RESEARCH PROTOCOL 2/11/2022 VERSION 18

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Study Title: Stepped Care for Children after Trauma: Optimizing Treatment
Document title: Study protocol and statistical analysis plan
Document date: 2/11/22
NCT number: NCT02537678

PROJECT SUMMARY/ABSTRACT

Approximately 68-80% of youth will experience at least one potentially traumatic event during their childhood with about one third experiencing more than one traumatic event. Exposure to traumatic events markedly elevates the risk of developing posttraumatic stress disorder (PTSD) and associated impairment. Despite advances in effective trauma-focused treatments for children, the lack of efficient, accessible, personalized, and cost-effective trauma treatment for children is a major public health concern. Thus, there is a critical need for interventions to improve efficiency, access, and cost-effectiveness and to offer tailored approaches that meet the unique needs of the child. The present study builds on our NIH-funded pilot work (1R34MH092373-01A1) that developed an innovative Stepped Care Trauma-Focused Cognitive Behavioral Therapy (SC-TF-CBT). The purpose of the proposed study is to examine how to optimize the efficiency (e.g., via matching children to appropriate treatment dosage at baseline, utilizing second-stage tailoring variables, and identifying mechanisms of change) and cost-effectiveness of Stepped Care TF-CBT. The long-term goal is to develop an effective, efficient, accessible, and cost-effective adaptive Stepped Care TF-CBT intervention that can be available to more trauma-exposed children, and to advance knowledge about service delivery approaches that may be applicable to providing treatment for other childhood mental health disorders. Our goal is consistent with the strategic objective to “Develop New and Better Interventions that Incorporate the Diverse Needs and Circumstances of People with Mental Illness,” and the research priorities that call for trials that foster prescriptive, personalized mental health care, incorporate tailoring variables to match patient interventions, improve access to services, decrease costs of services, and incorporate measures of putative mechanisms of action in trials in “real world” settings. In a randomized clinical trial with 216 children ages 4 to 12 years at community-based agencies, we are proposing the following aims: Aim 1: To examine Stepped Care TF-CBT (e.g., starting with Step One parent-led, therapist-assisted treatment and then either maintenance or Step Two TF-CBT) relative to standard TF-CBT (e.g., therapist-led treatment); Aim 2: To examine tailoring variables that could be used to individualize (i.e., tailor) the decision of which children should be assigned at baseline to Stepped Care TF-CBT versus standard TF-CBT; Aim 3: To examine if changes in the potential mechanisms of change variables (e.g., fear arousal, maladaptive cognitions, negative expectancy, and fear toleration) mediate treatment on child PTSD symptoms (PTSS) and impairment; and Aim 4: To examine the economic cost of delivering Stepped Care TF-CBT versus standard TF-CBT. Children with PTSD are at considerable risk for numerous biopsychosocial problems. Without accessible, effective treatment, these problems tend to persist into adulthood. This study will yield clinically important data which will improve the value and efficiency of treatment of children with PTSD, thereby reducing childhood PTSD and related societal impacts and costs.

2. SPECIFIC AIMS PURPOSE, AIMS, HYPOTHESES

Service delivery approaches such as stepped care interventions are needed in "real world" settings to address treatment barriers such as costs, logistical barriers, limited availability of trained therapists [1] and parents' desire to solve the problem on their own.[2, 3] We have successfully developed and pilot tested a two-step Stepped Care Trauma-Focused Cognitive Behavioral Therapy (SC-TF-CBT) model with young children (ages 3-7; R34MH092373-01A1)[4, 5] and with older children (ages 8-12). Preliminary data suggest that Step One of SC-TF-CBT (a first-line, parent-led therapist-assisted treatment) is a feasible and efficacious first-stage treatment for traumatized children, and the cost of intervention delivery is quite low (~$486).[4] Further research on SC-TF-CBT is needed. First, research on SC-TF-CBT relative to standard care including the long-term outcomes is needed. Second, how to assign children to the optimal level of treatment intensity at stage-one and stage-two and to individualize treatment remains to be understood. Pilot data suggest that high internalizing problems and critical life events are potential first-stage tailoring variables that could be used to personalize care such that children are assigned to the optimal treatment intensity at baseline. In addition, the proposed intervention utilizes second-stage tailoring variables (i.e., non-adherence, new trauma exposure, non-treatment response) to increase subsequent treatment intensity. Third, understanding the role of potential mechanisms of change (i.e., based on emotional processing and inhibitory learning theory) in Step One and in standard TF-CBT for children needing more intensive treatment will lead to further optimization of trauma-focused care, and contribute more broadly to exposure-based therapies for anxiety. Finally, further research is needed to test the economic costs of SC-TF-CBT relative to the current practice of therapist-directed treatment.

Building on the development of the SC-TF-CBT model,[4-7] this R01 application examines how to optimize the efficiency and cost-effectiveness of SC-TF-CBT, a personalized adaptive intervention, under "real world" settings. The proposed research is in line with NIMH research priorities for trials that foster personalized mental health care, incorporating tailoring variables to match interventions to patient needs, and to optimize interventions.[8] Consistent with RFA-MH-15-320, this application proposes to test a new service delivery approach compared to existing practice and to elucidate mechanisms of change within two-trauma focused interventions with the goal of improving the value and efficiency of trauma-focused treatment compared to standard practice. This project has the potential to improve the accessibility, efficiency, and effectiveness of clinical practice, while reducing the cost of treatment and reducing the societal impact of childhood PTSD.

Aim 1: To examine the relative efficacy of SC-TF-CBT (e.g., starting with Step One parent-led, therapist-assisted treatment and then either maintenance or Step Two TF-CBT) versus standard TF-CBT (e.g., therapist-led treatment).

1.1. Hypothesis: Given the second-stage treatments provided (maintenance, TF-CBT), children in SC-TF-CBT will demonstrate comparable improvements to children in standard TF-CBT in: (a) child outcomes: PTSD symptoms (PTSS) and functional impairment (primary outcomes), internalizing and externalizing behaviors, PTSD severity, and global improvement; (b) acceptability and satisfaction levels; and (c) parent secondary outcomes: parenting stress, depression, and PTSD symptoms.

1.2. Hypothesis: Children in SC-TF-CBT and standard TF-CBT will continue to have comparable improvements in child and parent outcomes throughout the 6- and 12-month follow-up period.

Aim 2: To examine tailoring variables that could be used to individualize (i.e., tailor) the decision of which children should be assigned at baseline to SC-TF-CBT versus standard TF-CBT.

2.1. Hypothesis: Children with high internalizing problems or high perceived critical life events are less likely to respond to first-stage Step One.

Aim 3: To examine if changes in the following potential mechanisms of change variables mediate treatment effects (e.g., Step One and standard TF-CBT) on child PTSS and impairment: (a) fear habitation: decreases in child's fear-based arousal; (b) cognitive changes: reductions in child's negative trauma-related cognitions; (c) inhibitory learning: child's decrease in expectancy of negative outcomes; and (d) fear toleration: extent of child's toleration of fear activation.

3.1. Hypothesis: Decreases in children's fear-based arousal, improvements in negative trauma-related cognitions, decreases in children's expectancy of negative outcomes, and changes in fear toleration over time will mediate Step One and standard TF-CBT treatment outcomes in PTSS and impairment.

3.2. Secondary Hypothesis: The mechanisms of change (e.g., a, b, c and d in Aim 3) will occur during all components of treatment but greater changes in these processes will occur during more direct exposure activities (e.g., imaginal and *in vivo* exposure in Step One) than less direct exposure activities (e.g., developing a trauma narrative in Standard TF-CBT) and during coping skills in both treatments.

Aim 4: To examine the economic cost of delivering SC-TF-CBT versus standard TF-CBT.

4.1. Hypothesis: Stepped Care TF-CBT will be more cost-effective than standard TF-CBT.

3. RESEARCH STRATEGY BACKGROUND INFORMATION

a. SIGNIFICANCE

a.1. Prevalence and Impact of Trauma. Between 68-80% of youth will experience at least one potentially traumatic event during their childhood with ~33% experiencing more than one trauma.[9, 10] Approximately 16% to 33% of trauma-exposed children will develop PTSD.[11] Children exposed to trauma are twice as likely to have a psychiatric disorder as non-exposed children. Studies have shown comparable levels of functional impairment whether the child has significant PTSD symptoms or meets full PTSD criteria,[12, 13] but the rate of impairment increases as trauma exposure increases.[9] PTSD in childhood has been associated with numerous biopsychosocial problems including academic problems, poor social support, suicide, poor physical health, depression, anxiety, somatic complaints, substance abuse, neurological changes, problematic sexual behaviors,[14-16] and high levels of internalizing and externalizing problems.[17] Without effective treatment, childhood PTSD and associated deleterious outcomes persist over time.[12] Whether traumatic events occur in children's everyday life (e.g., sexual abuse, domestic violence, life-threatening illness, death of parent) or are the result of mass trauma (e.g., terrorist attacks, school shootings, disasters), the lack of accessible, efficient, personalized, cost-effective trauma treatment is a major public health concern.

a.2. Barriers to Treatment: Need for Accessible, Efficient, Personalized, Cost-Effective Treatment.

Barriers to mental health treatment are a major public health concern. Barriers include limited availability of trained therapists, costs, stigma, logistical barriers (e.g., time, work demands, child care, transportation),[1] and treatment not meeting parents' expectations.[18] In the National Comorbidity Survey, the primary reason people did not seek treatment (72%) or dropped out of treatment (58%) was due to their desire to solve the problem on their own.[2] Likewise, a major barrier for parents seeking treatment for themselves and for their child is the desire to be able to solve the problem on their own.[3] Treatment and service delivery approaches are needed to address barriers to mental health care.[19] When children do not receive effective treatment and systems fail to provide accessible, affordable and effective treatment, children are at risk for illness chronicity and associated impairment. The newly developed treatment being further refined and tested in the proposed study, Stepped Care Trauma-Focused Cognitive Behavioral Therapy (SC-TF-CBT) was developed (1R34MH092373-01A1)[4-7] to address treatment barriers such as cost (including less therapist and patient time), parent's desire to be involved in solving the child's problem, logistical barriers, and availability of trained therapists.

Many evidence-based practices (EBP) are delivered by therapists as "full-packages" which can be therapist-intensive, costly, and limit individualizing treatment. For example, trauma-focused cognitive behavioral therapy (TF-CBT), a component-based, therapist-directed EBP, is typically provided in-office in 12- 16 sessions.[19, 20] TF-CBT has demonstrated to be superior to psychosocial treatments (e.g., child-centered therapy, non-directive supportive therapy, treatment as usual)[20-23] and to waitlist controls.[24, 25] A recent study on TF-CBT[26] suggests that some children may need shorter or longer treatment packages and matching treatment to their needs and tailoring subsequent treatment may be an efficient and effective treatment approach. The current paradigm of offering a labor-intensive, therapist-directed, in-office full treatment package for all children does not address salient treatment barriers. Further, the current paradigm of full-package EBPs, including TF-CBT, does not provide patients with choice or allow for a more personalized, adaptive treatment approach. Consistent with NIMH strategic research priorities (Objective 3), research is needed on personalized stepped care approaches that utilize tailoring variables to match patients to treatment based on presenting conditions and incorporate prior treatment response to improve outcomes.[8]

a.3. New Service Delivery Approaches are Needed. Alternatives to treatment and delivery systems, such as stepped care models that improve accessibility, are efficient, provide personalized care, and lower mental health treatment cost, are needed. Stepped care models provide a lower-intensity first step (e.g., less therapist time, less costly, and more convenient for parents) as the initial treatment, with the assumption that a proportion of patients will respond to the first step and other patients will need to step up to more intensive treatment.[27] Stepped Care interventions have pre-established monitoring systems, such as predefined treatment response, that are used to indicate subsequent treatment needs.[27] Given the potential benefits of stepped care models to provide accessible, efficient, low cost, acceptable, and effective individualized treatments, NIMH as well as other countries[28] are encouraging stepped care mental health approaches. However, the development of stepped care models,[29-33] also known as adaptive interventions,[34] including our pilot work for outpatient treatment for children with PTSD,[4-6] are still in the early stages of development, and systematic research on

stepped care models for children that address treatment barriers are lagging.[35]

a.4. Understanding Mechanisms of Change Within Stepped Care Can Lead to More Targeted, Optimized Interventions. While recent adult trials on trauma-focused treatment examined changes during treatment that account for improved outcomes,[36-38] research on mechanisms of change in child trauma-focused treatment is limited. Despite the trials on TF-CBT, our understanding of mechanisms of change is limited.[39] For children needing to be matched directly to TF-CBT or to Step One within SC-TF-CBT, targeting the mechanisms of change could optimize treatment such that clinicians could target these processes and monitor progress, thus tailoring treatment delivery. The one dismantling study on TF-CBT components suggest that although all children improved across outcomes, there were differential responses based on receiving the trauma narrative only (e.g., less parental distress about the abuse) versus coping skills only (e.g., improvements in parenting practices).[26] This study did not examine within session mechanisms of change and the authors suggest that by virtue of discussing coping skills in the context of trauma, exposure occurs. In the proposed study, we will examine in Step One and TF-CBT four potential mechanisms of change (e.g., fear arousal, maladaptive cognitions, expectancy of negative outcomes, fear toleration) based on two prevailing theories (e.g., emotional processing theory and inhibitory learning; Primary Aim 3). Step One, a parent-led therapist-assisted treatment and TF-CBT include coping skills (e.g., affect management, stress management) and exposure, but exposure methods are more direct in Step One (e.g., imaginal and *in vivo*) than TF-CBT (e.g., gradual trauma narration). Patterns of change among the potential mechanisms of change during different treatment components will be explored. Understanding mechanisms of action will have implications not only for these two trauma interventions, but will be applicable more broadly to therapies for anxiety.

