the therapy.

As part of the study, 11 assessors will be trained on a comprehensive intake assessment process. The process uses an adapted initial intake form that is currently used by the partner organization to collect basic demographic, health, and other information about the client and a parent or guardian and adds a standard mental health and functioning assessment instrument based on the earlier qualitative and quantitative research conducted by the JHU faculty. All children age 5-8 enrolled in the study will receive the demographics section, the PTSD-RI and the Shame measures as well as section one of the World AIDS Foundation measure that covers the topics of HIV Testing and Substance Abuse. Children ages 12 years and older will also receive the World Aids Foundation (WAF) questionnaire section 2 that asks questions related self-efficacy and sexual relationships and violence. Only children ages 12 and older who report yes to having experienced sexual intercourse of any form will be asked section 3 of the WAF which includes questions related to their relationship with their partner, sexual behaviors and HIV-risk behaviors commonly connected to trauma and mental health symptoms. In Zambia questions similar to those asked in the WAF sections 2 and 3 are typically used with adolescents aged 12 and above only given that children do not commonly engage in sexual behavior prior to this age. Adults participating in the study will be given a demographics section, a section related to services received and the Child Behavior Checklist (CBCL) (See Zambia RCT Child Assessment Tool version 1 and Zambia RCT Adult Assessment Tool version 1 in miscellaneous documents).

The proposed study will be embedded within the ongoing SHARPZ program. That is, we are proposing to study the effectiveness of these intervention strategies in a subset of the clients that SHARPZ partner organizations will serve – those affected by trauma with significant mental health symptomatology. The partner organizations will continue to provide services to anyone who seeks their services regardless of whether they meet eligibility for our proposed study, however those who meet our inclusion criteria will be invited to participate in the research component of the SHARPZ service program.

3. Participants:

- a.** Persons eligible for participation in this study will be: children and adolescents aged 5-18 years living in Lusaka, Zambia with significant mental health problems, who report experiencing a minimum of one traumatic experience, who are not in danger of committing suicide, and whose legal guardians are willing and able (mentally competent) to give consent. For the purposes of the study, ‘traumatic events’ will include:
 - i.** Being in an Earthquake that badly damaged the building you were in
 - ii.** Being in another type of disaster like a fire
 - iii.** Being in an accident, like a very serious car accident
 - iv.** Being in a place where a war was going on around you
 - v.** Being hit, punched, or kicked very hard at home. (DO NOT INCLUDE ordinary fights between brothers & sisters)
 - vi.** Seeing a family member being hit, punched or kicked very hard at home. (DO NOT INCLUDE ordinary fights between brothers & sisters).
 - vii.** Being beaten up, shot at or threatened to be hurt badly in your community
 - viii.** Seeing someone in your community being beaten up, shot at or killed.
 - ix.** Seeing a dead body in your community (do not include funerals).

- x. Having an adult or someone much older touch your private sexual body parts when you did not want them to.
- xi. Hearing about the violent death or serious injury of a loved one.
- xii. Having painful and scary medical treatment in a hospital when you were very sick or badly injured.
- xiii. OTHER than the situations described above, has ANYTHING ELSE ever happened to you that was REALLY SCARY, DANGEROUS OR VIOLENT?

Children and families will be accessed through one of SHARPZ 4 partnering organizations including: **(1) Barefeet** a community based organization that works in compounds throughout Lusaka and uses live arts to engage street youth in a 12 week psychosocial, educational and prevention program **(2) Ngombe Home Based Care (HBC)** a community based organization based in Ngombe compound Lusaka. Ngombe HBC uses volunteer caregivers to identify children and families infected or affected by HIV and in need of services **(3) Kaunda Square Ministry of Health Clinic** a Zambian Ministry of Health Clinic providing primary care at the community level for residents of Kaunda Sq. Lusaka **(4) City of Hope** a community school of vulnerable and displaced children and youth in Makeni Lusaka, which includes a residential center for girls who have been abused or who can no longer live with their families **(5) Saint Pauls School** a community based school in Chipata compound Lusaka.

Eligible persons will be located through the regular intake process at the partner organizations. All those who are found to be eligible will be invited to join the trial.

- b. Screening will be done using an interviewer-administered assessment instrument previously developed for use among this population (See Zambia RCT Child Assessment Tool version 1 and Zambia RCT Adult Assessment Tool version 1 in miscellaneous documents). Interviewers will include health care or other personnel currently employed by the partner organizations and who are currently responsible for the intake of new clients (i.e. social workers, nurses, teachers). Persons found to exhibit significant trauma symptomatology as evidenced by a score of 39 or above on the previously validated PTSD-RI symptom scale (Murray, et al. 2011) (trauma severity is the main study outcome) will be invited to join the trial. Exceptions will be persons visiting but not living in Lusaka, Zambia, persons who are not mentally competent to give assent or whose legal guardians are not mentally competent to give consent to participate in the intervention, or who are otherwise unwilling or unable to receive an intervention for any reason, persons who are in danger of suicide (as determined on the assessment), and persons who are currently receiving treatment for mental health problems by psychiatrists.
- c. Given previous data from the small pilot study we have an estimate that a 20% reduction in symptom severity (compared with controls) would be clinically significant (i.e. worth finding). Using data from a previous instrument validation study among the same target population, we calculated that 20% difference in symptom reduction would require 100 persons in each study arm in order to have 80% power to detect this reduction. Performing the same sample size calculations based on a moderate effect size instead of percentage improvement we calculate a sample size of 100 in each study arm. Since there are 2 study arms (TF-CBT and a wait-list control group), this equals 200 participants. Based on previous studies we estimate that 50% of those children screened will be eligible for services, 50% of eligible families will consent to treatment and 20% of those who initiate treatment will drop out and therefore estimate that up to 540 children and families need to be screened to reach the needed sample size.
- d. As part of the monitoring process the collaborating NGO, SHARPZ, and its partners, will collect the following identifying information for each client on a single separate intake

page: respondent's name, town/village, address and phone. In addition, they also fill assist the child and their parent in filling out the full assessment tool (See Zambia RCT Child Assessment Tool version 1 and Zambia RCT Adult Assessment Tool version 1 in miscellaneous documents) to monitor the progress of the clients. The intake page and every page of the assessment instrument will include a unique code. The first intake page will be kept separate from the rest of the instrument and stored separately with the counselor who is providing services to the client as per normal program practice. The assessment instrument will be handed over to SHARPZ for data entry. There will be two supervisors for the intervention condition. The supervisors will keep a list of all the names, contact information and ID numbers. These lists and all of the assessment forms will be kept securely under lock and key with access only by the research team.

Collection of identifiers is necessary to allow the counselors and partner organizations to keep track of their clients and in order to link the results of the screening interview with the repeat interview done after the intervention is completed. Only by having the personal identifiers linked to the code can we ensure that both interviews are with the same person.

