Date: Monday, March 11, 2019 3:40:41 PM
View: 01. Study Title and Research Personnel

Print Close

01. Study Title and Research Personnel

User Guide

*** Short Title:**
CBT 2

*** Full Title:**
Improving Health Outcomes for Orphaned Youth: Implementation of Trauma-focused Cognitive Behavioral Therapy

*** Study Organization:**
Sanford School of Public Policy

CRU (Clinical Research Unit) or Oversight Organization Selection:

* Is Duke University Hospital, Durham Regional Hospital, Duke Raleigh Hospital, any Duke Clinic or any other Duke Medicine entity a site where interventions or interactions with research subjects will occur as part of this study?
○ Yes ◉ **No**

* Will a Duke faculty or staff member be involved with interventions, observations, surveys or interactions with Duke patients?
○ Yes ◉ **No**

* Does this study involve the use of biological specimens from Duke patients?
○ Yes ◉ **No**

* Does this study involve access to confidential, private information from Duke patients?
○ Yes ◉ **No**

* Does this study require CRU oversight for any other reason not listed above?
○ Yes ◉ **No**

Note: Only people with current Human Subjects Protection (HSP) certification appear on the Select Person lists. If you cannot find the person, go to the FAQ section of the eIRB Home page and click the link *I'm trying to add someone to my study, but I can't find their name.*

*** Principal Investigator:**
Kathryn Whetten

Primary Study Coordinator (CRC):
Andrew Weinhold

Primary Regulatory Coordinator:
Andrew Weinhold

Co-Principal Investigators:

First Name	Last Name	Department
There are no items to display		

Other Key Personnel:

	Name of Individual	Role on study	Edit Rights	Receive Email	CITI Expiration
View	Morgan Barlow	Other	yes	no	12/22/2019
View	Amy Hobbie	Data Technician	no	no	10/11/2020
View	Melissa McGovern	Data Technician	no	no	3/1/2020
View	Leonard Ng'Eno	Data Manager	no	no	12/29/2019
View	Karen O'Donnell	Investigator	no	no	1/14/2021
View	Jan Ostermann	Statistician	no	no	12/23/2019
View	Jasmine Tran	Other	no	no	7/29/2019
View	Rachel Whetten	Grant Support Personnel	yes	yes	12/14/2019

View: 02. Study Personnel Outside Duke

02. Study Personnel Outside Duke

User Guide

For all Key Personnel who are not Duke employees, complete and attach an Outside Duke Key Personnel Form.

Document Name	Date Created	Last Modified	Revision
Katherine Benjamin CITI Certification	5/26/2017 4:03 PM	5/26/2017 4:03 PM	0.01
Kevin King CITI certification	10/29/2014 4:21 PM	10/29/2014 4:21 PM	0.01
Leah Lucid CITI	7/23/2012 4:14 PM	7/23/2012 4:14 PM	0.01
Manna Sirak CITI Certification	4/4/2017 1:28 PM	4/4/2017 1:28 PM	0.01
Oriana Messer CITI Certification.pdf	6/8/2017 5:11 PM	6/8/2017 5:11 PM	0.01
Outside Duke Key Personnel Form 04.04.2017.doc	4/4/2017 1:32 PM	4/4/2017 1:32 PM	0.01
Outside Duke Key Personnel Form 05.08.2017.doc	5/11/2017 4:19 PM	5/11/2017 4:19 PM	0.01
Outside Duke Key Personnel Form 05.15.2017.doc	5/15/2017 10:39 AM	5/15/2017 11:30 AM	0.02
Outside Duke Key Personnel Form 05.26.2017.doc	5/26/2017 4:03 PM	5/26/2017 4:03 PM	0.01
Outside Duke Key Personnel Form 06.06.2017.doc	6/6/2017 2:05 PM	6/6/2017 2:11 PM	0.02
Outside Duke Key Personnel Form 10.06.2016	10/6/2016 4:14 PM	10/6/2016 4:14 PM	0.01
Shannon Dorsey CITI certification	1/10/2014 11:37 AM	1/10/2014 11:37 AM	0.01
University of Washington Insurance	7/23/2012 4:50 PM	7/23/2012 4:50 PM	0.01
Volunteer Approval-Oriana Messer_Whetten_06Jun17_Signed.pdf	6/8/2017 5:11 PM	6/8/2017 5:11 PM	0.01
Volunteer Background Check Confirmation - Messer.docx	6/8/2017 5:15 PM	6/8/2017 5:15 PM	0.01