a.5. Practical Impact of SC-TF-CBT Compared to Standard TF-CBT. Based on our pilot data, we estimate that the cost savings of SC-TF-CBT compared to standard TF-CBT to be 56.7% ($1,188; Cohen's *d*=2.01) This savings not only represents a significant impact in value, but also in efficiency in terms of therapists time and patients receiving treatment in a more efficient manner. Mental health care costs more per child than any other health care expenditure for children. Medicaid paid for most of the costs (45.6%) followed by private health insurance (31.4%) and families paying out of pocket (13.6%).[40] The average cost per child ages 5-17 for mental health treatment in the U.S. is $2,192.[41] Cost is a significant barrier to mental health treatment.[42] Despite repeated calls from researchers[43] to include outcome measures such as time and cost of treatment, research examining the costs associated with child trauma treatment remains limited. A recent statewide TF-CBT implementation study suggests the cost of mental health care services for trauma-exposed youth (public-insured) who received TF-CBT was lower than the mental health care costs for youth who did not receive TF-CBT. In fact, youth who received TF-CBT had significantly less costs for intensive services (e.g., crisis intervention, hospitalization, residential care) (*M*=$497.89, *SD*=$1,431.94) than youth who did not receive TF-CBT (*M*=$3,030.43; *SD*=$6,898.97).[44] Given the development of first-stage tailoring variables, we recognize that SC-TF-CBT is not clinically optimal for all children, but in such cases the cost of standard TF-CBT remains significantly less than the cost of high end services.[44] SC-TF-CBT has the potential to provide an innovative approach to providing a low cost effective treatment that can be more readily available than standard practice, and serves as a model for other childhood mental health treatments.

a.6. Scalable Delivery Approach and Available Infrastructure Provides for Dissemination into Practice. Given TF-CBT is being widely disseminated,[45-47] the development of TF-CBT into a stepped care model that optimizes and personalizes treatment would have a significant public health impact. TF-CBT presents as an ideal basis for a stepped care model given its wide dissemination,[48],[46] and using CBT throughout treatment steps, rather than using various practices that require different trainings and certifications, will make training easier and accelerate uptake in community practice. There is a free web-based course for clinicians to learn the components of TF-CBT (http://tfcbt.musc.edu/), several states have initiated statewide trainings,[45, 49, 50] and current research about how to most effectively train community clinicians and implement TF-CBT in community settings is underway.[51-53] These dissemination efforts and tested strategies for community uptake will provide the platform to disseminate SC-TF-CBT. For rapid dissemination, there would be three areas to address: 1) Providers would need to consider reimbursement for the phone support. Step One provides 6 (15 min) phone support sessions and while 20 states mandate reimbursement for telehealth, not all private insurance plans cover these costs.[54] 2) Additional training based on knowledge gained about the mechanisms of change would be needed so that clinicians can effectively tailor treatment; and with this training, 3) clinicians would benefit from lessons learned from this trial on how to implement Step One, the parent-led treatment, in community settings.[5] TF-CBT continues to be delivered in a traditional "full-package" therapist-led manner, but given the resources

invested in dissemination of TF-CBT, this new service delivery approach leading to substantial changes in value and efficiency is primed to be scalable and disseminated into community practice.

b. INNOVATION

b.1. Improving Clinical Practice: Personalized Adaptive Interventions

The proposed study is highly innovative in five ways. **First,** the service delivery approach being tested can lead to more children receiving effective trauma-focused treatment while reducing the overall burden of cost to the provider, patient, payer and society. **Second,** within-treatment changes will identify potential mechanisms of change within standard TF-CBT and Step One to produce practice-relevant information to refine treatment delivery within both treatments. **Third**, SC-TF-CBT utilizes a multi-method minimal therapist-assisted approach based on newer methods (i.e., parent-led treatment, internet and website support [e.g., information and video demonstration], telehealth, and converting a therapist EBP manual into a tool for patients) to deliver Step One, a novel first-line at-home parent-led treatment (see b.2.) contributing to improved access. In fact, our pilot data indicated that a substantial percentage of children (77.6%) responded to Step One. **Fourth**, behavioral and environmental first-stage treatment tailoring variables are being examined to create an adaptive intervention where children can be matched to the appropriate intensity level *prior* to starting treatment. We will use a randomized block design to ensure that the two treatment conditions are balanced in regard to the candidate first-stage tailoring variables (see c.4. and c.4.1.). **Fifth**, within SC-TF-CBT, we will be utilizing time-varying tailoring variables that were identified from our pilot work to identify patients who need to step up immediately during stage-one treatment, and patients who are early responders and do not need stage-two treatment, thus leading to more personalized care.

Effective, efficient and cost-effective models that match patients to the appropriate level of care at baseline, have guidelines to indicate when to change treatment approaches, monitor and target mechanisms of action, provide alternatives to traditional costly and limited access care, and actively involve parents in helping his/her child will shift clinical practice paradigms from providing full-package, therapist-directed treatment to all patients to providing more optimized, accessible treatment. Stepped care delivery models provide an advantage over existing delivery systems of "full-package" EBP in that interventions are optimized by using data to provide efficient, effective, and personalized care that is designed to address treatment barriers. In a study with primary care physicians and child psychiatrists, both groups agreed that one of the major barriers to referring children for mental health treatment was long waiting periods, as well as concerns about treatment quality.[55] With a stepped care approach, wait times could decrease as children can begin immediately with the first-line minimal therapist assistance treatment and therapists could spend more time with patients who need intensive therapist-directed care.[27, 56] A first-line treatment with minimal therapist assistance may be useful for providing treatment to children who live in rural areas where there are fewer trained therapists.[57]

b.2. Stepped Care TF-CBT: Innovative Optimization of Treatment Components

An innovative stepped care treatment for children has been developed and further testing to optimize the treatment is needed. The initial development, feasibility, patient acceptability, and preliminary efficacy of SC-TF-CBT for children ages 3-7 years was evaluated in our NIH-funded pilot work (R34MH092373-01A1).[4, 5, 7] Subsequently, due to the enthusiasm expressed by a local community agency (Crisis Center of Tampa Bay) about the potential of SC-TF-CBT, the agency provided funding to expand the development of the model to included children ages 8-12 years. The clinical components for both ages are similar and are now combined such that SC-TF-CBT is designed for children ages 4-12. The broader age range of SC-TF-CBT increases the generalizability of the treatment and will be included in the proposed study. Children younger than age 4 years will not be included due to the investigators' experience, and prior research[25] that younger children often struggle to grasp assessment ratings that are used in SC-TF-CBT (see 7). Careful consideration of type and number of steps, training of providers, entry point, parent inclusion, treatment components, non-compliance, and a self-correcting monitoring system were taken into account when developing SC-TF-CBT.[4, 5]

SC-TF-CBT consists of two main steps (see Figure 1). Step One (e.g., low intensity) involves a novel parent-led, therapist-assisted treatment with multi-faceted components based on empirical support from CBT for children after trauma,[20, 25] research on the use of minimal therapist assistance,[35, 58] telehealth, bibliotherapy,[57] and computer-assisted treatments.[59] In Step One, parents and children meet only three times (for 60 min. each) with a therapist over a 6-week period and each time parents receive a section of the parent-child workbook called *Stepping Together* for young children or for children ages 8-12.[60, 61] The workbooks, based on the therapist treatment manual for Preschool PTSD Treatment (PPT), which used imaginal and *in vivo* exposure,[25] were refined based on parent, child, community therapists, and national trauma expert

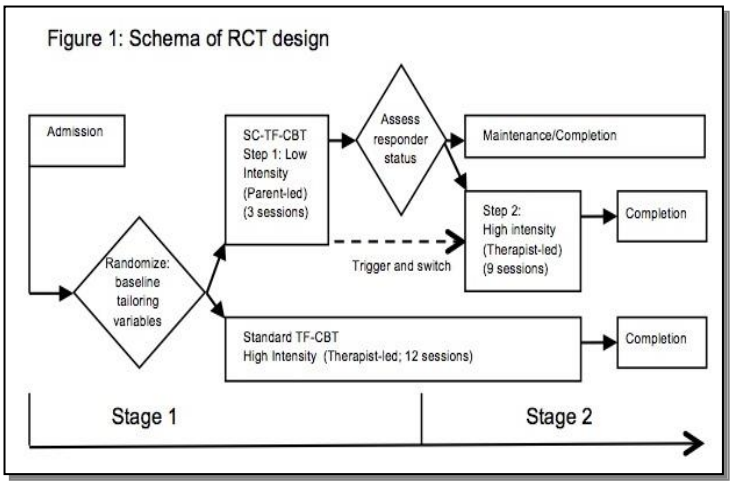
feedback. *Stepping Together*, written on a 6th grade level, provides a step-by-step approach for parents to provide treatment at-home with 11 parent-child meetings. Weekly phone support is provided for support, coaching and motivation. Pilot data suggest that ~89% of scheduled phone calls occurred. When calls did not occur, the therapist or parent would leave a message confirming the next time available to talk. There is also a *Stepping Together* website with two video demonstrations (see Appendix). Step Two is therapist-led and consists of 9 weekly (90 minute) TF-CBT therapy sessions [62, 63](see c.3.1.).

After completing Step One, a brief assessment occurs. If responder status is met, the parent and child end treatment and proceed to the Maintenance phase which is designed to further open parent-child communication and encourage the parent and child to use the tools that they learned in Step One. Responder status criteria was developed and tested in the pilot studies.[7] Establishing responder status involves three methods of measuring treatment response/nonresponse: 1) a semi-structured interview (with parents for young children ages 4-6 and with parents and children for children ages 7-12) about PTSD symptoms. Responders must have 3 or fewer symptoms for younger children and 4 or fewer symptoms for older children. The one symptom difference is based on prior research on PTSD with young children that documented that fewer symptoms are needed for young children to meet criteria[64] and recent differences in number of symptoms needed for PTSD diagnosis based on age according to DSM-V[65]; or 2) below the clinical cut off score on a continuous measure of PTSD symptom severity (completed by parents for young children and by the child for older children); and 3) a rating of 3 (improved), 2 (much improved), or 1 (free of symptoms) on the Clinical Global Impression–Improvement scale (CGI-I)[66] that takes into account impairment. Results from our pilot data on SC-TF-CBT suggest even before responder status is determined, there are two additional second-stage tailoring variables (e.g., non-compliance and concurrent trauma exposure) that should indicate a "trigger and switch" approach to an immediate step-up to Step Two (see c.1.3.).

Understanding mechanisms of change within Step One and standard TF-CBT can further optimize these treatments. Emotional processing theory (EPT), the theoretical basis for prolonged exposure with adults, posits that cognitive and behavioral avoidance maintains PTSD symptoms due to misconceptions about danger and self. Corrective learning occurs during exposures such that activation of fear structures leads to within and between session fear habituation (measured by physiological and subjective measures) resulting in cognitive corrections which in turn leads to decreased PTSD symptoms.[67-69] Most studies fail to find a relationship between within session habituation and outcome, and results for between session habituation and outcome are more mixed, but with more evidence towards supporting the EPT premise.[70-72] The study of fear activation, and within and between session habituation as mechanisms of change has been predominantly with adults, and many studies were limited due to methodological issues such as not including both self-reports of fear and physiological measures.[70] To date, there is only one pilot study examining the relationship between physiological responses and treatment outcome for youth with PTSD, and while there were differences in acoustic startle response and skin conductance responses between traumatized and non-traumatized youth, associations in these differences at treatment outcome to TF-CBT were not found. This study did not examine fear habituation during treatment and the small sample size (n=19 in each group) was a major limitation.[73] A recent study with 268 adults found that weekly changes in cognitive appraisals predicted decreases in PTSD symptoms (and not vice versa) supporting changes in cognitions as a mediator, although this study did not include other potential mediators to explore interactions, link changes to session content or obtain fidelity ratings.[74] A pilot study with 24 children (ages 8-12) assigned to CBT for PTSD for single incident trauma or a waitlist condition demonstrated that CBT effects were partially mediated by changes in maladaptive cognitions; although the sample size was small, changes were not linked to content, and children with only single incident trauma were included.[75] In the proposed study, we will examine decreases in fear-based arousal and improvements in negative trauma-related cognitions as potential mechanisms of change and explore changes over time during phases of treatment (hypotheses 3.1. and 3.2.). Between habituation will be tested but within session ratings will be collected since there is so little data on these potential mechanisms with children.