4. Study procedures:

1) General study design.

This is a two arm controlled trial design. Twenty community based counselors working in health clinics, schools, home based care and outreach programs across Lusaka, Zambia will be allocated to provide TF-CBT to children who are either currently enrolled or become enrolled in their local partner organizations' services during the study period. This study expands SHARPZ and SHARPZ partners' capacity by expanding the number of counselors trained in the TF-CBT treatment and the hours dedicated to counseling.

Half of the children found to be eligible for treatment will be randomly allocated to the wait control condition. They will be asked to wait for approximately 4 1/2 months before being reassessed and then receiving the intervention being provided by the counselor. The wait control group will form the 2ND arm of the trial.

2) Study procedures, including their sequence and timing.

	Month																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
1. Training on the intervention	X																
2. Pilot case trial		X	X	X													
3. Training on screening and consent process	X	X															
2. Active recruitment - rolling basis					X	X	X	X	X	X	X	X	X	X			
3. Service provision – rolling basis					X	X	X	X	X	X	X	X	X	X			
4. Qualitative exit interviews									X								
5. Post-intervention assessments										X	X	X	X	X	X	X	X

Training on the intervention: We plan to begin the actual intervention evaluation trial at the end of February 2012 (corresponding to Month 1 in the table above). During the last week of

February and first week of March a U.S. based TF-CBT trainer (Dr. Dorsey) will travel to Lusaka, Zambia to provide a 10-day training in TF-CBT.

Pilot Cases: following the training of the intervention, it is beneficial for each counselor and supervisor to take on one pilot case. Pilot cases give the counselors and supervisors time to practice the intervention, and the supervisors and trainers an opportunity to observe skills and abilities and help assure fidelity to the treatment model. Following the pilot case, the intervention trainers and supervisors can make recommendations on caseload size per counselor based on their observations of each counselor's clinical skills, ability to adhere to the intervention. These cases will be required to meet the inclusion criteria so we will know whether TF-CBT is appropriate for our target population. All recipients will be given a post-treatment assessment form.

Training on screening and consent: Prior to beginning pilot cases or recruitment, JHU study faculty (Ms. Skavenski), based in Lusaka, Zambia, will provide training to assessors in the process of a) administering the assessment tool to children/youth and caregivers, b) for determining whether a person is eligible for participation in the trial, including interpreting trauma severity scores, and c) administering trial consent form. This training will occur on 2 separate occasions. The training for assessors in relation to recruiting pilot cases will take place in mid-March. A second training will take place at the end of May as a review and will clarify the process for consenting to the randomized controlled trial.

Active Recruitment: Following the pilot and training, active recruitment for the evaluation study will begin. Active recruiting of persons to be screened will be done through including the assessment measures into the current intake systems of the five partner organizations. Rolling screening and allocation to either an intervention arm or temporarily to a wait-control condition will continue until sample sizes for each arm are achieved.

Service Provision: Rolling recruitment and provision of TF-CBT by the counselors will then be done, with supervision provided weekly in person by SHARPZ staff TF-CBT supervisors (which will be supervised weekly by TF-CBT trainers).

Qualitative exit interviews: Following completion of the therapy by the first set of 20 participants, assessors will ask these intervention participants what has changed since the intervention began and what change they attribute to the intervention. Interviews will be open ended, written by the assessors (not tape recorded) and identifying information will not be recorded. The research team will review these qualitative exit interviews to identify any unexpected positive or negative effects of the intervention. Questions on the more significant and/or frequent responses will be added to the original assessment instrument.

Post-intervention quantitative assessments will be done with the expanded assessment instrument (see qualitative exit interviews above). All post intervention quantitative interviews (including with the wait controls) will be conducted approximately 2-3 weeks after the client has completed the treatment or control period (approximately 12 weeks). Those randomized to the treatment will also receive a second post assessment 4 months after receiving the first post assessment. Control cases will only receive on post assessment after the wait list period so that they may then receive the treatment as soon as their wait list period is over.

Following completion of the trial, the data will be analyzed, and if the intervention is found to be effective, it will become a permanent part of the services provided by the counselors at SHARPZ and the partner organizations.

- 3) We expect at most 2-3 research contacts with each intervention participant for the purposes of the study - for the initial screening, the qualitative exit interview, and the post intervention

assessment. For the wait controls, program staff will be in monthly contact with all control cases however, research contacts of controls will only be done at the initial screening and post intervention assessment.

- 4) We expect the study will last up to two years, not including the data analysis period.
- 5) Describe how subjects will be screened for eligibility and assigned to study/intervention and comparison/control groups.

As part of the standard programming at SHARPZ and SHARPZ partner organizations, all clients enrolled in services will initially meet with personnel responsible for intakes (nurses, facilitators, etc.) and are interviewed using some form of intake form. Enrollment into the partner organizations services typically occurs through 2 channels 1) a client walks into the center or clinic and requests services 2) a referral is made for a client to receive services from either a community outreach worker or another organization. There will be no additional outreach for the study. The mental health assessment tool developed during a prior study with the same population will be added to this intake process. Following the completion of the interview, the intake personnel, referred to as assessors, at each partner organization will confirm that the person lives in Lusaka and within the catchment area of SHARPZ or its partner, will be available for the duration of the study, meets our definition of exposure to trauma, and has significant trauma symptoms.

The criteria for exposure to trauma will be evaluated through a review of the trauma exposure questions on the assessment interview. There are 13 questions that ask about exposure to traumatic events. If the respondent indicates that they personally experienced any of these exposures they will qualify as having been exposed to trauma for this study.

The criteria of having significant trauma symptoms will be evaluated based on the responses to the section of the PTSD-RI symptoms questions on the assessment interview (questions 28-65). The assessors will calculate the total score for these 38 questions (defined as the total trauma subscale) at the time when the respondent is still there. If this meets or exceeds a cutoff score (>38) reflecting likely clinically significant trauma (based on results of a previous validity study of the instrument among the same population) the child and parent/caregiver will then be invited to join the trial. The parent/caregiver will be read a consent form. If the caregiver gives consent, then and only then will the child be read an assent form which explains the trial. The consent and assent will clearly state that if they agree they will be assigned either to receive treatment beginning immediately or will need to wait approximately 3 ½ to 4 months before receiving treatment. During this wait period, the child/caregiver is able to still seek other services regularly offered by SHARPZ or partnering organizations.

Treatment selection process:

Clients will be assigned to the treatment group based on randomization. Clients who are randomized to waitlist control will continue to receive or be offered the currently available standard services that are offered at SHARPZ or the partner organization by counselors or service providers outside of the study.