View: 03. Protocol Application Type

03. Protocol Application Type

User Guide

* **Select the type of protocol you are creating:**

Regular Study Application
Most common. The IRB will determine if the study is eligible for expedited review or requires

(●) ***full board review upon submission.***

Application for Exemption from IRB Review
( ) *Includes Exempt (45 CFR 46.101 (b)), Not Human Subject Research (45 CFR 46.102 (f)), & Not Research (45 CFR 46.102 (d)).*

External IRB Application
( ) *Includes phase II, phase III, phase IV protocols that are industry sponsored multi-site studies, and includes selected DCRU phase I protocols.*

Trainee Research While Away from Duke
( ) *Research conducted by medical students overseen by the Office of Curriculum & other student/trainee research away from Duke.*

Emergency Use of a Test Article
( ) *Emergency use of an investigational drug or biologic, emergency use of an unapproved device.*

View: 04. Sponsor and Funding Source

04. Sponsor and Funding Source

User Guide

* **Add all funding sources for this study:**

Name	Acronym	Type
National Institutes of Mental Health	NIMH	Federal Government

* **Is the Sponsor of this study listed above as one of the funding sources?**
(●) **Yes** ( ) No

If No, Select the Sponsor:

***As part of this study, will any samples or PHI be transferred to/from Duke to/from anyone other than the Sponsor, a Sponsor subcontractor, or a Funding Source?**
( ) Yes (●) **No**

Enter the SPS (Sponsored Projects System) number, if applicable:

For Federally funded studies:

Is your funding subject to, and does it comply with, the funding agency's policy for data sharing?
( ) Yes ( ) No

If Yes, check all that apply:

- [ ] NIH Genome Sharing - dbGaP
- [ ] NIH Genome Sharing - GWAS
- [ ] NIH Genome Sharing - NCI databases
- [ ] NIH Genome Sharing - other
- [ ] Non-NIH Genomic
- [ ] General Data Sharing

Enter the Grant Number or Other Federal Agency Proposal or Application Number:
1R01MH096633

Attach the following:
(1) The entire grant, or an explanation of why a grant is not needed.
(2) NIH institutional Certificate form related to data sharing (if applicable).

Name	Date Modified

View: 05. Multi-site Research

05. Multi-site Research

User Guide

* **Is this a multi-site study?**
Yes No

If Yes, complete the following:

Is the PI/Co-PI the lead investigator or primary grant awardee?
Yes No

Is Duke the central coordinating center for this study?
Yes No

Is Duke serving as a central statistical center for this study?
Yes **No**

Is Duke serving as a central laboratory, reading center, analysis center or other central resource for this study?
Yes No

List all sites at which you will conduct the research or be principal investigator responsible for the conduct of the research:

	Name/Location	IRB Approval Expiration Date
View	ACE Africa	5/16/2018
View	Tanzania Women's Research Foundation	
View	University of Washington	

View: 05.1 Research at Sites External to DUMC

05.1 Research at Sites External to DUMC

User Guide

Provide a description of the procedures that will be used to inform sites of unanticipated problems involving risks to subjects or others, interim results, protocol modifications and other information that may be relevant to the protection of subjects:
All substantive changes, protocol annual reviews, and adverse event reporting are reported to the local site IRBs and national ethical committees (when required) as well as the Duke IRB.

View: 05.3 Multi-site Coordinating Center

05.3 Multi-site Coordinating Center

User Guide

How will you ensure that management, data analysis, and data safety and monitoring systems are adequate, given the nature of the research involved?
The TAWREF and ACE study coordinators, trained by Duke researchers, manage other personnel and will be in regular at least weekly contact with the Duke and University of Washington Study Coordinators. Data analysis will be done by Duke and University of Washington researchers on a secure database managed by the University of Washington's data analyst . Results will be disseminated without identifiers and are based on group findings, rather than individuals. A Data and Safety Monitoring Board (DSMB) has been organized to participate in meetings via teleconference to review child and guardian data for both the KE and TZ study sites to: 1) review interim analyses at the point that half the study sample reaches the 12-month follow up, 2) address any adverse events, and 3) respond to data or clinical impressions about a child or guardian who might have worsening clinical

status during the intervention.