Newer theory purports that inhibitory learning is the mechanism associated with improved treatment outcomes in exposure therapies rather than fear levels. Therefore, the proposed study seeks to test both theories (EPT and inhibitory learning) as mechanisms of change as both have documented support.[69, 76] Including both theories will lead to a broader understanding of how these mechanisms of action lead to improvements, as researchers[72] have called for a more integrated theory. Inhibitory learning suggests that the original conditioned stimulus [77] to unconditioned stimulus (US) association during exposures or fear conditioning is not eliminated, but rather new learning and meaning about the CS-US relationship

develops.[70] One primary mechanism of inhibitory learning (i.e., CS does not predict US) is changes in negative expectancy.[70] Fear toleration is considered a secondary mechanism of inhibitory learning where patients learn that they can tolerate the fear and expected negative outcomes are not likely.[76] The proposed study will test inhibitory learning theory by measuring expectancy in negative outcomes and fear toleration as potential mechanisms of change and explore changes over time during phases of treatment (hypothesis 3.1. and 3.2.). We will also explore therapeutic alliance as a potential mechanism of change. A recent study found that therapeutic alliance was a significant predictor of child outcome for TF-CBT but not for nonspecific psychotherapy (Ormhaug, Jensen, Wentzel-Larsen, & Shirk, 2014). It would be interesting to study the role of therapeutic alliance in parent-led treatment versus therapist-led treatment, and to explore if there are other differentiating mechanisms of change between the two service delivery approaches.



b.3. Aims. The proposed study seeks to identify at the first-stage of treatment (i.e., baseline) which children should start with the parent-led treatment and which children need to be assigned immediately to intensive therapist-led treatment. Mechanisms of change in Step One and standard TF-CBT will be examined and changes throughout treatment components will be explored. While standard TF-CBT is the comparison condition to SC-TF-CBT, standard TF-CBT will also be tested as part of an adaptive intervention where SC-TF-CBT would include TF-CBT as a first-stage treatment for a subgroup of children needing immediate high intensity care. If the proposed aims are met, there would be an efficient and cost-effective adaptive Stepped Care TF-CBT intervention that includes all of the treatment components illustrated in Figure 1 where clinicians could target and monitor the mechanisms of change. Consistent with the NIMH strategic research priority that focuses on comparative effectiveness research with the goal of developing personalized treatment, "information regarding differential responses can inform more prescriptive, personalized approaches for matching individuals to interventions or suggest subgroups for whom alternative or optimized interventions are needed".[8]

c. APPROACH

c.1. Preliminary Studies. Preliminary data from our pilot studies on SC-TF-CBT guided the development of this proposal (N=95 children ages 3-12 years; R34MH092373-01A1 [n= 62, of which 9 were from an open trial][4]; Crisis Center of Tampa Bay [n=33]; and random assignment: n=57, SC-TF-CBT; n=29, TF-CBT).

c1.1. Preliminary Main-effects of SC-TF-CBT relative to TF-CBT. Our pilot studies on SC-TF-CBT showed no statistically significant group differences between the children of the two treatment conditions at either post-treatment or 3-month follow-up on parent-rated PTSD, CGI-Severity (CGI-S), CGI-I, and CBCL internalizing and externalizing problem T-scores. Generalized linear modeling (GLM) was used to accommodate variation in baseline risks and non-standard distribution forms of the outcome variables. More rigorous equivalence tests were also performed, although we did not have sufficient power given the preliminary nature of the study. Non-inferiority of SC-TF-CBT at post-treatment and follow-up were concluded on its effect for parent-rated PTSD (p<.01, p<.01), CGI-S (p<.01, p<.01), CGI-I (p=.05, p=.02), acceptability and satisfaction (post: p<.01), and internalizing total T-scores (p=.04, p=.03), but not on externalizing total T-scores (p=.15, p=.17).

c.1.2. Candidate First-Stage Tailoring Variables. An exploratory aim of the R34 was to explore differential characteristics of Step One responders/non-responders to identify potential first-stage tailoring variables. Based on prior literature and our clinical experience, we first explored differences in child variables (PTSD symptoms, internalizing and externalizing problems, depression, polytrauma (>1 traumatic event), interpersonal/non-interpersonal trauma, and age), parent variables (PTSD, depression and parenting stress) and environmental factors (treatment barriers) between Step One responders/non-responders. Two measures that showed substantial differences between responders and non-responders were internalizing problem T- scores and critical life events regarding barriers to treatment. We further applied classification tree method[78] to find the optimal cutoff values that maximally distinguished responder/non-responders after Step One. Regarding total internalizing T-scores, those children (16/49=32.7%) with a score >71 had a response rate of 56.3%, and those with a score ≤71 had a response rate of 87.9% (X^2=6.19, p=.01). Regarding critical life events, those children

(28%) with a score >16 had a response rate of 44.4%, and those with a score ≤16 had a response rate of 82.6% (X^2=4.66, p=.03). We recognize that given the small sample size, some of the results did not reach significance especially when adjusting for multiple comparisons. However, high internalizing problems is consistent with the literature suggesting that these children may need more intensive treatment [79, 80] and our qualitative findings are consistent with critical life event barriers as a theme for Step One non-responders. We considered externalizing problems as a first-stage tailoring variable since non-inferiority was not supported; however, there was not a significant difference between responders/non-responders and externalizing problems after Step One; nor was there a clear significant optimal cutoff value. Further, since GLM results and percentages of those above the clinical cutoff revealed no significant differences between SC-TF-CBT and TF-CBT at post- and follow-up, the evidence did not support externalizing problems as a tailoring variable. These results provide suggestive evidence of effect moderation and a preliminary establishment of candidate first-stage tailoring variables to be tested in the proposed application.

c.1.3. Time-Varying Stage Two Tailoring Variables and Step One Responder Status. Based on our pilot data, we are proposing to incorporate into SC-TF-CBT two new time-varying tailoring variables that may occur during stage-one treatment that will lead to a "trigger and switch" approach. **1)** Child exposed to a new traumatic event after baseline assessment. In the R34 study, Step One non-responders experienced significantly more new traumatic events than Step One responders (92% vs. 36%, Fisher's exact test, p<.001). When a new traumatic event occurred during the parent-led treatment, it was challenging for the parent and child to process the additional trauma thus indicating that more intensive therapist-led treatment (i.e., Step Two) was needed. TF-CBT has established methods for working with children with on-going traumas.[81] **2)** Early non-adherence to Step One. We had a three-step noncompliance process which involved problem-solving, allowing additional weeks for making up activities, and stepping up if significant progress completing Step One was not being made. Six of 13 Step One dropouts only attended the 1st therapist meeting. The therapists made numerous follow-up calls to problem-solve, and additional time to complete activities before scheduling the 2nd therapist meeting was allowed. Additional time did not result in adherence. We have carefully re-considered the non-compliance protocol and developed a revised non-adherence plan that will allow for early identification of non-compliance. During the phone meetings, therapists will encourage parents to complete the parent-child meetings and problem-solve if meetings are not occurring. The 2nd therapist meeting will not be postponed if the parent-child meetings were not completed. Instead, the therapist will review adherence (see c.6.7.) and if < 75% is completed, the child will be stepped up to therapist-led treatment. Some parents may not be able to lead treatment due to various reasons including uncertainty or their own emotional reactions; thus, more quickly stepping-up treatment may minimize drop outs.

The third time-varying variable that was piloted is the response/nonresponse criteria after Step One. Of the 49 patients across both pilot studies who completed an assessment after Step One, 38 (77.6%) responded after Step One (see b.2. for responder status criteria). Congruency between responder status criteria and parents' thoughts about if more treatment was needed was as follows: 75.5% congruent, 20.4% incongruent (with one parent wanting to end when more treatment was recommended), and 4.1% unsure. As per our pilot protocol, parents who think more treatment is needed after Step One are offered two additional sessions, and if a child relapses after the maintenance phase, they can step up (no child stepped up after the post-assessment). Given these results, we will use the same responder status criteria derived from our pilot work.

c.1.4. Cost Measures and Preliminary Costs of Delivering Stepped Care and TF-CBT. The R34 stepped care grant: 1) piloted data collection methods on the costs of delivering SC-TF-CBT and TF-CBT, and 2) conducted a preliminary comparison of costs associated with delivering SC-TF-CBT and TF-CBT. These cost methods were incorporated into the SC-TF-CBT trial with older children. 1) *Costs Characteristics Information* (CCI)[82] consists of 11 items to measure estimated costs such as out-of-pocket expenses for treatment, lost income due to missing work to attend therapy, patient time associated with treatment, and other cost-related information. We have been successful capturing these cost-related data and procedures for collecting missing data regarding parent's co-pay have been established. 2) *The Therapist/Patient Time Tracking System* (TTTS)[83] measures the therapist time associated with 14 types of treatment delivery activities (e.g., therapist meetings, phone support, documentation) and parent/child time associated with 9 types of treatment participation (e.g., therapist meetings, phone support, homework). The Service Assessment for Children and Adolescents (SACA)[84] will be administered to track other services used and estimated costs of other services. These cost measures will be used in the proposed study to address the next important step of examining the economic cost of delivering SC-TF-CBT and standard TF-CBT (Aim 4). Also, if tailoring variables effectively distinguish child

response/nonresponse to Step One (Aim 2), costs will be compared for SC-TF-CBT and TF-CBT for children who are most appropriate for SC-TF-CBT.

Our preliminary data provide a limited comparison because children with higher and lower probabilities of response to Step One were included, and costs for other services were excluded. Further, the sample size was insufficient to examine costs at a more detailed level. Patient costs and therapist time were lower with SC-TF-CBT versus TF-CBT ($215 vs. $470; 425 vs. 1158 minutes per patient, respectively). For SC-TF-CBT, 76% of total costs ($690) involved direct and indirect therapist costs with direct therapist costs averaging $405 per patient; whereas with TF-CBT 78% of total costs ($1,624) involved direct and indirect therapist costs with direct therapist costs averaging $1,097 per patient. The total average economic cost to deliver treatment was lower for SC-TF-CBT than TF-CBT, $906 vs. $2,094, Cohen's *d*=2.01.

c.2. Treatment Study Procedures

c.2.1.Telephone Screening. Structured telephone screenings with all potential participants who call regarding the study will be conducted by the Agency Coordinators/Screeners. If the child appears to meet the general study criteria, the parent will be given further information about the study and those who are interested will be scheduled for an in-person screening and, if criteria are met, baseline assessment (same visit). We anticipate that the phone screening will minimize screen failures (15% screen failures; consistent with our pilot data).

STUDY INCLUSION/EXCLUSION

c.2.2. Inclusion/Exclusion Criteria. Inclusion Criteria: 1) Child experienced at least one traumatic event after the age of 36 months (to ensure that children have sufficient developmental capacities of memory and autobiographical recall to access a traumatic memory for therapeutic work). **2)** Consistent with other NIMH-funded child PTSD outcome studies [20, 25, 26] (R10MH55963; R10MH56224), and our pilot SC-TF-CBT trials, the children age 4-6 must meet at least four PTSD symptoms and children age 7 to 12 must meet at least five PTSD symptoms (now DSM-5 defined) with at least one symptom in re-experiencing or one symptom in avoidance in order for exposure exercises to be salient. 3**)** At enrollment, the child must be between 4-12 years of age. **4)** The parent/guardian must be willing and able to participate in the treatment and complete informed consent. **Exclusion Criteria**: **1)** Psychosis, mental retardation, autism spectrum disorder in the child or any condition that would limit the caregiver's ability to understand CBT and the child's ability to follow instructions. **2)** Parent has had substance use disorder (SUD) within the past 3 months. Patients w/SUD can participate in PTSD treatment,[86] but the parent is not the primary patient and at-home parent-led treatment is provided. For child safety, parents with recent w/SUD are excluded. **3)** Child or parent is suicidal. A delayed entry once the parent or child is stabilized (> 6 months post suicidal) and not having suicidal ideation will be allowed if appropriate. **4)** Child or parent is not fluent in English. **5)** If child is taking psychotropic medication regimen must be stable for 4 weeks. For stimulants or benzodiazepines, the medication regimen must be stable for 2 weeks. If appropriate, a delayed entry will be allowed so that once a child is on a stable dosage the child may be enrolled in the study. **6)** Child is receiving trauma-focused psychotherapy during study treatment. **7)** Parent/caregiver who would be treatment participant was the perpetrator, or the child was perpetrated by a person who still lives in the home. **8)** Consistent with Deblinger et al.,[26] child is having unsupervised face-to-face contact with the identified perpetrator. **9)** Siblings will be excluded & referred to community treatment. If siblings meet criteria, selection of patient will be random.

c.3. Treatment Conditions INTERVENTIONS PROVIDED

c.3.1. Treatments. Each treatment will be provided over 12-14 weeks, although flexibility will be allowed to minimize drop out. SC-TF-CBT patients will receive Step One: 3 (1 hr.) in-office therapist-led sessions over 6 weeks, the parent-child workbook (*Stepping Together*),[60, 61] scheduled weekly phone meetings (15 minutes), and information from the Stepping Together website and the National Center for Childhood Traumatic Stress website (via web or paper for those without access). Children who do not meet responder status will receive Step Two: 9 (1.5 hr.) in-office therapist-directed sessions of TF-CBT over 6 to 8 weeks. Standard TF-CBT patients will receive 12 (1.5 hr.) standard weekly in-office therapist-directed sessions (2 additional weeks allow for scheduling difficulty). TF-CBT includes child, parent and conjoint parent-child sessions addressing the 10 core trauma treatment components of TF-CBT (e.g., parenting skills, affect modulation, cognitive coping, trauma

narrative, etc.).[87] Is early termination of Step Two possible? For patients receiving step two TF-CBT, 9 sessions will be provided. However, in some cases, early termination may be possible. If two consecutive CGI-I parent and therapist ratings independently indicate a 2 (much improved), or 1 (free of symptoms) and the child is not in the middle of the trauma narration or conjoint component, the TSCYC-PTS total will be administered. If there is a 40 or less on the PTS total on the TSCYC measure, a post assessment with the IE may be scheduled. If responder status is met, the therapist will discuss with the parent the option of an early termination or continuing treatment. If treatment ends early, a final termination session may occur to discuss progress and relapse prevention. If the responder status is not met, the child will complete the step two treatment and there will be a post assessment upon completion.

c.3.2. **Why use standard TF-CBT as the comparison condition?** The proposed study design allows for the direct comparison of Stepped Care TF-CBT, which is designed to increase efficiency, accessibility and cost effectiveness, to the traditional delivery of standard TF-CBT. TF-CBT has undergone RCTs comparing it to other active psychosocial treatments and waitlist controls. Another study demonstrating that trauma-focused components are superior to no treatment or to an inferior (and potentially non-credible) comparison does not challenge the current paradigm about how the field is delivering treatment (e.g., therapist-directed, "full treatment package" for everyone), nor does it allow for the comparison of value, efficiency, and non-inferiority relative to the current standard treatment. Within an adaptive treatment model that matches children to the appropriate level of care, some children will need standard TF-CBT and understanding mechanisms of change will allow clinicians to tailor treatment. Standard TF-CBT consists of 12 sessions [88] although some children may need less or more treatment.[26] When 8 vs. 16 TF-CBT sessions were tested, only 54% completed all 16 sessions, whereas 72% completed all 8 sessions [26] suggesting that barriers to treatment or perhaps early improvement led to dropping out. It is likely that children who respond in fewer sessions would also have the characteristics of the children who would respond to Step One. To optimize treatment in future practice, children who respond early to TF-CBT would be assigned to Step One first. Consistent with our pilot work, children may receive two additional sessions (see 5.1.1.a.) allowing some children to receive 14 sessions.