Randomization process:

If the youth and the youth's parents/guardians agree to join the trial, the assessor will determine whether the person has been allocated to receive treatment immediately or to the wait control group. The randomization process will be as follows:

1. A randomization list will be generated for each site. This list will include a patient ID number in sequence (i.e. 1-20). Next to each patient ID number will be an assignment to immediate therapy or waiting list. This will be generated at random via a random number generator, with a 1 to 1 ratio of therapy to waiting list. There will be one list for each site. This list will not be available to the field staff but used by the JHU-based faculty to check whether persons were correctly assigned to intervention or control.
2. For each site, individual sealed envelopes with a paper indicating the treatment assignment (immediate therapy or wait control) will be stapled directly to consent forms that are pre-numbered with a patient ID number.
3. Once the patient has consented to be in the study, the assessor will open the envelope attached to the form, and will inform the patient whether they will begin the therapy immediately or be a wait control.

Persons in the wait control group will be contacted monthly by the assessor to check for significant worsening of symptoms or wanting to hurt or kill themselves or others. They will also be instructed to check in with the assessor between monthly calls if any of these changes occur. Where such changes are reported the person will be reviewed by the SHARPZ clinical team to decide whether they should be referred for treatment and/or cease involvement in the study.

- 6) Explain and justify whether there will be blinding.
Assessors based at each site will conduct the initial intakes and randomization process for clients coming into their centers. At post assessment all cases and controls completing the treatment or wait list period that month will be asked to come to one center where they will be re-assessed by an assessor from a different site (i.e. not from their treatment site). Given the randomization process assessors will know which clients will receive treatment and which clients will be wait list controls. Furthermore assessors are currently located at the same centers as the counselors- the centers where the clients will receive active treatment. Assessors will be able to see who comes in for the treatment on a weekly basis. Both of these factors may create a bias in the group and therefore blinding at post assessment is necessary to prevent biased results.
- 7) Explain and justify whether participants will not receive routine care or will have current therapy stopped.

Currently no routine care exists for mental health services for this target population. The only available interventions at present are from those health care workers trained in general supportive counseling interventions such as one off counseling sessions (i.e. VCT) or supportive group activities related to HIV or orphan status (post-test clubs). These forms of counseling will be tracked, however, a client will not be ruled out of a study based on their attendance in one of these forms of "one-off" counseling sessions. There may be a few individuals that are currently receiving psychiatric services from the local hospitals. Any respondent currently receiving psychiatric services will also be excluded from the study.

- 8) Explain and justify the use of a placebo or non-treatment group.

No placebos will be used. There will be a wait-control group who will not initially receive treatment. Instead they will wait for a period of approximately 3 ½ to 4 months. They will then be reassessed and offered the intervention. The reason for the initial non-treatment is that we do not have evidence of the effectiveness of the treatment. We are therefore in a state of clinical equipoise with regards to the intervention. Participation in the study in either the

intervention or control arm will not affect ability to make use of existing services. Currently there are no readily available mental health treatment. There are social and psychosocial supports such as a one-off individual treatment session and support groups which typically extend for 12 weeks. Both formats are typically done with a lay counselor or health care worker as needed.

- 9) Provide a definition of treatment failure or participant removal criteria.

Treatment failure will not be assessed at the individual level but only at the group level. Failure at the group level for the intervention would consist of less than a 20% difference in change in mean trauma severity score between pre and post intervention assessment (trauma severity scores consist of simple summation of scores on all trauma symptom questions) compared with the wait control group.

Participants will be removed from the study if they are in danger of suicide or of harming others. This will be defined by demonstrating actively suicidal or homicidal thoughts. Anyone who develops psychosis will also be removed. At that point, assessors and counselors will work with their supervisors to seek more specific psychiatric assistance with the individual.

- 10) Describe what happens to participants receiving therapy when the study ends or if a subject's participation ends prematurely.

At the end of the study if the intervention is found to be effective the counselors trained in it will continue to provide treatment, both to those currently receiving the treatment and to new clients. Persons who have not yet received the new intervention will be eligible to receive it regardless of whether they had previously received any treatments. If a subject's participation ends prematurely because they were identified as being in danger of suicide or homicide or became psychotic (see above), then they will continue to work with the psychiatrist or other care services as needed (see below).

As per standard procedures with SHARPZ, any participant who does not come to a regularly scheduled session will be followed up by a staff member to determine whether they are a formal withdrawal or if there is some other barrier that can be overcome to continue treatment (e.g., transport problems). If the participant does not want to participate further, the staff member will try to find out the reason for withdrawal and address them if possible. Otherwise, no further action will be taken. Our sample size calculations are based on an assumption that around 20% of participants will choose to withdraw from the study. This assumption is based on discussions with SHARPZ about their experience working with this population and JHU previous experience working with this population for the past 6 years.

- 11) Describe the process for referring subjects to care outside the study, if needed.

Our collaborator on this study, SHARPZ, runs outpatient services for substance abusers and people with mental health problems in the city of Lusaka in Zambia. This center is staffed by a clinical psychologist as well as other staff with advanced training in various counseling approaches. Persons who are found on screening or during the study to be in danger of suicide will be referred to the clinic and provided with funds to travel there. The Center will be notified by telephone and will expect the referral.

- 12) For clinical trials, provide power calculations for sample size.

Group sample sizes of 100 and 100 achieve 80% power to detect a difference of -10.0 between the null hypothesis that both group means are 30.0 and the alternative hypothesis that the mean of group 2 is 40.0 with estimated group standard deviations of 25.0 and 25.0 and with a significance level (alpha) of 0.05000 using a two-sided two-sample t-test.

Table 1. Two-Sample T-Test Power Analysis
Numeric Results for Two-Sample T-Test
 Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1≠Mean2
 The standard deviations were assumed to be unknown and equal.

Allocation									
Power	N1	N2	Ration	Alpha	Beta	Mean1	Mean2	S1	S2
0.80365	100	100	1.000	0.05000	0.19635	30.0	40.0	25.0	25.0

Given the high rates of symptomatology found during the previous study, we estimate needing to screen approximately 540 children and families to identify 200 eligible and willing participants.

- 13) Describe any plan for reporting test results to participants.

After the intake interview is complete, the assessors will review the results of the trauma symptoms scale (1-38) with the clients to indicate whether they are eligible for the study. Data from the other scales will not be available to the clients at the time of the intake.

At the completion of the study, all study participants, including wait controls at that time, will be told what the general results were and informed as to their options for receiving the intervention (if it is shown to be effective).

5. Confidentiality:

- a. Provide a plan for minimizing breach of confidentiality, including coding and data security, and protections for portable electronic devices (laptops, CDs, USB keys, etc.).