How will you ensure that sample protocols and informed consent documents are developed and distributed to each collaborating institution?
Protocols, survey instruments and consents are developed jointly by the Duke and University of Washington team. Some of the instruments were piloted and used our feasibility study, so they have been adapted by the Duke-TAWREF- UW research team to ensure their cultural appropriateness. Translation and backtranslation is conducted either by a professional translation service or by qualified site staff. Our ongoing collaboration and communication with TAWREF, ACE Africa and UW study personnel ensures that correct documents are in use.

How will you ensure that each collaborating institution holds an applicable OHRP-approved Assurance?
TAWREF has an FWA number and is linked to the KCMC IRB. ACE Africa also has an FWA number and is linked to KEMRI IRB.

How will you ensure that each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects?
The Duke Study Coordinator and the local staff work together to obtain all clearances and plan the timeline for research with human subjects based on approval.

How will you ensure that any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified?
Collaborating institutions are consulted about the risks and alternative procedures for this study in the development phase and incorporated into the final consent. For this therapy intervention study, there are no alternative procedures.

How will you ensure that informed consent is obtained from each subject in compliance with DHHS regulations?
Before the study begins, extensive staff training is conducted by a team of Duke researchers on site. The training includes all aspects of conducting ethical research with human subjects.

View: 06. Research Summary

06. Research Summary & Abstract

User Guide

The Research Summary should include sufficient information for evaluation of the proposed study, independent of any other document, though the PI is expected to include additional information considered important for review by the IRB.

* **Attach Research Summary here:**

Name	Date Modified
CBT-II Research Summary 6June17_trackchanges.docx	6/13/2017 11:13 AM

The Research Abstract should summarize the main points of your study in one paragraph. The following guidelines may help you:

1. Purpose and objective (1-2 sentences)
2. Study activities and population group (2-4 sentences)
3. Data analysis and risk/safety issues (1-2 sentences)

Please type your Research Abstract here:
The primary goal of this R01 proposal is to use a randomized controlled trial (RCT) to study the effectiveness of Trauma-focused Cognitive Behavioral Therapy (TF-CBT) in treating traumatic grief and traumatic stress compared to usual care, for orphaned children and young adolescents in two East African sites with high prevalence HIV, Moshi, Tanzania (TZ) and Bungoma, Kenya (KE). We expect this trial to yield recommendations regarding an effective intervention for orphans that is acceptable, feasible, and includes local responsibility as a means to enhance potential sustainability in LAMICs. Using a task-shifting approach, in which lay individuals are trained as counselors, we will train six counselors in each country, who deliver 20 groups in each site (10 rural, 10 urban), resulting in 320 children and adolescents (ages 7-13) who receive TF-CBT and 320 who receive usual care. Outcomes for children are assessed at 12-14 weeks (i.e., corresponding with the end of TF-CBT), 6-months post-treatment, and 12-months post-treatment. Statistical analyses for the main aims will be conducted using the SPSS, Stata and Multilevel/Hierarchical Level Modeling (MLM/HLM) software program. These will be used to ascertain if TF-CBT produces significant reductions in symptoms compared to usual care, test whether country or setting explain between-condition differences in treatment outcomes at specific time point and test whether implementation variables (such as attendance, fidelity, provider knowledge) are related to outcomes at 12-14 weeks (end of TF-CBT) and

at the follow-ups. The risk of emotional distress on some questions for caregivers and children will be addressed by careful training of interviewers to provide support and make referrals. Risks of confidentiality will be addressed by separating identifiers from surveys by assigning unique codes to participants and locked storage of data.

View: 07. Full Protocol

07. Full Protocol

User Guide

* **Indicate the Protocol source below (check only one):**

Check all that apply:

- [x] **PI initiated**
- [ ] Commercial / Industry (for-profit group) initiated
- [ ] Federal Government initiated
- [ ] Cooperative Group Initiated
- [ ] Foundation (non-profit group) initiated
- [ ] Other

Attach the full protocol and any related documents, such as questionnaires, test scripts, or images that may be used in the study:

Name	Date Modified
12 Week Group Schedule	7/23/2012 9:38 PM
Demographic Survey English	7/23/2012 9:40 PM
Counselor Self Report Fidelity Forms - English	7/23/2012 9:41 PM
Free Listing Interview Guide - English	7/23/2012 9:47 PM
Key Informant Interview Guide - English	7/23/2012 9:47 PM
Trauma exposure child - English	7/23/2012 10:34 PM
Trauma exposure parent - English	7/23/2012 11:07 PM
CPSS PTSD Symptoms Child - English	7/23/2012 11:14 PM
CPSS PTSD Symptoms Parent - English	7/23/2012 11:15 PM
Strengths and Difficulties Child 11-13 - English	7/23/2012 11:17 PM
Strengths and Difficulties 7-13 Guardian - English	7/23/2012 11:19 PM
CBCL 6-18 Guardian - English	7/23/2012 11:30 PM
Youth Self Report (YSR) - English	7/23/2012 11:40 PM
ICGRC - Inventory of Complicated Grief Revised - English	7/23/2012 11:44 PM
Involvement Scale - English	7/23/2012 11:46 PM
Moods and Feelings Questionnaire - English	7/23/2012 11:47 PM
Receipt of Support Services - English	7/23/2012 11:48 PM
Exit Interview - English	7/23/2012 11:49 PM
Supervision Alliance Scale - English	7/23/2012 11:52 PM
TF-CBT Group Self Report	7/23/2012 11:53 PM
TF-CBT Knowledge Test	7/23/2012 11:54 PM
Standard of Care - English	7/23/2012 11:57 PM
Duke:UI Final signed IAA.PDF	8/5/2013 1:19 PM
JHU IRB Determination Notice for Data Transfer Agreement	5/10/2017 3:55 PM
Data Transfer Agreement - Akiba	5/11/2017 3:54 PM

View: 07.1 Study Scope

07.1 Study Scope

User Guide

* **Are you using a drug, biologic, food, or dietary supplement in this study?**

Yes No

*Does the study involve either of the following:

- Use of an algorithm (whether computer based or not), a medical device, a mobile app, an in vitro diagnostic test, or using samples to look for biomarkers in this study?
- Use of a humanitarian use device (HUD)?

Yes No

* Is this study retrospective, prospective, or both?

- Retrospective
- Prospective
- Retrospective and Prospective

* Who is providing Statistical Support for this study?

- Study Team
- Statistical - Internal
- Statistical - External
- Need it
- Other

If Other, describe:

View: 10. Subject Population and Enrollment

10. Subject Population Groups and Enrollment

User Guide

* Population Groups (Select targeted population groups only):

- [x] **Adults**
- [ ] Minors who are Wards of State
- [x] **Minors**
- [ ] Patients
- [ ] Pregnant Women
- [ ] Fetuses
- [ ] Prisoners
- [ ] Adults incapable of giving consent
- [ ] Adults with diminished capacity
- [ ] Handicapped subjects
- [ ] Students[1]
- [ ] Employees[1]
- [ ] Healthy Controls[2]
- [ ] Deceased subjects[3]
- [ ] Blanket Protocol

Population Groups excluded from participation in this study:

☐ Pregnant Women

* **Maximum number of subjects to be consented at Duke:** 0

Maximum number of subjects to be consented at all sites: 1280

For retrospective/repository studies:

Maximum number of patient records / samples to be used:

View: 10.1 Subject Procedures and Costs

10.1 Subject Procedures and Costs

User Guide

Biobank

* Does this study involve the collection, use, tracking, banking (storage) or distribution of human biological specimens?

○ Yes ◉ **No**

Procedures

Check all that apply:

- ☐ Genetic Testing
- ☐ Gene Transfer
- ☐ DNA Banking
- ☐ Testing for Reportable Infectious Diseases
- ☐ Human Cell Banking
- ☐ *Use of Human Embryonic Stem Cells
- ☐ *Use of Human-induced Pluripotent Stem Cells
- ☐ *Use of Other Cells Derived from Human Embryos
- ☐ *Use of Human/Animal Chimeric Cells
- ☐ *Specialized Cell Populations for Cell Therapy

Will blood be drawn in this study for research purposes?

○ Yes ◉ **No**

If Yes:
Maximum amount to be drawn in any 8 week period (ml):
Number of blood draws per week:

Will the Operating Room be used in this study?

○ Yes ◉ **No**

If Yes, Anesthesia time in minutes required (for research purposes):

Costs and Compensation

* **Will there be extra costs to subjects or insurance as a result of the research (e.g. tests, hospitalization)?**

○ Yes ◉ **No**

* **Will there be Subject Compensation?**

◉ **Yes** ○ No

If Yes:
Compensation for Travel / Lost Income: $ 2.50
Other Subject Compensation:
Gifts such as soap, sugar, stationery. Together with transport compensation will not exceed a value of

$2.50.