STUDY DESIGN AND SAMPLE SIZE

c.4. Design/Randomization. Participants (N=216, ages 4-12) are randomized and will receive SC-TF-CBT or TF-CBT in a 1:1 ratio within community-based agencies. To ensure the two treatment conditions are balanced in regard to candidate first-stage tailoring variables, a randomized block design will be used. Based on pilot results (see c.1.3.), we will divide our sample into four cells based on whether the child has internalizing T- scores > or ≤71 and whether s/he has a critical life events score > or ≤16. Each cell will have equal numbers of children assigned to SC-TF-CBT and TF-CBT. See "Other Attachment" for study timeline.

c.4.1. Design Considerations. Why not conduct a Sequential Multiple Assignment Randomized Trial (SMART) to build the adaptive intervention?[34, 89] **1)** The adaptive SC-TF-CBT has been developed [4-6] and is at the developmental stage of comparing it to the standard in the field (i.e., TF-CBT). Many of the questions that would have been examined in a SMART, such as effectiveness with different ages,[25, 90, 91] different types of traumas,[25, 63, 92] different components and different lengths,[26] and with and without medication[93] have consistently suggested that standard TF-CBT is the recommended treatment. **2)** Our pilot studies, designed to inform this R01 application, documented that a first-line parent-led approach is feasible and acceptable, identified an estimated number of Step One responders, demonstrated the clinical utility of the responder status criteria, and identified candidate first-stage tailoring variables and second stage time-varying tailoring variable. Thus, there is ample evidence for testing the confirmatory stage of an optimized adaptive intervention with a randomized clinical trial in community settings. **3)** In order to re-randomize after non-response there typically needs to be least 35% to 65% non-responders,[94] and our preliminary data after Step One indicate that 22% were non-responders. Once the first-stage tailoring variables are identified and children can be matched to appropriate treatment at baseline, we anticipate that the Step One non-response rate would be even less.

c.5. Therapist Training. Prior to recruitment, therapists will receive detailed training in both SC-TF-CBT and standard TF-CBT (e.g., CBT, trauma narratives, establishing hierarchies, treatment protocols). Dr. Salloum will use audiotapes of SC-TF-CBT and standard TF-CBT sessions from the pilot study to train therapists. The therapists will participate in weekly clinical supervision with the PI, and quarterly and as needed clinical consultation with Drs. Cohen, Scheeringa, and Craske (see letters of support).

c.5.1. Treatment Integrity. Treatment integrity in both conditions will be vigorously monitored through the use

of therapy manuals and adherence checklists (c.6.7.) on-going supervision, and regular monitoring and rating of video or audio taped therapy sessions. Manualized treatment protocols have been designed in our pilot work to standardize treatment.

Given that treatment will be provided by community therapists who may not have experience with these treatments, and there may be turnover with new therapists starting mid trial, we think it is important for the integrity of the study to ensure that both treatments are provided as intended and that fidelity be monitored in real time as therapists begin providing treatment. For each study therapist, the project coordinator under the supervision of the PI will review the first case for each type of treatment (e.g., Step One, Step Two, standard TF-CBT). If the first patient ends treatment early, sessions from the next patient will be reviewed so that three sessions for Step One, 9 sessions for Step Two and 12 sessions for standard TF-CBT are reviewed for each therapist. The PI will provide feedback to the therapist if any fidelity ratings are not completely met. In cases where there might be adherence concerns the project coordinator, under the supervision of the PI will review additional cases.

Table 1. ***Study Visit and Assessment Schedule***

	Timeframe			
Characteristics, outcome variables, tailoring variables	Screening baseline	Mid (week 6)	Post (week 13)	6 and 12 month follow-up
Demographics, EPF, SCID, TWQ, BIS	X			
DIPA; K-SADS,*, TSCYC, UCLA PTSD Index, CSI-S, CSDS-P/C	X	X	X	X
CBCL, PCL-C, DASS, PSS, FASA, SDSC, RSS	X		X	X
CGI-I*		X	X	X
BTPS/*critical events	X		X	
CSQ			X	
Cost Measures				
CCI, SASA	X	X	X	X
TTTS	Every session/parent-child mtg. or activity			
Mechanisms of change				
CSDS-P, TSCYC (outcomes)	Every session and/or parent-child mtg.			
HR, SC. TASC (P, C, T) CPTCI	Weeks, 0, 2,4 = Step One & 0,5,8= TF-CBT And at post-assessment			
SUD, ENOs, CFT	Every session and/or parent-child mtg.And at post assessment			

* Trauma checklist section = every week in Step One. CGI-I = throughout treatment by therapists and caregivers. Critical events = baseline.

An independent rater will review study tapes (with parental permission) for adherence. The PI will train the rater using four cases from our pilot studies from each type of treatment (e.g., Step One, Step Two and standard TF-CBT). All three treatments address coping skills, trauma narrative and cognitive coping and processing. Therefore, to ensure that these components are being delivered as intended, the non-affiliated rater will review for each patient and for each treatment either one coping skills session, or one cognitive processing session, or one trauma narration session. The rater will be provided with a list developed by the biostatistician that specifies which component for each case and which specific session are to be reviewed. This list will ensure that at least one of the three components (coping skills, trauma narration, cognitive coping) is covered for each case for each treatment and that an equal number of specific sessions are reviewed. If a patient ends treatment prematurely, the last session attended of the coping skills, trauma narrative or cognitive processing component sessions will be reviewed. These procedures will result in an adherence rating for every patient and therapist, and 33% of the coping skills, trauma narrative and cognitive processing components reviewed for all treatments.

MEASURES

c.6. Brief Description of Assessment Measures. All patients will be asked to participate in assessments that will occur at screening/baseline, mid- post- treatment, and 6- and 12-month follow-up. Some data will be collected weekly (W). Demographic and web access information will be collected at screening (see Table 1).

c.6.1. Measures Regarding the Child: Child PTSD: Given empirical evidence for different manifestations of PTSD in children 6 and younger,[64, 65, 95] challenges of assessing PTSD directly with very young children, limited young child self-report measures,[96] and recommendations to include parent and child reports for older

children,[97] developmentally specific measures for child PTSD will be used. The Diagnostic Infant and Preschool Assessment (DIPA)[98-100] is a semi-structured diagnostic instrument administered with caregivers on mental health disorders specific to young children. The DIPA will be used to screen for suicidality, and the PTSD module will assess for presence of PTSD and total number of PTSD symptoms in children ages 4-6. The K-SADS is a structured interview to assess for diagnostic criteria for children ages 7 and older. The child/parent versions will be administered independently to assess for the presence of PTSD and total number of PTSD symptoms. Sections of this measure will be used with all parents and with children ages 7-12 to screen for exposure to traumatic events (types and number; W), psychosis, mental retardation, autism spectrum disorder and child suicidality. The Trauma Symptom Checklist for Young Children (TSCYC)[101, 102] is a caregiver report measure of trauma symptom severity in children ages 3-12 years that includes a 27-item PTS symptom total subscale (PSS-total). The UCLA PTSD Index for DSM-5 is a 31-item child-report (ages 7-12) measure of child PTSD symptom severity with a clinical assessment of impairment. The Child Behavior Checklist (CBCL) for children ages 1½ to 5 years[104] or ages 6-18[105] will be completed by the caregiver to assess behavioral and emotional functioning across a variety of domains (e.g., internalizing and externalizing). The Brief Impairment Scale (Briere, #99)[84, 106] is a caregiver reported multidimensional scale of child functional impairment that has good psychometric properties with young and older children. To further examine impairment, the Family Accommodation Scale-Anxiety (FASA; Lebowitz, et al 2012), Sleep Disturbances Scale for Children (SDSC; Bruni et al., 1996) and Rage Severity Scale (RSS) will be administered as exploratory measures. The Clinical Global Impression-Severity (CGI-S)[107] is a widely used 7-point rating of severity of psychopathology including impairment (0=no illness, 6=extremely severe). As in our pilot studies, the Clinical Global Impression-Improvement (CGI-I)[108] modified version, 8-point rating will be used for treatment response (1, 2, 3)[66] and clinical worsening (see 5.1.). The Child Sheehan Disability Scale (CSDS-P)- parent version will be used to measure childhood impairment (Whiteside, 2009) and will be used as a primary outcome. The Child Sheehan Disability Scale (CSDS-C) child version (3-items) will be used to measure childhood impairment (Whiteside, 2009) and will be administered to children ages 7-12 (exploratory measure).

c.6.2. Measures Regarding the Parent. The Structured Clinical Interview for DSM-IV-TR Axis I Disorders, (SCID-RV) [109] or soon to be SCID-5-PD will be used to screen parent psychosis, SUD, and suicidality and assess PTSD and depression diagnostic status. The PTSD Checklist-Civilian (PCL-C)[110] is a 17-item parent self-report of PTSD symptom severity. The Depression Anxiety and Stress (short form) will be used to measure parent depression (Page, Hooke, & Morrison, 2007). The Parenting Stress Scale (PSS) Is a 18-item measure of parenting stress (Berry & Jones, 1995). The Barriers to Treatment Participation Scale (BTPS)[113] is a 58-item measure of perceived barriers to treatment. The critical events subscale consists of 14 life events that might affect treatment participation (range=14-28). Consistent with other studies,[114, 115] parents will provide anticipated critical events.

c.6.3. Measures of Acceptability and Satisfaction. Expectancy Rating Form (Horwitz, #81)[116] is an adapted version concerning the parent's expectations of treatment success and treatment credibility (B). Client Satisfaction Questionnaire (CSQ)[117] is an 8-item self-report measure to assess satisfaction with counseling services.

c.6.4. Costs Measures. The Therapist/Patient Time Tracking System (TTTS)[82] is a tracking system of associated therapist and patient time for delivering both conditions completed by the study therapists (W). The Costs Characteristics Information (CCI)[81] measures estimated costs such as out-of-pocket expenses for treatment, lost income due to missing work to attend therapy, patient time associated with treatment, and other cost-related information. The Service Assessment for Children and Adolescents (SACA),[83] a psychometrically sound parent interview about the broad use of mental health services, will track other service use.

c.6.5. Mechanism of Change Measures. Children's fear habituation: Children's fear arousal/distress will be measured using physiological measures and child self-reports which take into account the NIMH RDoc negative valence system domain.[118] 1) Fear-based autonomic arousal will be assessed by measuring children's heart rate (HR) and skin conductance (SC) responses according to published guidelines.[119, 120] Children's pulse waves and skin conductance will be collected using the E4 wristband that looks very much like a wristwatch. It will be attached around the wrist of the child's non-dominant arm For the autonomic fear response protocol, children will first engage in a brief 5-minute resting period to allow them to acclimate to the environment and the recording equipment. A "vanilla baseline" procedure [121] will be used such that children will watch a mildly engaging, emotionally neutral film clip appropriate for their age. Following the resting baseline, children will be asked to engage in a 5-minute structured interview about their trauma.[122-124] Reactivity will be assessed as the

change in HR and SC responses to the interview relative to baseline. 2) A subjective unit of distress (SUD) scale which is commonly used[125] will be rated by the child using a developmentally appropriate SUD rating (i.e., "scary feeling score," 0-3 or 4). Prior research with young children[35] as well as our experience suggests that children age 4 and older understand the rating scale and can provide these data. Similar to our pilot work, children will provide six ratings during exposure or trauma-related activities and parents will record these ratings. In TF-CBT, the child ratings will be recorded by the therapist. The first rating will occur before the exposure/activity, four during the activity with the highest being recorded as the peak rating and one after the exposure/activity. Changes in trauma-related negative appraisals: The *Post-Traumatic Cognitions Inventory-child version (CPTCI)*,[126, 127] is a 25-item child report of negative trauma-related cognitions. The CPTCI has demonstrated excellent psychometrics and no age-related differences in scores for children ages 6-18. The measure will be administered with children ages 6 to 12 (~78% of the sample). Expectancy of negative outcomes (ENOs): The *ENOs* measure, modified from Craske et al.[128] and similar to Deacon et al.,[76] is a 3-item parent report of the child's perceived expectancy of a negative outcome that is rated (0 to 100) before and after the trauma-related activity. Children's fear toleration (CFT): Similar to Deacon et al.,[76] parents will rate (0-100) the extent of the child's fear toleration when participating in the trauma-focused activity. Therapeutic worry and alliance will also be examined as potential mechanisms of change which will be measured using the treatment worry questionnaire at baseline only (child and parent version) and the Therapeutic Alliance Scale for Children (TASC, parent, child, and therapist version) administered the same assessment time periods as the HR and SC (i.e., Weeks, 0, 2,4 = Step One & 0,5,8= TF-CBT and at post-assessment) (Keeley et al. 2011). As indicated in Table 1, the mechanism of change measures will occur at post-assessment too. The "trauma-related activity" will be a 5 minute semi-structured interview that consists of the same guide that is used during the HR and SK test. After these measures are completed the parent and child will be asked independently 6 questions about their experiences talking about what happened, including how they may have changed. These responses will be used to triangulate the quantitative measures.

c.6.6. Plan to explicitly address whether the intervention engages the mechanism. To demonstrate that the hypothesized mediators changed before the primary outcomes,[129] we will administer the assessments of the mediators and primary outcomes during the course of treatment. Parents will complete the primary outcome measures TSCYC-PTS total and the Child Sheen Disability Scale- parent version during the five outcome assessment periods, and at the beginning of each therapy session and/or parent-child meeting. We used the parent rating of child PTS since the TSCYC is for children ages 4 to 12 and to minimize the burden of children completing another measure every session.