When clients first meet with the Assessors they are interviewed using a standard intake form, which includes the study participant's name, address, phone number and a unique ID code. Subsequent to the intake form, the client is interviewed with a complete assessment tool which will have on each page the unique ID code only. The intake form and the assessment instruments will be kept separately – with the counselors and supervisors having access to the intake form and the SHRAPZ staff, not including SHARPZ clinical staff, and JHU researchers having access to the rest of the assessment instruments. Following an intake with a potential participant the assessor will remove the 1 page intake form and log the date, name, phone number and ID number into a log form that is then placed in a sealed envelop and locked into a cabinet for pick up from the SHARPZ team. They will then insert the one page intake form into a binder with other intake forms for that site. All forms will be kept in locked file cabinets. Once a week the SHARPZ clinical staff will pick up the log form in a

sealed envelop and bring it back to the SHARPZ office. This form will be kept in a lock cabinet that only the SHARPZ clinical team will have access to.

Throughout the study, the assessors will meet with the SHARPZ M&E officer on a weekly basis. The M&E officer will collect all assessment interviews completed that week and record the ID numbers and contact information on a separate form. All forms will be stored under lock and key. The completed assessment interviews will be transferred to the study headquarters at the SHARPZ office in Lusaka and stored under the same conditions, with access only by the on-site study manager and M&E officer. At the SHARPZ office, the assessment instruments will be entered into one of two secure computers. Only those forms that are associated with clients involved in the research study will be sent by email to the USA for analysis. Data entry will not include names and addresses. The intake forms will be collected with the assessment forms and given to the head program manager/lead supervisors for case assignment. All intake forms will then be given to the counselors in their treatment files as per standard SHARPZ procedures

b. Explain whether application will be made for a Certificate of Confidentiality. No certificate of confidentiality will be sought

c. Describe plans for disposing of identifiers, including when and how that will be done.

At the end of the study (after completion of analysis comparing pre and post intervention results) the lists that the supervisors made that connect the intake forms with the assessment interviews will be destroyed. This will be done by shredder. All other forms will be kept per SHARPZ protocols for their own treatment files.

d. Describe plans for retaining and storing records and data.

The original assessment instruments will be kept in the SHARPZ office in Lusaka. Electronic records will be stored on a single, secure SHARPZ computer and on the PI and co-I's computers and on a separate hard drive.

e. Describe plans for destroying data and/or specimens, including when and how it will be done.

The electronic copies will not be destroyed.

Secondary data studies stop here, unless a category below is relevant to this particular proposal

6. Risks:

a. Describe the risks associated with the study and its procedures, including physical, psychological, emotional, social, legal, or economic risks.

There is some risk that persons completing the assessment forms may be reminded of past traumatic events and become distressed. This occurred only a few times during our previous study testing the validity of the instruments. Such persons always recovered by the end of the assessment and, in response to enquiry by an interviewer, said that they felt no ongoing distress.

With respect to the TF-CBT intervention, the basis of this treatment includes discussion and recollection of the traumatic exposure with management of the emotional reactions with the counselor. Research and experience in the West suggests that exposure-based therapies are likely to be effective when treating individuals with post-trauma syndromes.

With TF-CBT there is a risk that such exposure could be harmful if the reactions are not properly managed. However, the emphasis of the training is on correct management, so that the result should be symptomatic relief. Two previous feasibility studies in Zambia show that TF-CBT is not harmful and instead showed reduction in symptoms, as well as client acceptability.

Respondents who are distressed may reveal severe depression and/or suicidal intent during the course of the assessment or RCT. Although this is not a direct risk with participation of this study, and thus a low likelihood, it is important to have a plan in place. All assessors and counselors will be trained specifically in how to assess for suicide risk, and the procedure to follow if there is intent. The procedure to follow includes: a) immediately contacting their supervisor, b) the supervisor will guide them through additional questions and help make a decision if the child needs to be brought to see someone, or if a 1-day safety contract may be completed, c) the local program manager and Dr. Baxter will be contacted immediately by the supervisor to further assess and give recommendations, and d) Dr. Murray will be notified of the situation. The protocol will include an immediate evaluation by a clinician of the seriousness of the suicidal ideation/intent and activation of a safety plan for the individual. This includes a range of activities from setting up a suicide contract that includes 24-hour supervision of the individual by a community member(s) until the crisis subsides, to having the individual transported to the University of Zambia (UNZA) for a full evaluation by a psychiatrist. The child's caregiver will be apprised of the situation and become involved in the plan in either circumstance. The exception to the involvement of the minor's parent or legal guardian would be if the minor indicates that this will escalate their risk of suicide. In this case, informing the parent would be delayed until the team (clinician, supervisor, program manager, Dr. Baxter and Dr. Murray) determines it would be safe to do so. The parent or legal guardian would be informed at that point.

There is always the possibility of a breach of confidentiality when conducting research. While this is acknowledged, there is very low likelihood because of the precautions that will be taken to protect confidentiality. Efforts to minimize this possibility include: 1) all staff will be well trained in confidentiality and data security procedures; 2) data will be rendered anonymous to the degree possible to minimize likelihood of any individual being identified; 3) all data will be kept locked at all times in a secure office building; and 4) all electronic records will be password protected.

There is a possibility that disclosure of significant social problems such as child abuse, domestic violence, substance abuse, and suicide and the disclosure of HIV/AIDS status may result in stigma for the individual and/or family. This is unlikely given the method of referral. However, all attempts will be made to protect against this potential risk by maintaining the anonymity of the individuals and families in all reported findings, unless someone explicitly requests in writing that they be identified.

b. Describe steps to be taken to minimize those risks.

Before any data collection begins, a community meeting will take place in order to explain the procedures of the study, the risk and benefits, the confidentiality of results, and to allow for any questions. During the meeting approval will be sought to proceed with the study by affirmation of those present and local key stakeholders for OVC. This approach to obtaining community affirmation for qualitative research has been utilized by other researchers in similar settings (Bolton, 2001a; Seedat et al., 2004; Willging, 2002). Based on prior experience, good relationships with the local population, and experience using this approach in Zambia and many other low-resource countries in the region, there are no anticipated difficulties in obtaining community approval.

Trained local interviewers will conduct the informed consent process. Following determination of eligibility to participate in the study, the local interviewer will discuss the study with children and caregivers, respectively, answer questions, and assure that the respective parties understand consent or assent forms and wish to agree to participate in the study. For all child participants, consent will be obtained from their parent or legal guardian, with accompanying verbal assent from the child. If families are not interested in participation, no further contact with them about the study will be made but they will be able to access all the normal local resources. Consent forms will explain the purpose of the study in laymen's terms; assent forms are written at the 4th grade reading level. All activities will be compliant with local IRB. Following the consent process, the interviewer will complete a standardized form that documents the process, noting who was present and what questions were asked by the family. At the beginning of the study and periodically, any IRB or privacy requirements that may be in effect at that time also will be checked to assure that plans are compliant with current rules.