View: 11. Subject Recruitment Materials

11. Subject Recruitment Materials

User Guide

All materials that will be used to advertise the study in order to recruit subjects must be approved by the IRB.
Note - when referencing the study ID in recruitment materials, use the full Protocol ID ("Pro" + 8 digit number). Do not use "IRB".

Attach a copy of each advertisement that you will be using with this study. If any Ad will have multiple wording variations, attach a copy of each version of the Ad.

Document Name	Category	Previously Approved by IRB	Date Modified
There are no items to display			

View: 12. Privacy and Confidentiality

12. Privacy and Confidentiality

User Guide

* **Explain how you will ensure that the subject's privacy will be protected:**
The subjects are interviewed either in their own homes or in a private room at TAWREF/ACE Africa. The interviews takes place in a private room. Participants will be reminded that they do not have to discuss anything they do not want to and that the interviewers are required to keep their information confidential

* **Describe how research data will be stored and secured to ensure confidentiality:**
All study documents are keep in a locked file cabinet at the local sites in a lockable office. The database and computers used are password protected. All information that links identifying information to a participant's study ID is stored separately from the data. All study staff are experienced in sensitive mental health interventions and receive further training during project start up

View: 12.1 Research Data Security Plan

12.1 Research Data Security Plan

User Guide

Research Data Security Plans are required for every study, but are reviewed and approved independently from the Protocol. Click the link below to go to the Research Data Security Plan workspace. To access the plan from the study workspace, click the link under the "Review Status" column in the "HRPP Reviews Required" section.

Research Data Security Plan: RDS_Pro00039770

Current Status of this plan: **Approved**

View: 13. Protected Health Information (PHI)

13. Protected Health Information (PHI)

User Guide

* **Indicate how you intend to use potential subjects' Protected Health Information (PHI):**

- ○ I will review, but not record, PHI prior to consent.
- ○ I will record PHI prior to consent.
- ◉ **I do not intend to use PHI prior to consent.**
- ○ I will record PHI without consent. (decedent research, database repository, chart review)

View: 14. Consent Process

User Guide

14. Consent Process

Attach draft consent forms. To attach a revised version of an existing document, click the [Edit] **link.**

Document Name	Date Created	Last Modified	Revision
Kenya-ACE CBT II Adult Consent - 01.25.13 clean final.docx	1/25/2013 4:42 PM	1/25/2013 4:42 PM	0.01
Kenya-ACE CBT II Adult Consent - New Caregiver - 07.02.2013.docx	7/2/2013 1:27 PM	7/2/2013 1:27 PM	0.01
Kenya-ACE CBT II Adult Consent - New Caregiver - Kiswahili 07.22.2013.docx	7/23/2013 10:26 AM	7/25/2013 9:09 AM	0.02
Kenya-ACE CBT II Adult Consent Kiswahili - 04.09.13.doc	4/9/2013 11:55 AM	4/9/2013 2:09 PM	0.02
Kenya-ACE CBT II Child Assent - 01.25.13 clean final.docx	1/25/2013 4:43 PM	1/25/2013 4:43 PM	0.01
Kenya-ACE CBT II Child Assent Kiswahili - 04.09.13.doc	4/9/2013 11:55 AM	4/9/2013 2:34 PM	0.03
Tanzania-TAWREF CBT II Adult Consent - 01.25.13 clean final.docx	1/25/2013 4:43 PM	1/25/2013 4:43 PM	0.01
Tanzania-TAWREF CBT II Adult Consent - New Caregiver - 07.02.2013.docx	7/2/2013 1:27 PM	7/2/2013 1:27 PM	0.01
Tanzania-TAWREF CBT II Adult Consent - New Caregiver - Kiswahili 07.22.2013.docx	7/23/2013 10:27 AM	7/25/2013 9:10 AM	0.02
Tanzania-TAWREF CBT II Adult Consent Kiswahili - 04.09.13.docx	4/9/2013 11:55 AM	4/9/2013 2:11 PM	0.02
Tanzania-TAWREF CBT II Child Assent - 01.25.13 clean final.docx	1/25/2013 4:43 PM	1/25/2013 4:43 PM	0.01
Tanzania-TAWREF CBT II Child Assent Kiswahili - 04.09.13.docx	4/9/2013 11:56 AM	4/9/2013 2:31 PM	0.02

Who will conduct the consent process with prospective participants? Give the person's role in this study (PI, Study Coordinator, etc.)
The local interviewers will conduct the consent process with participants. They are trained in research able to explain the research and the consent without being coercive, as well as being able to answer all questions.