Within session ratings. Parents will rate fear toleration and negative expectancy after each trauma-related activity in therapy sessions and parent-child meetings. As in previous NIH-funded clinical trials (PI: Scheeringa, study therapist Salloum, R34MH070827-01A1; 1RC1MH-088969-01), therapist-directed sessions will be video taped. We will systematically identify the child's participation in the trauma-focused activity within each session and have parents review that segment via video (~15 min.) during the beginning of the time when the parent meets with the therapist. These research procedures will not significantly influence treatment outcome as discussing with the parent what the child completed in therapist-led sessions is current protocol for both treatments, and similar procedures have been used in previous trauma-focused clinical trials with children 3-12.[25, 130] This procedure allows the parent to have direct observation of the child and allows the parent time to process the observations with the therapist. Viewing video segments will not be needed when there are conjoint sessions. For the at-home parent-child meetings, the parent will complete the ratings immediately after the meetings. Children will complete the *CPTCI* at the beginning of Weeks, 0, 2,4 in Step One & 0,5,8 in TF-CBT and the SUDS rating during treatment. For Step One, measures will be in the parent's *Stepping Together* book, and therapists will collect these measures at each meeting and will remind parents about the measures during the phone meetings. Since Step One and TF-CBT occur within different timeframes (6wks vs. 3mo), the physiological measures will be administered based on when components are covered and during scheduled in-office visits for Step One patients: at session 1, after the coping skills components, and after four exposures in Step One or the trauma narrative in TF-CBT (Table 1). The frequency of four potential mechanism of change measures (e.g., fear based arousal measure (subjective unit of distress), trauma-related negative appraisals, expectancy of negative outcomes, and fear toleration) will be 12 for both conditions. Step One patients will not complete these measures during parent-child meetings 1 and 2 as these meeting occur directly after the first therapist meeting.

c.6.7. Fidelity Measures. All of the fidelity measures were successfully utilized in the pilot trials of SC-TF-CBT.

The Parent Completion and Effort Rating (PCER) adapted from Tolin et al.[131] was developed in the pilot trial of SC-TF-CBT and includes a therapist rating of parent's completion of homework tasks and the amount of effort the parent put into completing tasks (W). The Adaptation Checklist-Child (ACC)[132] has been adapted to a checklist of task completion for Step One. Therapists rate (0 to 1) if the child completed the activity in the parent-child workbook to track the extent to which the prescribed CBT tasks were completed (W). The Step One Treatment Checklist (SO-TC) is a 38-item checklist developed in the pilot trial of SC-TF-CBT to track therapist adherence to Step One of SC-TF-CBT (W). The Standard TF-CBT Treatment Checklist (S-TF-CBT-TC)[133] is an 11-item checklist to monitor the integrity of administering TF-CBT components (W).

c.6.8. Tailoring Variables. (described in c.6.1 & c.6.2.). The internalizing T-score and the critical barriers score will be used as first-stage tailoring variables. For second-stage tailoring variables, the trauma checklist on the ADIS-P/C will be used to track new traumatic events; the PCER and ACC will be used to measure adherence; and the ADIS-C/P, DIPA, TSCYC, CPSS, and CGI-I will be used to measure responder status.

c.7. Rater Training and Ensuring Blindness. Dr. Storch has extensive expertise on administering study measures and will be the lead trainer on measures. At study start-up, Dr. Storch will provide a day training on administering study measures and Dr. Scheeringa will provide a half-day training on assessing trauma in children. The start-up training will consist of a review of each measure and the IE and GRA will independently rate the DIPA, ADIS-C/P, CGI-Severity, CGI-Improvement and SCID based on four audiotaped assessments from SC-TF-CBT pilot studies. Therapists will read several case study vignettes for the CGI-Improvement ratings. Ratings will be reviewed and discussed with Dr. Storch. Dr. Storch will provide weekly clinical supervision for the IEs. Measures will be taken to ensure IE blindness of the conditions (e.g., not attending clinical meetings, reminders to patients to not disclose assignment). The therapists and participants cannot be blinded to treatment assignment. 20% of IEs audiotaped interviews will be blindly reviewed by the Graduate Research Assistant under Dr. Storch's supervision to assess inter-rater reliability and rater drift. If concerns are noted, the IE will not conduct another assessment until assessment procedures have been reviewed.

c.8. Data Analysis

c.8.1. Overview. As in the R34 study, Dr. Wang will design a customized web-based randomization, data entry and management system for this project. We will use Qualtrics, a widely used secure web-based software package to collect data. Therapist will also use Excel to enter de-identified fidelity and cost data. Data will uploaded to Box. (see Protection of Human Subjects 5.1.1.a.). Dr. Wang will work closely with the PI on the development of the data management system and with the PI/ Co-Is in the data management/analysis of the psychological, physiological and cost-related data.

c.8.2. General Analytic Plan. Descriptive and graphical statistics will be used to summarize the data on all randomized patients and to confirm that there are no group or site differences (p<.10) in baseline demographics and clinical characteristics. If, for example, site differences are detected, we will account for it by including site indicators as fixed effects in the model. Distributional assumptions will be checked and appropriate transformations or non-parametric methods will be applied as necessary. For Primary Aim 1, we will use methods that are based upon establishing equivalence or non-inferiority of outcomes across treatment arms. These methods are used classically to evaluate whether a new treatment or condition is not inferior to an existing treatment. In general, Generalized Linear Models (GLM)[135] will be used throughout. These models account for deviation from normal assumption of the dependent variables and to control for baseline covariates including patients' demographics and corresponding child and parents assessment measures. For Primary Aim 2, GLM will be used to quantify the relation between the value of the tailoring variables and the propensity of not responding to Step One. For Primary Aim 3, latent difference score models (LDS) will be applied. We will mainly use SAS 9.3 and Mplus 7.1[136] for GLM and mediation analysis. For Primary Aim 4, a cost effectiveness analysis (CEA)) will be performed. CEA measures the incremental cost per unit improvement in outcomes. In the absence of outcome differences, costs will be examined using GLM.

c.8.3. Specific Analyses for the Individual Study Aims

Primary Aim 1: For the primary and secondary hypotheses, one-sided tests for non-inferiority will be applied as our goal is to show that the performance of the children in SC-TF-CBT will demonstrate comparable improvements to children in standard TF-CBT. For this non-inferiority test, the null hypothesis is written as H_0: $\mu_1 - \mu_2 > r^*$, where μ_1 denotes the average improvement in standard TF-CBT and μ_2 denotes the average improvement among children in SC-TF-CBT, and r* represents the clinically significant difference expressed as common standard deviation units. The test will be applied to child outcomes, acceptability/satisfaction levels and parent outcomes that will be measured at post-treatment and at 6- and 12-month follow-up respectively.

Rejection of the null hypothesis will indicate that treatment outcomes of SC-TF-CBT are comparable to those from standard TF-CBT. For child and parent outcomes only, we will further apply GLM with repeated measures to detect whether the two treatment groups perform differently at any one time point. We will also document the percentage of responders to Step One and numbers and reasons for trigger and switch.

Primary Aim 2: To examine tailoring variables that could be used to individualize the decision of which children should be assigned at baseline to SC-TF-CBT versus standard TF-CBT, we will compare the responders/non-responders of Step One with regard to the value of the tailoring variables. Based on results from pilot studies, we hypothesized that children with more internalizing problems at baseline and those from families with potential life event barriers are less suitable for SC-TF-CBT. A Chi Square test will be first applied to evaluate the association between the dichotomized candidate tailoring variable and responding status. Next, we will use GLM, in which responding status will be treated as the dependent variable and tailoring variables as continuous predictors. To further quantify the relation between the value of the tailoring variables and the propensity of not responding to Step One, we will include in the GLM the products of the tailoring variables to evaluate their interactions. Demographics will also be controlled in the model. While it was not a primary aim, we will further explore whether race/ethnicity or gender moderate the dropout rate and treatment outcomes (see 6.). This will be done in a separate analysis where interactions with treatment condition are included.

Primary Aim 3: We will examine four potential mechanisms of change on both Step One and TF-CBT including fear arousal, maladaptive cognitions, expectancy of negative outcomes, and fear toleration. The analysis of mechanism of change will have two phases. First, we will run univariate latent difference score (Goldstein, #1) models on the longitudinal observations of potential mediator and outcome variables. Since the fear-arousal variables (HR and SC) that both assess sympathetic nervous system activation are typically correlated,[137] and combining physiological responses into single indices is common (e.g.,[138-140]), we will attempt to combine them into a single index. LDS incorporates features of latent growth curve modeling and cross-lagged regression models and is appropriate in research on mechanisms of change.[141-143] We will compare univariate LDS models for time invariant and time-varying proportional coefficients as well as a no change score LDS model to find the model that best depicts the mechanism. The model selection process will run independently across all potential mediators and outcome variables. Second, we will run bivariate LDS by pairing between two univariate LDS models that have been identified. These pairings include mediator-mediator, mediator-outcome, and outcome-outcome types. We will identify coupling pattern by comparing three candidate models (within the bivariate LDS models): no coupling between the two series, unidirectional coupling in which the change in one variable leads to the other, and bidirectional coupling or cross lagged pattern. For the secondary hypothesis 3.2., we will add a time varying qualitative indicator for direct exposure activities and its interaction with the change component. A significant interaction term indicates the mechanisms are different for the more direct (i.e., Step One) and less direct exposure activities (i.e., TF-CBT). We will also use open coding methods to capture a range of categories related to children and parents experience of talking about the trauma narrative (a trauma related activity used during the mechanism of change measures) and changes that may have occurred during treatment. Thematic content analysis (Patton, 2002; Corbin & Strauss, 2008) will be used to establish the range of participants' experiences and changes.