If persons experience distress while completing the assessment form they will be asked to notify the assessor and are free to pause or stop the assessment. If they remain distressed the assessor will contact a counselor who can conduct a further assessment, provide counseling based on their existing skills and knowledge, and will offer to see the person again in a day or two for further treatment or refer them for higher level services by the supervisors or Dr. Baxter if needed. With regards to TF-CBT, the training emphasizes the management of reactions to exposure, so that the exposure should result in improvement and relief.

For the intervention, during each treatment session the current state of participant's symptoms is assessed. If improvement does not occur (or symptoms worsen) they will cease treatment by the counselor temporarily and will be referred to the SHARPZ office for further assessment and treatment by the specialists there. The study supervisors will meet with the counselors weekly to monitor the progress of the program and how things are going with each client. To monitor the individual clients, the counselors will fill out session monitoring forms for each client after each session (an example of the form is included in miscellaneous documents). As part of this form, the counselors will record any changes in symptoms and problems that the client has. This form, together with the supervision discussions, will form the basis for monitoring the current state of participants' symptoms and will be able to pick up if symptoms worsen and the client needs additional services.

- c. Describe the research burden for participants, including time, inconvenience, out-of-pocket costs, etc.

Burden will be a two-hour session for the initial assessment in addition to a one hour a week session at one of the 5 partner sites for approximately 12 weeks of services for those who are eligible for the study and randomized into the treatment group. This includes the time and costs to get to the sites. The sites are located within the communities where the children enrolled in the study live and/or go to school. Therefore the cost and time required to get to them are minimal.

7. Benefits:

- a. Describe any potential direct benefits to participants from participating in the research (not including payment for participation).
Through participation in the research participants will receive assessments that may benefit them by providing information about some of their problems. Further, they will be

provided treatment (TF-CBT) that is likely to be of benefit in addressing their mental health problems and functioning. Also, due to the contingency plans, those individuals that do report abuse, violence or severe mental problems will receive helpful assistance. In addition, some individuals may choose to take advantage of a referral to someone in the community they can talk with, and therefore benefit.

- b.** Describe potential societal benefits likely to derive from the research.
Previous research has suggested that OVC who have experienced trauma feel (and are perceived by others to be) a burden to their families and communities because of reduced functioning. Our intention is that one or more of these interventions will improve social, emotional, cognitive and physical functioning and enable them to be more active and contributory members of their community. This would reduce the burden on families and society while improving their status within society.

Furthermore By training local interviewers in the assessment tools and counselors in the intervention, there is local clinical and research skill-building. Clinicians who are trained will have received advanced clinical training and ongoing consultation in one of two models that addresses child functioning and mental health. This has enormous benefit for them as individual professionals living in a low-resource country.

8. Payment:

- a.** Describe the form, amount, and schedule of payment to participants.
We will provide financial assistance to cover any transportation costs of participation only where needed. Otherwise no payments will be made.
- b.** Include the possible total remuneration and any consequences for not completing all phases of the research.
Payments will be made to cover costs only, so there is no predicted total remuneration. There are also no consequences for non-completion (we would not be asking for the cost reimbursements to be repaid).

9. Recruitment process:

- a.** Describe how participants will be recruited.
We will work with the local partner organizations to screen individuals who present themselves for services at each of the sites. All children and adolescents who meet criteria described in section 3 above will be viewed as potential participants.
- b.** Explain how your recruitment materials will be used.
The intake form and trial consent forms will act as a recruitment material by way of explaining the study. No other recruitment material will be used.
- c.** If relevant, address any privacy concerns associated with the recruitment process.
Based on our previous studies using the same approach, we do not have any privacy concerns for the recruitment process as children and youth with trauma histories are already identified as such by themselves and within the community.

10. Consent process and documentation:

- a.** Describe who will obtain informed consent from participants, and how, when and where consent will be obtained.
On completion of the intake interview, the assessor will meet with the Monitoring and Evaluation officer to score the trauma symptoms scale and review the trauma exposure responses and determine if the child or adolescent is eligible for the trial. If they are eligible, they will be read the consent form to the caregiver. If and only if the caregiver

agrees, then the assessor will read the assent form to the child/youth. The assessor will sign it if the parent/guardian and child/adolescent agrees participate.

- b. If the study will involve vulnerable populations (e.g., children, prisoners, cognitively impaired adults, non-English-speakers, etc.) describe efforts to ensure their understanding of the research and the extra protections that will be in place to ensure their voluntary participation.

Assessors will explain to the parents/ guardians the procedures of the study, the risk and benefits, the confidentiality of results and allow for any questions. Parents/guardians will then be asked for their consent for their child or adolescent to participate in the trial.

Once a parent/guardians consent has been given the child will be read and explained one of two versions of an assent form. The assent form given will depend on the child/adolescents age and developmental level to ensure that they understand all procedures, risks, benefits, and aspects of confidentiality. Children and adolescents will also be encouraged to ask questions.

All materials and verbal discussions will be in the two local languages (Nyanja and Bemba) as well as English.

- c. If a waiver of consent or a waiver or alteration of signed consent is requested, provide a justification for the waiver/alteration, and describe any alternate procedures for informing participants about the research.
A waiver is not being requested. However, given the sensitive nature of people signing documents in this population, we will have the assessors sign the consent and assent forms rather than the client and family sign themselves. The assessors will sign the forms as a proxy for the clients, after explaining the form and receiving agreement from the client. If a client does not want to participate, the assessor will mark that the box indicating that the client did not want to participate and then will not sign the form. The client can still receive services provided by the assessor and/or have access to all other services at the site but they will not be part of the study.

11. FDA regulated studies:

- a. Drug products: N/A
- b. Devices: N/A

12. Safety monitoring:

- a. Describe how safety will be monitored, by whom, and how often.
During each treatment session of the intervention level of symptom severity is assessed by the counselor (see the example treatment monitoring form included under miscellaneous documents). If symptoms worsen the supervisor will be informed and the person will be referred to a supervisor or Dr. Baxter at SHARPZ for further assessment and treatment.
- b. If a DSMB (or equivalent) will be established, describe the following: **N/A**
- c. Describe plans for interim analysis and stopping rules.

We are not planning to establish a DSMB. Instead patient risk will be monitored at the individual level as in #12 above.

- 13. Plan for reporting unanticipated problems/adverse events:** Describe plan for reporting to the IRB and (if applicable) to the sponsor. Include plan for government-mandated reporting of abuse or illegal activity.

All of the counselors will be supervised by local SHARPZ staff as well as their own supervisors within the partnering organizations. The supervisors will also be in frequent contact with the TF-CBT trainers in the US. The supervision process will include review of how the participants are doing. Any significant worsening of symptoms among any of the participants will be reported to the IRB, along with the measures taken and the results.

In accordance with Zambian law, all incidences of child abuse will be reported to the Victim Support Unit, a unit of the Zambian Police and then to a “one stop centre” or hospital for a physical exam, HIV and STD testing, VCT, legal advice, and post-exposure prophylaxis. The potential benefit to the child in terms of their safety outweighs the potential negative consequences for the child and the alleged perpetrator. In reporting to the VSU, there may be significant benefits from receiving their help, if the individual or family so chooses. In addition, any individual or family disclosing child abuse will be given a list of individuals in the community identified as knowledgeable about child abuse and able to help with these problems.

Previously undisclosed domestic violence incidents may be revealed. In Zambia, domestic violence is usually not reported to any officials. However, if there is physical harm being caused (i.e., not just verbal abuse), it will be reported to the local VSU in accordance with Zambian law. This report may result in unwanted intervention and consequences for the individual responsible. We also recognize that given the gender-based hierarchies present in Zambian culture, this may have a detrimental effect on the child and his/her mother who may be dependent on the perpetrator. To address this potential risk, this research protocol will not in any explicit way seek out disclosures of previously undisclosed domestic violence. The potential benefit to the safety of the woman and her children is deemed as outweighing the potential negative consequences for the alleged perpetrator. In reporting to the VSU there are anticipated benefits from receiving their help, if the woman so chooses. In addition, child and families who disclose experiences of domestic violence will be given a list of individuals in the community identified as knowledgeable on this issue, by community members, and able to help. In the event of severe psychiatric difficulties, Dr. Philip Baxter will aid in appropriate referral for services.

During the study counselors will remain the employees of their partner organizations. In addition to the study requirements the counselors and assessors will be instructed to deal with any reports of abuse or illegal activity as they normally would, consist with Zambian law.

14. Other IRBs:

If the research will require review by other IRBs, provide the name and contact information for each IRB and its FWA (available on OHRP's website at <http://www.hhs.gov/ohrp/assurances>).

As in previous studies, the research will be reviewed by a local IRB: ERES CONVERGE, 33 Joseph Mwilwa Road, Rhodes Park, Lusaka, Zambia Telephone: +260-955-155-633, +260-955-155-634

15. Outside collaborations:

For studies that involve collaboration with non-JHSPH institutions, describe the collaboration and the roles of each collaborator, including the JHSPH investigator.

Laura Murray, the study Co-PI, will oversee the set-up of the project locally in Zambia, beginning in Year 1. She will work with the on site co-PI and together, hire all local staff including confirming whom among the counselors will be part of the study and assure their commitment. She and Dr. Dorsey will also provide the training and supervision for TF-CBT, and develop all clinically related study protocols.

Stephanie Skavenski, the study Co-PI will oversee the daily operations of the project. In Year I, she will be responsible for local hiring and study set up. She will supervise the data collection team, train staff and undergraduate assistants in data collection, organize clinical trainings and supervision groups, and submit local human subjects applications and renewals. She will conduct weekly research meetings and trouble-shoot problems that arise with data collection and/or implementation. She will also coordinate activities and maintain relationships with community agencies, therapists, and the MoH. She will oversee the local M&E staff who will be trained in all questionnaire data.

The Serenity Harm Reduction Programme Zambia (SHARPZ) is the AMHR implementing partner located in Lusaka Zambia. They will oversee the daily operations of the project including supervising the data collection team, organizing clinical trainings and supervision groups, and helping to submit local human subjects applications and renewals. They will conduct weekly research meetings and trouble-shoot problems that arise with data collection and/or implementation. They will also coordinate activities and maintain relationships with their community agencies, therapists, and the MoH. They will oversee the local M&E staff who will be trained handling all questionnaire data. Finally they will be responsible for management of their budget and all sub contractors.

Barefeet, Ngombe HBC, Kaunda Sq. Clinic, City of Hope and St. Pauls School are the SHARPZ local community partners selected to be trained in the research and treatment methods in order to take part the study. The local partners will be responsible for management and support for several of the counselors and assessors that will be involved in the study. They will be responsible for ensuring that the staff selected for the study are allocated the necessary time to participate in the study as set out in their Memorandums of Understanding with SHARPZ and receive their regular salary and benefits in accordance with their human resource policies and Zambian law. They will also be responsible for providing all staff with additional funds or materials as determined by SHARPZ in their subcontract. All partnering organizations will need to continue to provide supervision and support for all activities outside of the study.

16. Oversight plan for student studies:

For student-initiated studies, explain how the PI will monitor the student's adherence to the IRB-approved research plan, such as communication frequency and form, training, reporting requirements, anticipated time frame for the research, and who will have direct oversight of the student if the study site is not local.

N/A

17. Oversight plan for studies conducted at non-JHSPH sites, including international venues, for which the JHSPH investigator is the responsible PI:

Explain how the study will be managed, the qualifications of study personnel managing the project, and how personnel involved with the data collection and analysis will be trained in human subjects research protections. If the PI will not personally be on-site during the data collection process, provide details about the communication plan between the PI and study team to assure adherence to the IRB-approved research plan.

Stephanie Skavenski, the study Co-PI along with JHU research staff, will be on site to provide the training in study and consent procedures as well as setting up the study itself. Stephanie Skavenski is based in Zambia, she along with Dr. Amara Robinson and SHARPZ employees in Zambia, will be responsible for on-site program management in close collaboration with the US based JHU investigators by phone and email. Stephanie is an associate at JHU and has been the Zambia study director for the past 3 years and is a trained social worker and Amara is the study manager

for JHU. Stephanie, Dr. Robinson, Dr. Baxter and the study supervisors will complete the NIH on-line human subjects research protection training. Stephanie, Dr. Robinson and JHU staff will instead provide them with training in human subjects research protection as part of the training in study procedures while in Zambia.

All SHARPZ supervisory and study staff will complete the NIH-required training online. The mental health workers will receive a brief training on human subjects' ethics and protection from the JHU study investigators. Included as an attachment with this application are the slides that will be used for this human subjects training that we have previously used with earlier trials and research studies.

- 18. Creation of a biospecimen repository: N/A**
- 19. Data Coordinating Center: N/A**

DCOF Data Analysis Steps

Background and Cleaning

For this study, a longitudinal random effects model will be used to examine the interaction of client group with time as a measure of the difference between the intervention and control group at post intervention. Missing data will be handled using multiple imputation for all missing data including data lost to follow up. The following is the process taken to conduct the analysis starting from data extraction from the study database.