Primary Aim 4*:* CEA examines the relative value of SC-TF-CBT (versus standard TF-CBT).[144] CEA is performed from a societal perspective, meaning the costs to the health care system and the patient/parents are included.[145] Treatment costs include direct (e.g., cost of therapy session), indirect (e.g., travel costs, missed work), and opportunity costs (e.g., value of lost time; see c.1.5. & c.7.4. for cost measures). CEA often incorrectly omits the opportunity cost of patient/parent time spent on therapy, phone support, and at-home parent-child meetings.[146] Non-study mental health service costs include inpatient, outpatient, and school-based services and will be priced using the Florida Medicaid fee schedule. Research-specific costs (e.g., screening, research consent) for patients and staff are excluded. GLM will be used to examine differential treatment costs for SC-TF-CBT and standard TF-CBT. GLM can account for the likely skewed distribution of costs, differences in child characteristics, and a potential lack of independence within treatment locations.[147] Incremental cost effectiveness ratios (ICER) are computed as incremental costs divided by incremental changes in morbidity/outcomes (symptom reduction and change in impairment/functioning). A single outcome measure (e.g., Quality Adjusted Life Years) might be preferable,[145] but no established parameters for estimating morbidity in young children with trauma exist.[148] If outcomes differ significantly, a non-parametric bootstrap with replacement method is used to generate a joint distribution of differential costs and outcomes.[149] If outcomes do not differ, cost-effectiveness is determined by comparing treatment costs. Mean and median ICER ratios are reported as well as 95% confidence

intervals. Cost-effectiveness acceptability curves examine the probability of falling below a variety of cost-effectiveness thresholds.[149] In addition to the ICER approach, the net-benefit approach[150] will be used to determine if findings are sensitive to method. If tailoring variables effectively distinguish children who respond to Step One, CEA will also be performed for children with low scores on tailoring variables. CEA will not be performed for children with high scores on the tailoring variables since the preliminary data indicate that standard TF-CBT is necessary for these children (c.1.2.). Race/ethnicity and gender differences in CEA will be assessed if treatment outcomes vary (see 6. Inclusion of Women and Minorities).

c.9. Sample Size Considerations and Power Analyses. We will enroll a total of N=216 subjects with a 1:1 randomization between SC-TF-CBT and standard TF-CBT. Based on our successful track record in obtaining post and follow-up data in our R34 SC-TF-CBT trial (only 3.77% missing post- data, and 6.1% missing 3-mo. follow-up data, N=53), and the PIs previous child trauma clinical trial with a 1-year follow-up (8.57% attrition),[151] we conservatively anticipate 15% attrition at post-assessment resulting in 184 subjects (92 per group) and a 10% lost to follow-up at 6- and 12-months resulting in 166 subjects (83 per group) and 150 subjects (75 per group), respectively. Sample size requirement was determined by CEA for Primary Aim 4 and it also provides sufficient power for Primary Aims 1 to 3 under various assumptions. **Primary Aim 1**, Hypothesis 1.1, the study will have 80% power to show that SC-TF-CBT is at least as effective as standard TF-CBT. This assumes an alpha of .05, sample size of 92 per group after attrition and a difference of 0.41 SD units or less as unimportant. We expect to maintain the same power of 80% in testing the hypothesis (1.2.) that focuses on the outcomes at follow-up (6- and 12-months). Though we may lose an additional 10% of participants at each follow-up point, reduction in measurement error through repeated measures and use of multiple imputation method will mitigate the sample size loss. For **Primary Aim 2**, 80% power will be achieved for detecting responding rates difference between 62% and 30%, 72% and 40%, or 80% and 50%. This assumes that we divide the patients into two equal size groups based on the tailoring variable value with a total of 92 patients (SC-TF-CBT condition only). For **Primary Aim 3**, we will have >80% power to detect a small to moderate effect (0.29) in a unidirectional bivariate latent different score model with complete longitudinal observation for the 184 children under both conditions (for analyses involving CPTCI, the detectable effect size is 0.33). For the secondary hypothesis 3.2., we have moderate power (.57) to detect different strengths of the unidirectional prediction between the two conditions (e.g., 0.15 vs 0.45 or .00 vs .30; for the CPTCI, the power for the same comparisons is .55). For **Primary Aim 4**, the study will have 80% power to detect cost differences between SC-TF-CBT and standard TF-CBT, assuming medium effect size (.5), an alpha of .05 and sample size of 92 per group. The sample size will also be sufficient to maintain 80% power to detect a medium effect size for children with low values for the tailoring variable, and to detect a large effect size for children with high values.

c.10. Attrition and Missing Data. Overall retention rate at each data point is expected to fall within the acceptable range, with percentages of missing data well within acceptable ranges for statistical correction (10 to 15%). The IE will be alerted via Qualtrics™ if any items are missing during assessment and any paper-and-pencil measures will be visually screened for any missing items. Participants will be asked if they want to complete any unanswered items. Every effort will be made to prevent dropouts/missing data, and to complete relevant assessments for patients who drop out or are withdrawn, including reasons why treatment was ended. As is typical in longitudinal research, we must anticipate non-random missing data. We plan to use multiple imputation methods developed by Schafer.[152]

Amendment to the analysis plan 2.11.2022

Aim 1. We applied linear mixed-effect models (LME; SAS Institute Inc, 2015) with repeated measures to detect whether the two treatments performed differently at post-, 6- and 12-month assessments. Instead of 5% alpha we used a more stringent 2.5% alpha (Piagio et al, 2012) for the non-inferiority analysis with the .41 margin. For the non-inferiority margin for the PCL-5, the clinically significant change threshold is 10 points although adult PTSD trials have used -5 (Foa et al., 2019) to -10 (Mathersul et al., 2019) points. We used -8.8 as the margin which was based on an expert panel and prior studies with adults (Acierno et al., 2017). Due to attrition (27.87%) being higher than planned (15%) and enrollment (N = 183) lower than the planned enrollment (N = 216), the power analysis was based on the actual randomization of 183 participants (SC-TF-CBT=91; standard TF-CBT=92).

Aim 2. We used backward stepwise logistic regression with predictors with p <. 01. Besides predictors in the unadjusted model, demographics including children gender, age and race were included in the partially adjusted

model. In addition, three child primary outcomes were added for the full adjusted model.
Aim 3. Instead of LDS we used Linear mixed-effect models (LME) with repeated measures were used to detect whether the potential mechanisms of change declined significantly over time and whether the rate of change differed by treatment group with standard TF-CBT coded as 0 and Step One responders coded as 1. Further, we tested mediation and moderated mediation. If moderated mediation was not found mediation was tested with two regression equations: the first equation included mediators regressed on treatment condition and outcome variables at baseline; the second equation included outcomes regressed on treatment condition, mediators, and outcome variables at baseline. If there was no evidence of significant mediation, linear regression model (OLS) was applied to test the linear estimates as predictors for both outcome (TSCYC-PTS and CSDS-P).
Aim 4. A cost comparison analysis of SC-TF-CBT and TF-CBT was performed instead of CEA, given the non-inferiority results. We used generalized linear models using a loglink to determine if differences in costs between the two treatments were statistically significant (two-tailed tests). Effect sizes were estimated based on the logged cost values and statistical significance was inferred via bootstrapped estimation (Algina et al., 2006).

References for analysis amendment

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Note. 8.7.2020. De-identified data will be shared with University Children's Hospital Zurich (Lasse Bartels, M.Sc and Prof. Markus A. Landolt, Ph.D). The de-identified data will be used for the following aims: a) to verify the validity of the current CBCL PTSD subscale for young children by comparing it to a DSM-5 based measure and b) to potentially develop an alternative CBCL PTSD subscale for young children.

5.1 PROTECTION OF HUMAN SUBJECTS

5.1.1 Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

Participants will be 216 children ages 4 to 12 years who have been exposed to traumatic event(s) and who are experiencing at least five PTSD symptoms. Parents/guardians must be able to provide written consent in order for their child to participate, and the parent/guardian must be willing to participate. Male and female parents and children will be included. There are no participant restrictions on ethnicity, social background, or gender. Study participation is entirely voluntary. If at any time a participant wishes to discontinue study participation, they can notify the PI and the participant will be withdrawn from the study at that time without any adverse consequences. It is necessary to include children in this research because the study aims focus on how to optimize the efficiency and cost-effectiveness of Stepped Care TF-CBT, a personalized adaptive intervention for traumatized children ages 4 to 12 years, under "real world" settings (i.e., in community mental health clinics).

Recruitment will occur at two community mental health clinics in Florida that specialize in mental health treatment for children who have experienced trauma: The Crisis Center of Tampa Bay (CCTB; Hillbsbrough County) and Pasco Kids First (PKF; Pasco and Hernando Counties). A back-up agency, Suncoast Center Inc (Pinellas County). Children's Home Society Duval, Clay, Baker, Nassau, and St. John) USF St. Petersburg Family Study Center (Pinellas County) and Directions for Living (Pinellas County) will be involved if recruitment goals are not being met (see Other Attachment). The role of these sites will be to recruit patients, coordinate study procedures with the Project Coordinator, comply with all study procedures and Institutional Review Board (Ebert, #51) requirements, and provide study treatment. Parents/guardians who seek trauma-focused services at these two/three community centers and have children between the ages of 4 to 12 years will be informed about the study and if interested, participate in a brief phone screening prior to setting up an assessment. Consistent with our approved study protocol implemented for our NIMH R34 Stepped Care TF-CBT grant, data will be obtained on site at the community centers. These centers currently provide psychotherapy and comply with confidentiality procedures consistent with agency policies including being compliant with the Health Insurance Portability and Accountability Act (HIPAA). For the proposed study, participants and/or research staff (e.g., independent evaluator, graduate research assistant, therapists) will enter scale responses directly into Research Electronic Data Capture (Qualtrics™) software system. Qualtrics™ is a secure web application (the site is encrypted using SSL and is backed up nightly) designed to manage on-line surveys and databases for clinical trials. Data captured in Qualtrics™ can be easily exported in statistical packages such Mplus, SAS and SPSS. USF is an institutional partner of Qualtrics™. Subjects will have access only to complete their own scales. Fidelity ratings will be entered into Excel by the study therapists which can be easily converted to SPSS. All computer-generated data will be maintained in password-protected computers. Any measures collected on paper such as the mechanism of change measures will be double data-entered into Qualtrics™ and paper documents will be stored in the PIs office in locked filing cabinets at USF. No patient names will be recorded on assessment information as each participant will be assigned a record number. A separate record linking the code numbers to participant identifiers will be kept in a locked file, completely separate from the data.

The study design consists of a randomized clinical trial where all participants will receive empirically-informed treatment based on TF-CBT, a well-established treatment. Specific inclusion and exclusion criteria are listed in Research Strategy (see Research Strategy section c.2.2.). The exclusion of non-English speaking patients is due to methodological issues and costs of including children and parents who speak other languages (e.g., measures and the parent-child workbook would need to be translated, and study staff would need to speak other languages). If findings are significant, the next step in the development of Stepped Care TF-CBT would be to provide the protocol in other languages (e.g., Spanish). Of note, in our pilot trials on Stepped Care TF-CBT, 35.8% of the child participants were Hispanic/Latino. In addition, any medication issues related to study exclusion will be discussed with the consulting psychiatrist, Tanya Murphy, M.D., who may contact the prescribing physician (see 5.1.1. c.). In our previous trials on Stepped Care TF-CBT, only 1.4% (6 of 419) screened out due to medication related factors.

Patients will be randomly assigned to either Stepped Care TF-CBT or standard TF-CBT. Once the patient has enrolled in treatment, we will allow for up to two contact sessions outside of the standardized treatment protocols regardless of condition. This flexibility of additional sessions to address individualized treatment needs is common in community mental health practice and this flexibility will be used to maximize retention. Other strategies to maximize retention include setting clear expectations about the research process, compensation

for assessments, transportation to the center for the assessments (if needed) and supervision of siblings during appointments (if needed).

b. Sources of Materials

The sources of research material obtained from each human subject will be in the form of information gathered specifically for research purposes. This will include data from the psychological assessments, behavioral rating scales, physiological measures (e.g., heart rate and skin conductance), cost-related data, and session/interview content. Data obtained from this study will be from individual meetings with the parent and child where they will be asked the questions from the listed measures or IE or therapist ratings of adherence and time. Data gathered from parents will be reports about their children or data about themselves. Data for treatment integrity will be obtained from videotaped therapy sessions (with the permission written consent from the parent and the therapist).

To protect subjects' confidentiality, only authorized persons from the University of South Florida, the sponsor (NIMH), and the USF Institutional Review Board will have the right to review research records. Confidentiality of those records will be protected to the full extent permitted by law. Research records will be kept secured in a locked archive and will not be released without the subject's consent unless required by law (e.g., suspected abuse) or a court order. When the results of this research are published or presented at scientific meetings, the identity of subjects will not be disclosed.

c. Potential Risks POTENTIAL RISK
Note. While [redacted] is on [redacted] Dr. Storch will serve in [redacted] role.

Please note, on 10/12/18 IRB approved an agreement where Baylor College of Medicine/PI, Eric A. Storch, PhD will be relying on USF IRB Approval. See IRB letter dated 10/12/18, RE: Approval to Proceed Ext00000337

Potential risks associated with this study may occur due to parents and children participating in assessments, participating in psychotherapy, and minimal intervention during the follow-up period. The potential risk of participating in the evaluations may result in discomfort discussing traumatic experiences, discomfort answering other subjectively difficult questions, or discomfort due to the time needed to complete the assessments. With regard to potential discomfort in answering questions, our experience indicates that many people welcome the opportunity to discuss their experiences with a trained clinician. The parents who are consenting to participate are aware that this study is for children who experienced a traumatic event and parents often welcome the opportunity to talk with a clinician about what has happened. If at any time a parent or child becomes overwhelmed during any assessment, we will pause or stop depending on the degree of distress. It is possible that the adhesives for the skin conductance test may cause skin irritation, and parents and children will be made aware of this possibility via the written consent and assent process and verbally prior to administering the tests. These electrodes are non-invasive and relatively unobtrusive. During the assessments, breaks will be given as often as possible to decrease boredom and physical/psychological discomfort.

If a child's symptoms worsen, whether the deterioration is linked to the treatment or not, we will discuss with the parent clinically appropriate alternatives, such as increasing therapist-directed therapy sessions during Step One (additional sessions are included in the protocol for situations where children need more therapy), stepping up to Step Two to receive therapist-directed TF-CBT, having a child undergo psychiatric evaluation to determine mental health status, or discontinuing the study and engaging community resources for additional help. Two additional therapy sessions are included in the study protocol for those situations where crises or worsening of symptoms occur (examples may include sexual aggression, danger to self or other). If clinical worsening occurs during treatment, the therapist will discuss this in team meetings. The therapist, parent and child (ages 7-12) will complete the CGI-I at each visit. As used in our pilot studies on Stepped Care TF-CBT, clinical worsening is operationalized as a therapist, parent, child or IE rating of 8 ("very much worse"), 7 ("much worse") or three consecutive ratings of 6 ("minimally worse") on the CGI-I. Three consecutive ratings of minimally worse instead of one rating of minimally worse was stated because it is possible that some children may exhibit some regression when processing the trauma narrative, thus resulting in a temporary minimally worse rating. As previously planned, the parent, child, and IE will complete the CGI-I at post-treatment and follow-up. The therapist will complete the CGI-I after every face-to-face session and one time a week via phone sessions during

Step One to consistently monitor possible clinical worsening. If clinical worsening occurs, the PI will consult with Dr. Storch about the appropriate course of treatment, which may include additional sessions, having a child undergo psychiatric evaluation to determine their mental health status and/or discontinuing the study and seeking additional help from community resources. If an additional session is indicated, the therapist will plan for the individualized session during the weekly team meeting so that an individualized targeted plan for the session(s) can be developed based on the noted concern(s). Including additional sessions does not compromise the integrity of the intervention, while balancing the well-being of participants. On balance, the majority of families in our pilot studies on Stepped Care TF-CBT and standard TF-CBT reported symptom reduction and improvement in functioning following participation.

Tanya Murphy, M.D. Professor and Rothman Endowed Chair, Director, Rothman Center for Pediatric Neuropsychiatry at the University of South Florida has agreed to be involved as an independent consultant who would be available to consult with the PI to make judgments about the appropriate course of treatment for children with ratings of clinical worsening. Dr. Murphy will not know treatment assignment. Dr. Murphy worked with Dr. Salloum on the NIMH R34 Stepped Care for Young Children study in this capacity where she reviewed cases with clinical worsening (4 occurrences of 53 children enrolled in treatment) or clinical concerns (5 occurrences of 53 children enrolled) such as encopresis, passive suicidal ideation, or inappropriate boundaries with other children. Dr. Murphy also met quarterly with Drs. Salloum (PI) and Wang (Co-I) to discuss tolerability and safety. Through this work, Drs. Salloum and Murphy have established a strong working relationship. Dr. Storch (Co-I) also has a long collaborative relationship with Dr. Murphy in the Departments of Pediatrics and Psychiatry at the Rothman Center for Pediatric Neuropsychiatry. Dr. Murphy is board certified in child and adolescent psychiatry and general psychiatry, has a Master's degree in Clinical Investigation, and has considerable experience conducting federally-funded clinical trials with children (e.g., 1R01MH078594-01; see Dr. Murphy's biosketch).

While it is possible that the viewing the brief segments of the child's session via video will affect the parent's distress level, parental distress about the child's trauma and depression did not mediate the effect of treatment (TAU and TF-CBT) on child PTSD symptoms, although there was an effect on child depression.[39] Sharing and discussing with the parent what the child completed in therapist-led session is current protocol for both treatments, and similar procedures have been used in previous trauma-focused clinical trials with children 3 to 12 (PI: Scheeringa, R34MH070827-01A1; 1RC1MH-088969-01). Research has shown that parent distress about the child's trauma improved during participation in TF-CBT.[20] If parents experience discomfort during the treatment, we will provide supportive counseling as part of the treatment. However, if parent distress continues and psychiatric attention is needed, parents will be provided with a list of community mental health resources. Parent participation in individual therapy outside of the study is not an exclusion criterion. If a parent participates in other therapy we will document this but will not exclude parents who are participating in their own therapy since we are not providing parent-focused mental health treatment. The treatment is child-focused although it is likely that some parents will benefit psychologically from their child's participation in treatment as well as from the supportive counseling that will be provided in both treatment arms.

Potential risks associated with this study may occur with the therapist as well who will be employed by one of the three agencies. Therapists must voluntarily agree to participate as a study therapist by notifying their agency Project Director. The agency Project Director will then inform the PI of the study therapist that will participate, and the PI will review the study and informed consent with the therapists. Therapists will provide written consent to participate as study therapists and will be informed about videotaping sessions, sessions being reviewed for adherence, process to maintain at least a 90% adherence, inter-rater agreement procedures, and disclosure of persistent non-adherence to the agency Project Director. If adherence drops below 90%, the PI will discuss adherence with the therapist. If there is a concern about adhering to the prescribed tasks, the clinical team will review the tape and any other relevant data to discuss if the therapist needs additional training and a way to maintain high treatment fidelity (see 3.c.5.1.). If adherence continues to be below 90%, the PI, therapist and agency Project Director will discuss how to help the therapist maintain adherence and/or the subcontracted agency will develop a plan of action.

Consistent with NIMH funded TF-CBT studies (J.A. Cohen, personal communication, November 14, 2013), all subjects who have clinical worsening at post-assessment (or anytime during the follow-up period) will be offered up to 3 booster sessions; if there is no response, they will be offered open treatment which may consist of additional TF-CBT sessions or more focused behavioral interventions. At the end of the study, patients will be referred to community open treatment if needed.

Dr. Salloum or Dr. Storch will be available at all times to study participants in the event of a clinical emergency; both this availability and relevant contact information for emergencies will be clearly communicated orally and in writing to study participants.

Procedures for suicidal ideation

Children exposed to trauma may experience suicidal ideation which may be reported at baseline and throughout treatment. Following is the plan to monitor suicidal ideation:

Suicidality is a study exclusion:" **3)** Child or parent is suicidal. A delayed entry once the parent or child is stabilized (> 6 months post suicidal) and not having suicidal ideation will be allowed if appropriate." As stated in the application, parents will be screened at baseline using the SCID (First, Spitzer, Miriam, & Williams, 2002) for suicidal ideation and suicidality. The IE will administer the semi-structured interviews about child suicidal ideation using the DIPA (Scheeringa & Haslett, 2010) or ADIS (Silverman & Albano, 1996) during the baseline, mid-treatment, post-treatment, 6- and 12-month follow-up. We will use the specific questions in the depression modules that inquire about suicidal thoughts, plans and past attempts. As with our pilot trials, if the answer is yes to any of these questions, we will inquire about the specific plans, time of occurrence, frequency, details of attempts, and current ideation. If the child is actively suicidal we immediately will make the appropriate referral for further evaluation and potential hospitalization. The community-based agencies are already well-trained in procedures when a patient is suicidal (i.e., the Crisis Center of Tampa Bay hosts the 211 emergency line and also has an ambulance service that transports suicidal patients), but we will provide additional training and the PI will be notified immediately. Parents will also be provided with appropriate community resources in instances of child or parent suicidality. Similar to our R34 study, Dr. Salloum will consult immediately with Dr. Eric Storch in cases of suicidal ideation and suicidality (although consultation in cases requiring immediate attention such as hospitalization may occur after safety precautions have occurred). For children who are enrolled in the study, the therapist providing treatment will be made aware of any reported suicidal ideation so that the clinician can work with the child and family to provide appropriate intervention and monitoring (see monitoring plan below).

As stated in the Protections of Human Subjects (c. Potential Risks), the therapists, parents and children ages 7 to 12 will complete the CGI-Improvement rating each week (or with the parents via phone for Step One). If clinical worsening (see operationalization in Potential Risk section) occurs, Dr. Storch will be consulted and a host of options considered, including psychiatric evaluation, additional sessions and/or discontinuing the study and seeking additional help from community resources. If it is determined that the child may proceed in study treatment, the therapist will monitor the suicidal ideation by completing a harm to self or other form with the child, and in cases of young children (ages 3 to 6) the parent will be asked these questions about his or her child. The question from the DIPA that asks parents about suicidal themes in play (drawing pictures of suicide, playing games in which the character kills himself) will be added to the form as young children may show signs of ideation through play. The harm to self or others form was created by the Child/Adolescent Anxiety Multimodal Study and NIMH and used in a recent childhood anxiety community-based trial (PI: Dr. Storch 1R18HS018665-01A1) where Dr. Salloum provided clinical supervision. The form includes questions about thoughts about not wanting to be alive or hurting oneself, non-suicidal self-harm (e.g., biting, cutting, or other means of affect regulation), passive death wishes, thoughts or wishing to kill self and plans, and questions about wanting to hurt or kill someone else. The parent will be informed of the child's suicidal ideation and will also be provided with appropriate resources should the child become suicidal such as taking the child to the hospital or to the community children's crisis center for an evaluation. We decided not to use the harm to self or others form for all children (i.e., children who are not having suicidal ideation) every session because in the R18 study many parents did not like the therapist asking about suicide every session when their child had never expressed ideation. We will follow the plans stated above if the child is suicidal (e.g., immediately make the appropriate referral for further evaluation and potential hospitalization, and consult with Dr. Storch).

5.1.2 ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent HUMAN SUBJECTS CONSIDERATION

Recruitment will occur through agencies and organizations that serve children in the Tampa Bay area, and that refer children to trauma-focused treatment at two community agencies: CCTB and PKF (and Suncoast

Center Inc. Children's Home Society, Directions for Living and USF St. Petersburg Family Study Center. if needed). These two/three community agencies are considered the lead agencies in their respective counties providing treatment to children after trauma and each one typically serves over 150 children ages 4 to 12 yearly. Referral sources will be from Child Protection Investigators, co-located agencies within the Child Advocacy Centers, day cares and schools, domestic violence shelters, and area hospitals such as Tampa General Hospital and All Children's Hospital.

When potential participants call regarding the study, they will be informed of the purpose of the study and the on-site Agency Coordinator/Screener at each site will utilize an identical telephone screen procedure as reviewed in the Research Strategy plan (see 3.c.2.1.). Those who appear eligible based on the phone screening will be scheduled for an in-person screening and baseline assessment. Those who are determined to be ineligible will be offered a range of community treatment referrals.

It will be the responsibility of Dr. Salloum to ensure that potential participants understand the extent of their role in the research. Specifically, the written parental consent and child assent documents (required for children age 7 and older; younger children will be explained the purpose in developmentally appropriate language as developed in the R34 pilot trial with young children) will be read with all potential participants, and focus will be placed on potential risks and benefits associated with study participation as well as any alternatives to participating in the research. The parental consent and child assent forms will be presented in simple language approved by the USF Institutional Review Board. Consent forms will include information from the sample language provided by NIMH related to data from this study being submitted to the National Database for Clinical Research Related to Mental Illness. Dr. Salloum will try to foster an open exchange of information, encouraging potential participants to discuss study particulars and ask questions prior to research involvement; to take a copy of the consent form home to discuss with family and friends, if desired; and to continue asking any questions that might arise during participation. Parental consent and child assent will be documented on the consent forms by the signature of the parent and therapist. Dr. Salloum will also review the study consent with participating study therapists.

Prior to study onset, approval will be obtained from the USF Institutional Review Board. The research team will protect confidentiality of participants' research information. Researchers will be carefully trained about the importance of confidentiality and will be required to undergo HIPAA training. In addition, all paper-generated data will be stored in a filing cabinet in the PI's office in locked filing cabinets at USF; and all computer-generated data will be maintained in password-protected computers. Participant names (or any other identifying information) will not be kept on the study measures themselves. Instead, code numbers will be used on the actual data-gathering tools. A separate record linking the code numbers to the participant identifiers will be kept in locked files, completely separate from the data. Participants will be told that they can discontinue participation at any time, or refuse to answer any study questions, without adverse consequences.

b. Protection Against Risk

The PI (Dr. Salloum), Co-I (Dr. Storch), and psychiatric consultant (Dr. Murphy) have considerable experience conducting research with participants with severe mental health conditions and monitoring the safety of subjects participating in research studies as they have been involved in NIH-funded clinical trials involving psychotherapy (Drs. Salloum, Storch, and Murphy) and pharmacotherapy (Drs. Storch and Murphy) for children.

Assessments will be conducted by a trained independent evaluator (or trained graduate research assistant who will serve as back up to the IE). Effective screening will rule out conditions that would prevent a child from participating. Participants who are ruled out will be provided with information about community resources. Participants who endorse any situation needing immediate attention (i.e., suicidal ideation) will be directed immediately to appropriate care. If at any time participants become overwhelmed during an assessment, we will pause or stop, depending on the degree of distress.

Once participants enter into the study, we will follow them closely. Drs. Salloum or Storch will be available for study therapist 24 hours a day, 7 days a week. Adverse effects will be monitored very closely throughout the study, through structured assessments, clinical interactions, and weekly CGI-I ratings. The independent evaluator will conduct a general inquiry regarding any health complaints, recent illness or injury, changes in psychotropic medications, new or exacerbated side effects from the baseline assessment, and any clinically significant changes since the last study assessment. Reported complaints will be coded as Mild, Moderate, Severe or Serious. Mild = minor complaint causing no interference and not requiring any intervention. Moderate = more than minimal problem, source of some interference and may require intervention. Severe = significant

complaint, definite interference requiring intervention. Serious = life threatening, a potential for long-term disability, and/or requiring hospitalization. Although unlikely, based on the nature of this study, the independent evaluator will also rate whether the adverse event is related to the study or not. Such complaints will be relayed to the PI, who will consult with Dr. Storch and appropriate action will be taken, which may include monitoring, adjunctive intervention within study protocol (see section 5.1.1.a.), or removal from the study and referrals to appropriate care (i.e., psychiatric evaluation, hospitalization, community treatment).