Each measure will be extracted from Epi-Info 7.1.3 and converted to an individual excel file using the “line listing” function of Epi-Info. When saving the excel file of each measure make sure to save as a non-web based file. The default is web based. The following excel files should be created:

1) Demographics (save this as ‘main outcomes’ because this will be the reference to merge all of the files); 2) Function; 3) PTSD-RI; 4) World AIDS Foundation; 5) ASSIST and 6) counselor and treatment type (this is already an excel file labelled ‘copy of counselors tracking sheet for sessions’). Each excel file needs to be reviewed so that all ID#’s are consistent in terms of format (i.e., ST 0123). Next, in each excel file create a new variable for Time, labelled Time_R (i.e., baseline =0 and post intervention =1).

Stata 12 will be used to create a merged file. First, a Stata file for each measure was created: 1) Main outcomes, which is demographics; 2) Function; 3) PTSD-RI; 4) World AIDS Foundation; 5) ASSIST and 6) counselor and type of treatment. Each Stata file then should be sorted in ascending order by the Time_R variable and Client ID# (except for the counselor and type of treatment which should just be sorted by Client ID # as there is no time variable here. Then run frequencies for Client ID# to make sure there is only 1 of each. This should be done for post cases as well. Once it is determined that duplicates and missing cases are accounted for, variables for the analysis should be recoded. Below is a list of all variables and how they are recoded.

Recoding of Variables

All outcome scores for the analysis will be defined as an average or mean score among the scale items, except where noted (i.e., where there is a variable where the item options are dichotomous).

1. Time_R (should already be complete before merge)

- 0- Baseline
- 1- Post intervention

2. Client group

- 0=intervention
- 1= control
- 2=ineligible

3. SITE_R (SITE already created before merge but need to recode with numerical categories)

- BF=0
- CH=1
- KS=2
- NG=3
- NH=4
- ST=5

This variable will need to be dummy coded to be able to interpret any potential differences across sites so the following variables will be created with BF as the reference group

	BFCH	BFKS	BFNG	BFNH	BFST
BF	0	0	0	0	0
CH	1	0	0	0	0
KS	0	1	0	0	0
NG	0	0	1	0	0
NH	0	0	0	1	0
ST	0	0	0	0	1

4. Sex will be recoded so that 0=male and 1=female

5.counselor-this is already coded 1-16, a number for each counselor. This will also need to be dummy coded as stated above with the SITE variable.

6.Session Type this is already coded with the following

Once per week = 0

Double session only =1

Variable =2

Only met between 1-4 session =3

7.Function scale—recode all variables into numbers (all labels should end in something to demarcate function item recoded e.g. ‘washfun’)

0-none

1-little

2-moderate amount

3-a lot

4-often cannot do

-7- not applicable

Create **Function mean** score variables

8.PTSD-RI –recode all trauma events (all labels should end with ‘trauma’). Do NOT include the item for ‘other’. The sum will include all listed experiences only so range 0-11

0-No

1-Yes

Create **trauma event sum** score

Trauma symptoms should be recoded so that all labels end with ‘ptsd’)

0- Never

1- Rarely

2- Some of the time

3- Much of the time

4- Most of the time

Create **PTSD mean** score variables

7. WAF measure

Create variable **HIVtest** from “Have you ever been tested for HIV”

- ‘0-No (GO TO Q5.2_1)’ = 0

- ‘1-Yes’=1

Create variable **HIVstatus** from 'If you had a HIV test done, what was the result'

- '0-Negative, I did not have HIV' = 0
- '1-Positive, I did have HIV (Go To Q5.3_2)' = 1

Create **HIVSelf-efficacy** variable (mean of 7 items under Self-Efficacy in WAF, starting with 'how comfortable are you to talk with your partner about HIV' through 'how confident are you to get condoms if you need them')

0-very sure I can't =0

1-I think I can't=1

2-I think I can= 2

3-Very sure I can =3

-7-Not applicable =-7

-8-Don't know =-8

-9-Refused=-9

Once each item is recoded create mean of all items **HIVSelf-efficacy**

Create **Risk Reduction** (sum of 8 items under Risk Reduction Intentions in WAF, starting with 'talking to my current partner about using condoms' through 'refusing to have sex with my partner if I don't want to')

1-I feel I am not strong enough to do this =0

2-I feel I am strong enough to do this =1

-7-Not applicable =-7

-8-Don't know =-8

-9-Refused=-9

Once each item is recoded create sum of all items as **Risk Reduction**

Create **Readiness to change** (mean of 5 items under Readiness to Change and HIV Risk in the WAF, starting with 'I am starting to think about the HIV risk from my sexual behavior' through 'I have already made some changes in my sexual behavior and I would like to keep from going back to my old behaviors')

0-Strongly disagree=0

1-Disagree=1

2-Agree=2

3-Strongly Agree=3

-7-Not applicable =-7

-8-Don't know =-8

-9-Refused=-9

Once each item is recoded create mean of all items as **Readiness to change**

Create **Sexual relations** (mean of 4 items under Sexual Relations and Violence in the WAF, starting with 'one sexual partner is not enough for a man' through 'it is OK for a man to sometimes beat up a woman as long as he looks after her')

0-Strongly disagree=0

1-Disagree=1

2-Agree=2

3-Strongly Agree=3

-7-Not applicable =-7

-8-Don't know =-8

-9-Refused=-9

Once each item is recoded create mean of all items as **Sexual relations**

8.ASSIST—recode the first three variables of the ASSIST related to substance use (alcoholuse, inhalantuse, and tobaccouse)

No=0

Yes=1

From the individual substance use variables create **anysubstance** (total of substances endorsed)

Also create **anysubdic** –dichotomized where 0 = no substance and 1=1 or more substances endorsed

Based on scoring from ASSIST the following variables should also be created

N421 – N453 recoded (named all smoke421, drink422, inhale423, smoke431, drink432, inhale433, etc)

-7- Not applicable= -7

0- Never=0

2- Once or twice=2

3- Monthly=3

4-Weekly=4

6-Daily or almost daily=6

N461 – N473 recoded (named smoke 461, drink462, inhale463, etc)

-7- not applicable

-7- not applicable/no one knows

0- No never

3- Yes but not in the past 3 months

6-Yes in the past 3 months

N411 – N413 recoded (this is similar to above but different scoring to create the global drug score)

0=no

3=yes

Create **Global drug score** which is the sum of all assist recoded variables

Create specific substance use sum score for each substance (this is a sum of each variable)

Drinktotal = sum of drink 421- drink 471

Smoketotal = sum of smoke422 –smoke472

Inhaletotal =sum of inhale423-inhale473

Missingness Analysis

After all variables are recoded, a file will be exported to excel than imported to STATA 12.0 for all subsequent analyses. Missingness should be explored by running frequencies for each item of the main outcomes as well as demographics. In other words, sex, age, site, all function items, all PTSD-RI items, all WAF items for each of the composite scores (so only those under sexual relations, readiness to change, HIV status, etc), all items of ASSIST, counselor and type of treatment. Counselor and type of treatment should be explored with only intervention group cases.