This project will be conducted in compliance with research statutes outlined in the Health Insurance Portability and Accountability Act. Confidentiality of participants' research information will be carefully protected by the research team. Research staff will be carefully trained regarding the importance of confidentiality and, consistent with USF regulations, will be required to sign confidentiality agreements. To the extent permitted by law, no participant information will be given to anyone without a signed release by the child's parent. In accordance with DHHS regulations, Florida state laws and USF Internal Review Board rules, the research will be explained to children under the age of seven in terms relative to their age and understanding. Children ages 7 through 11 years will have the research explained and assent will be verbally obtained and documented in the child's research records, children age 12 years will have an opportunity to read the assent and discuss questions, and written assent will be obtained. Written consent will be obtained from parents/guardians for their child to participate in the research study. In the state of Florida, temporary guardians (an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care) must provide documentation that the ward's participation in research has been granted by the court, or if parental rights have not been terminated, parents may sign consent along with the temporary guardian. Permanent guardians may consent for his/her child to participate in research. Parents and guardians will be informed in writing (i.e., in the consent) and verbally during the screening assessment that we will keep their child's study records confidential to the extent permitted by law. For example, if there is reasonable cause to suspect that a child is abused, neglected, or abandoned by a parent, legal custodian, caregiver, or other person responsible for the child's welfare, a report of such knowledge or suspicion will be made to the appropriate authorities. Any information shared by the parent/child will be kept confidential, as permitted by law. Of note, open cases with the state child protection agency through the Florida Child Protection Services are eligible as long as all study criteria are met.

All paper-generated data will be stored in locked files in the PI's office, and all computer-generated data will be maintained in password-limited hard drive files. All data will be entered into USF secured servers in a relational database environment. All data will be routinely backed up with support from our IT team. Participant names (and all other identifying information) will be kept separately from the study measures themselves. Instead, code numbers will be used on the actual data-gathering tools. A separate record linking the code numbers to participant identifiers will be kept in a locked file, completely separate from the data. The other procedures to ensure confidentiality follow the regulations and policies of USF. Data file archival and back-up will be performed on a regular basis. The routine monitoring, maintenance, and quality control of the databases will be the responsibility of Drs. Salloum and Wang.

5.1.3 POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

The potential benefits of the research to research participants and to the parent/guardian are several including receiving emotional, behavioral and physiological assessments, receiving an evidence-based psychological treatment from trained clinicians, and consistent monitoring of symptoms by extensive clinical contact. Most notably, children's quality of life, psychosocial functioning, and symptom-related impairment may improve. Intervening early by providing effective mental health trauma treatment for children with PTSD may prevent the child from prolonged suffering and challenges in functioning as they develop. The benefits to society are discussed below under the "Importance of the Knowledge to be Gained" section (5.1.4). **The risk to subjects is minimal. The minimal risks are reasonable in relation to the anticipated benefits to research participants, especially since upon entering the study children will be experiencing significant PTSD symptoms and impairment and it is anticipated that the subjects will experience improvements from participating in study treatment**. Potential benefits for the study therapists includes learning TF-CBT and Step One, consultation/training with the consultants (Drs. Cohen, Scheeringa, and Craske), and weekly supervision by the PI which includes participation with study team meetings about implementation of the treatments.

5.1.4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

EXPECTED RESULTS OF THE RESEARCH

There are several potential benefits of the adaptive Stepped Care TF-CBT being further refined and tested in the proposed application: 1) Stepped Care may serve as an efficient method of treatment delivery for the consumer and larger service systems, such as child welfare systems. 2) Patients and families are not subjected to tolerate more than is needed since children are matched to the optimal level of care upon starting treatment, and for some children treatment is provided in steps. 3) Specialty services are more efficiently reserved for patients needing more intensive therapist-led evidence-based practice expertise. 4) Parent-led treatment with minimal therapist support with empirically supported interventions and multimodal approaches (web-based information, telehealth, bibilotherapy) may be more convenient, take less time, and cost less than standard weekly therapist-led treatment. 5) We will have a better understanding of potential mechanisms of change that can lead to more targeted treatment. 6) For states that have adopted statewide evidence-based practices, a stepped care model such as SC-TF-CBT could provide a substantial cost savings in mental health care, thus allowing resources to be allocated to those in need of more intensive treatments. Despite these potential benefits, Stepped Care approaches are not employed in psychiatry with significant regularity although they have the potential to address treatment barriers such as time, cost, accessibility, and convenience. There has been considerable research on the effectiveness of TF-CBT,[20, 21, 26, 79, 153] yet there have been no innovative service delivery approaches to delivering TF-CBT other than our promising pilot work on Stepped Care TF-CBT (see Research Strategy, section 3.c.2.), and studies on the mechanisms of change that occur within treatment are limited. In order to have an impact in public health, alternative delivery approaches, such as an adaptive Stepped Care model rather than traditional weekly therapist-intensive treatments are needed. Importantly, the knowledge to be gained in this study will provide empirical evidence on how to optimize the efficiency and cost-effectiveness of Stepped Care TF-CBT, a personalized adaptive intervention, under “real world” settings (i.e., in community mental health clinics), and this new service delivery method may have implications for delivery of treatment for other childhood disorders. As to the risks to participants (as described above 5.1.1.c), we believe that any risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

The results of the study will result in publications.

5.1.5. DATA AND SAFETY MONITORING PLAN

This study involves minimal risk.

Once a subject is enrolled into the study, continuous close monitoring will be conducted by Dr. Salloum through weekly team meetings discussing patient responses to psychotherapy. If clinical worsening occurs (see 5.1.1 c.) the PI will consult with Dr. Storch about the appropriate course of treatment, which may include additional sessions, having a child undergo psychiatric evaluation to determine their mental health status and/or discontinuing the study and seeking additional help from community resources. Dr. Storch will be available for additional consultation and patient evaluation if needed. As previously noted (see Section 5.1.2 b. Protection Against Risks), should a participant have a significant adverse reaction to either Stepped Care TF-CBT or standard TF-CBT, the PI will be notified immediately and the appropriate action, which may include monitoring, adjunctive intervention within study protocol (see Section 5.1.1.a.), or removal from the study will be taken. Drs. Salloum, and Storch will meet weekly to discuss any adverse events experienced by participants; they will also discuss this at the conclusion of the study. Additionally, the USF Institutional Review Board will monitor this study through annual reports of progress and by immediate notification of serious and unexpected adverse events by the PI. This information, as well as any other unanticipated problems involving risks to children or others, will be reported to the NIMH Program Officer and the USF Institutional Review Board, as appropriate.

Approval will be obtained from the USF Institutional Review Board to conduct this study. The research team will carefully protect confidentiality of participants’ research information. Researchers will be carefully trained about the importance of confidentiality and will be required to undergo HIPAA training. In addition, all paper-generated data will be stored in double-locked files in the PI’s office located on the USF Tampa campus and all computer-generated data will be maintained in password-limited computers. The study laptops, which will be locked when not in use at CCTB and PKF (and Children’s Home Society, Directions For Living, and USF St.

Petersburg Family Study Center, if applicable) will be restricted to selected "authorized users". Participant names (or any other identifying information) will not be kept on any study measures themselves. Instead, code numbers will be used on the actual data-gathering tools. A separate record linking the code numbers to the participant identifiers will be kept in locked files, completely separate from the data. Participants will be told that they can discontinue participation at any time, or refuse to answer any study questions, without adverse consequences.

Although we expect that the psychotherapy provided in this study will benefit subjects, weekly contact (either by scheduled telephone calls or in-office sessions) will allow adequate monitoring of potential suicidality. Parents will be provided with clear directions on how to contact the study team during the follow-up phase should they need to do so. As noted above in 'Potential Risks,' all subjects who have clinical worsening or insufficient treatment response or who undergo some type of crisis (exposure to another traumatic event) will be offered the opportunity for additional sessions. If symptoms worsen, appropriate treatment alternatives will be discussed. If at any time, parents need additional treatment, beyond the general support provided as part of both conditions, parents will be provided with a list of community mental health resources for additional care.

The PI has overall responsibility for monitoring the integrity of the study data and participant safety. Once a subject is enrolled into the study, continuous close monitoring will be conducted by Drs. Salloum and Storch as well as USF Institutional Review Board, through annual reports of progress and by immediate notification of serious and unexpected adverse events. This information, as well as any other unanticipated problems involving risks to subjects or others, will also be reported to the NIMH Program Officer.

Procedures for Monitoring Participant Safety

We will implement the following procedures to ensure data integrity and the safety of patients during the study:

1) Many elements of the research plan are intended to minimize the risks of study participation. For example, we will exclude children who are experiencing clinically significant suicidality, or require a higher level of care than outpatient treatment. The study staff will carefully monitor patients at each study visit to ensure that they do not experience clinically significant deterioration or they are not at-risk for harming themselves; if indicated, we will evaluate them accordingly and, if indicated, refer them for immediate non-study treatment (e.g., alternative pharmacotherapy or inpatient). The PI or Co-I (Dr. Storch) will be available to subjects at all times in the event of an emergency.
2) The PI and Co-I (Dr. Storch) will discuss patient safety during clinical supervision meetings. They will also discuss and resolve any safety issues if necessary as such issues may arise (e.g., the occurrence of serious or moderate adverse events [see below], possible patient withdrawal from the study, or any safety concern).
3) Dr. Storch and Dr. Salloum will discuss issues concerning patient safety and tolerability should clinical worsening occur, and on an as needed basis.
4) We will review study risks and the status of patients' safety with our NIMH Program Officer every year (or more often if necessary). This review will include a discussion of any serious or moderate adverse events that have occurred, a review and reassessment of possible risks to patients, and any ethical issues that may arise.
5) Data integrity and confidentiality will be safeguarded as discussed in the Data Management section and in the Protection Against Risks section.

Data and Safety Monitoring Board

In addition to the above plans for monitoring and ensuring patient safety, we will have a Data and Safety Monitoring Board (DSMB) that will review the study twice a year for the purpose of monitoring subject safety and data integrity. The board will include four faculty members with experience in clinical trials research with vulnerable pediatric populations, including an expert in clinical trials in pediatric PTSD, a biostatistician with pediatric clinical trials experience, a child psychiatrist experienced in psychosocial clinical trials, and a clinical child psychologist with expertise in childhood anxiety. Individuals on the DSMB will not be affiliated with the study.

Specifically, the Monitoring Board will be responsible for:

1) Reviewing the research protocol and plans for data and safety monitoring.
2) Monitoring adverse event reports, study progression, and data quality issues every 6 months. Evaluating the progress of the trial may also consider factors external to the study when interpreting the data, such

as scientific or therapeutic developments that may have an effect on the safety of the patients or the ethics of the study.
3) Inquiring for further information as necessary to accomplish the mission.
4) Maintaining confidentiality during all phases of the trial including monitoring, preparation of interim results, review and response to monitoring recommendation,
5) Generating a report that will be provided to the PI and the IRB.

Reporting Adverse Events

Reporting of adverse events (AE) will occur in accordance with USF Institutional Review Board policy (HRPP Policy No. 212). Reporting of adverse events will occur as follows:

1. Serious adverse events such as death, life-threatening events, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant disability/incapacity will be reported immediately to the USF IRB by the PI. Adverse events must meet all of the following criteria: unexpected; related or possibly related; and increases risk of harm. In addition, as per USF HRPP policy no. 212, "any publication in the literature, safety monitoring report, interim analysis, or other finding that indicates an unexpected change to the risks or potential benefits of the research is considered an AE."
2. The USF IRB reviews the adverse event report and determines if the event is a result of study procedures. NIMH will be contacted within 24 hours after the IRB has determined that an adverse event has occurred.
3. Mild events that can reasonably be expected from the study procedures such as non-serious, expected or unrelated events or protocol deviations not involving risks to participants will be reported to the USF IRB during the continuing review process, and these events will be summarized in the annual NIMH report.
4. We will inform NIMH of actions, if any, taken by IRB as a result of their continuing review.

13. RESOURCE SHARING PLAN

Consistent with NIMH policy, the PI and Co-Is in the proposed application will facilitate NIMH's efforts to take full advantage of the invested resources by making the data, collected with public funds, available, on appropriate terms and conditions, to the research community in a timely manner. The data from this cooperative agreement will be analyzed and interpreted first by the investigators in the project. Because the creation of the dataset is funded through public monies, and because the data set will constitute a national scientific resource for the research community, it will be made available to the larger research community no later than the acceptance for publications of the main findings from the final dataset. However, as stated in the Data Sharing Expectations for NIMH-funded Clinical Trials (NOT-MH-14-015), we will work with NIMH to determine scheduling of depositing data into the National Database for Clinical Trials Related to Mental Illness (NDCT) as appropriate, including descriptive/raw data and analyzed data. We have anticipated sharing data on a semi-annual basis. We reviewed the Common Data Element (CDE) Resource Portal for possible use of CDEs in this clinical trial, but the core CDEs were not applicable to this trial.

In compliance with the spirit and regulations of HIPPA, data files without identifiers will be prepared by the PI and Co-I, when appropriate, and the investigators will assume responsibility for ensuring the content and accuracy of the data elements and documentation. As described in Protection of Human Subjects (see section 5.1.2.a.) we will include in the consent forms the sample language provided by NIMH about study data being submitted to NDCT. The research graduate assistant will assist with preparing the raw data for NDCT. The PI will provide necessary information for access to datasets that are comprised of the dataset for clinical trial (including screening, interim, and outcome data), as well as dataset documentation (i.e., description of all variables and their definitions). We will work with NIMH to develop appropriate data dictionaries relevant to the proposed study. Documentation will be sufficient to enable investigators who are not familiar with the specific dataset to use it. Documentation will include a description of the study, data collection forms, study protocol/procedures, descriptions of all variable recoding performed, and a list of major study publications and study investigators. Results and data will also be shared via publications.

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