To be conservative, variables with greater than or equal to 10% missingness will be further explored in this analysis. If a variable has greater than 10% missingness, Chi-Square should be explored with the variable and demographics to look for a significant pattern of missingness. If this occurs, the variable should be recoded to 0=missing and 1=not missing to explore for significant patterns with demographics. Patterns of significant missingness should be described. Regardless, however, multiple

imputation will be conducted for the analysis to deal with missingness of all variables (item level missing data) as well as missingness due to follow up.

Imputation

Missing data will be handled by multiply imputing all missing values. Where this is loss to follow up scores will be multiply imputed.

Multiple imputation is used for all variables except for those that are known at baseline and consistent (i.e., for variables where the information is known at baseline and would likely not change at post intervention, e.g., age, sex, site). If the information is known it will be used for post information. If not, it will be imputed.

Before imputation is conducted, basic descriptive statistics of all variables will be conducted. A table will be created to indicate the distribution of all variables at baseline (separating intervention and control), to assess any differences between groups and to assess missingness. Differences should be noted using t-tests and Chi-squares. Ineligible participants will not be included in this table or for the rest of the analysis.

Next, baseline demographics and baseline main outcome scores will be identified in terms of whether or not they predict loss to follow up. Any variable that is determined to predict loss to follow up at an alpha of 0.10 or less will be used as a covariate. If there are no variables that are predictive at the 0.10 level than it will be assumed that data missing that is lost to follow up is missing completely at random. In other words, if the data has missing data and is MCAR (missing completely at random), then the logistic regression model will not find covariates associated with loss to follow-up. If covariates are associated with loss to follow-up (at alpha of 0.10), the missing data is not MCAR but MAR (missing at random), and the missingness of the data must be accounted for with respect to those covariates.

Next, imputation will be conducted using the following steps in STATA 13.0

1. Use MI SET FLONG
2. Register all variables that have any missingness at baseline or follow up as imputed variables
3. Use MI impute Chained with 11 iterations (add(11)). Set the number seed and use the same one with each imputation so that you can update with each imputation.
4. Impute demographics first using other demographics with no missingness to predict
5. Use pmm in order to obtain estimates for variables within the legal ranges
6. Include all cluster variables above the individual level (e.g., counselor, SITE) as predictors in the imputation.
7. Impute all missing items for a particular scale, first by imputing follow-up based on the non-missing items and demographic variables; then impute any missing baseline items based only on baseline data.
8. Imputation will be done by combining treatment and control groups together
9. After imputing all missing item level data, generate total scores across imputations

Potential Covariates

Using the imputed dataset, explore for confounders and multicollinearity. A correlation table will be run with each main outcome and demographics to make sure there is some correlation between the main outcomes but very little correlation between the demographics. The correlational analysis can be used to determine which specific main outcome to use for the ASSIST variables (i.e. global drug score or each specific substance use total). The variable with the highest correlation to the other main outcome

variables should be used. To be conservative (without the power of including the complete dataset), the correlational analysis should only include baseline data.

To determine the level of noise in the baseline and to determine potential covariates for the specific models, a series of multiple regressions should be conducted with each main outcome variable as the DV and demographics (including age, sex, type of treatment, site and counselor) as IV. These regressions should be conducted both with and without main outcomes included in the model. That is, if you are looking at the PTSD-RI mean than a regression should be run a) using all demographics as well as function mean, assist score (determined previously) and WAF scores and b) using all demographics only. In addition, t-tests and Chi squares will be conducted with baseline variables to look for differences between control and intervention groups at baseline. Both t-tests and chi-square tests are bivariate tests, and will test for the equal distribution of the intervention and control group for each of the covariates. The regression will control for all other predictors in the model. If there is significance at 0.10 level between treatment and control, then the variable will be included as a covariate for that particular main outcome model. However when the baseline score is significantly different between groups, we will not include it as a covariate when looking at the same outcome in the final model.

All of the models will include gender, age, group (intervention or control). To determine other potential confounders, we will run xtmixed with an interaction of time and the variable of interest (as an interaction term). If the variable is associated with change in the outcome at the 0.10 level then it will be included in the final model. The following commands will be used in STATA to conduct this analysis:
 Mi estimate: xi: xtmixed PTS time*variable of interest || CMHW: || ClientID: , mle vce(robust)

Next we will check all demographic variables and time between baseline and follow-up and include the clustering variables (counselor and site) to assess for the inclusion of clustering variables in the final model. Finally, any variable that will be included in the model as a covariate or confounder will be centered.

Development of Final Models

In STATA 12.0, we will use the xtmixed/xtmelogit set of commands with the “mle” option and a robust standard error estimator.

We will identify levels for random effect modeling: individual (time), counselor, and site.

We will set the data in long form in STATA 13.0

- a. Each record represents an instance of an instrument
- b. Each client will have two records/rows

We will include a term for the interaction of study group (intervention or control) vs. time to test for the difference of differences between intervention and control between time intervals

- c. e.g., xtmixed outcome client group*time covariates || CMHW: || id: counselor: site:, mle vce(robust)
- d. Include all potential confounders in final model
- e. Coefficient of interaction term: The difference in the [difference between treated and controls] between baseline and follow up assessment, adjusting for covariates and correlations in Y attributable to each level in the model
- f. Alternative interpretation: The treatment effect on Y, adjusting for covariates and correlations in Y attributable to each level in the model

Effect Sizes

We will use Cohen's D to examine effect size. In this approach, the numerator is the difference between the intervention and control between time intervals. We will examine the beta coefficient for the interaction of the study group and time intervals. The denominator is the pooled standard deviation of the null model

- a. Null model = RE model with only Y and no covariates
 - b. Use "var" option to produce variance estimates for each level in the model
 - c. Calculate the square root of the sum of the variances produced by the null model
 - d. For stratified analysis, pooled baseline variances should be sub-group specific (i.e. if looking at effect of treatment on women, the pooled baseline variance should only be from the women).
2. Interpretation:
- a. "small" $\approx \pm 0.2$
 - b. "moderate" $\approx \pm 0.5$
 - c. "large" $\approx \pm 0.8$

Residual Diagnostics

Finally, we will run regression diagnostics on non-imputed data (if `mi_m=0`) with the following steps in STATA 13.0

1. Histogram of standardized residuals at each level (instance, client, therapist)
 - a. Identify outliers by looking at number above/below an absolute value of 3 SD against expected number
2. Depending on patterns in residuals:
 - a. Normal – no change in model
 - b. Not normal but relatively close to normal – use `vce(robust)` option in `xtmixed` model
 - c. Not normal, not close to normal – transform outcome variable