Who will provide consent or permission? (Select all that apply)

Consent Provider	
☑	**Participant**
☑	**Parent(s) or Legal Guardian(s)**
☐	Legally Authorized Representative (LAR)

How much time will the prospective participant (or legally authorized representative) have between being approached about participating in the study and needing to decide whether or not to participate? If you are not giving the person overnight to consider whether or not to participate, please justify.
The participants may have as long as they need within a two-week period from when they are presented with the option to participate in the research to when they may consent/assent or refuse. Many will be approached initially by telephone and an appointment made to explain the screening and the program. At the meeting, consent could be provided, but the caregiver has the option of having the interviewer return at a later time

Where will the consent process occur?
The consent process will take place in the participant's home.

What steps will be taken in that location to protect the privacy of the prospective participant?
Participants are approached individually and separately in their homes

How much time will be allocated for conducting the initial consent discussion, including presenting the information in the consent document and answering questions, with each

prospective participant?
We will plan for half an hour to an hour for each participant, but any prospective participant can take more time for questions.

What arrangements will be in place for answering participant questions before and after the consent is signed?
Participants can ask questions at any point during the consent process and are given information on how to contact the local study coordinatotor/lead investigator if they have questions at a later date.

Describe the steps taken to minimize the possibility of coercion or undue influence.

Emphasis is always placed on the right to refuse or withdraw. Incentives to participate are deliberately kept at a level that is not seen within the community as coercive. Any gifts or transport reimbursements are capped at an equivalent of $2.50 to minimize coercion.

What provisions will be in place to obtain consent from participants who do not read, are blind or who do not read/understand English?
The study interviewer will read the consent form to the participants. All consent forms are translated into the local language, Swahili, and backtranslated to compare against the original English for accuracy.

View: 15. Specialty Committee Reviews

15. Specialty Committee Reviews

User Guide

Select all committees which will be required to review this protocol:

Pediatric Risk Assessment

View: (i) Clinical Trials Memo

Required registration of studies in ClinicalTrials.gov

On September 27, 2007 Congress enacted U.S. Public Law 110-85 (also known as H.R. 3580, or Food and Drug Administration Amendments Act of 2007). This act mandates the expansion of ClinicalTrials.gov, expands the required submission elements and establishes penalties for not listing a trial. Investigators and sponsors must ensure that applicable drug, biologic and device trials are registered within 21 days of enrollment of the first subject and preferable before first subject enrollment.

Which studies must be registered?

Registration is required for any research study that:

- Uses a drug, biologic, or device as the intervention or control/comparison AND
- Prospectively assigns human subjects to intervention and at least one concurrent control or comparison groups AND
- Studies the safety, efficacy or cause-and-effect relationship between an intervention and a health outcome

The registration requirement does not apply to:

- **The use of FDA approved, marketed products used in the course of medical practice**
- **Phase I clinical investigations of drugs or biologics**
- **Small clinical trials to determine the feasibility of a device or clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes**
- **FDA required pediatric postmarketing surveillance of devices**

Investigators and sponsors are encouraged to register all studies to ensure they meet the publication

requirements of the International Committee of Medical Journal Editors (ICMJE) and to promote transparency in clinical research.

Who is responsible for registering the study?

- **For investigator-initiated trials, the lead principal investigator responsible for conducting and coordinating the overall clinical trail should take responsibility for registration**
- **For Sponsor-initiated trials the sponsor should take responsibility for registration**
- **Trials sponsored by the federal government (e.g. NIH) should be registered by the grantee**
- **Trials associated with Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications with the U.S. FDA should be register by the IND/IDE holder**
- **If the individual or sponsor who should register the trial is unwilling or unable to register the trial it should be registered by a participating investigator**

How do I register a study at Duke?

Contact the Department of Clinical Research by email (docr.help@dm.duke.edu) to establish a user account to register a study with the ClinicalTrials.gov Protocol Registration System (https://register.clinicaltrials.gov). Please label the message with "ClinicalTrials.gov Protocol Registration" in the subject line, and include your name, telephone number, and email address in the body of the email.

Who do I contact for more information?

Additional information about this process can be found on the Department of Clinical Research's website (http://docr.som.duke.edu/modules/flash_articles/). You may also contact the DOCR by email (docr.help@dm.duke.edu) or by phone (681-6665) with further questions.

View: 18. End of Application Form

End of Application Form

You have reached the end of the New Protocol Application form. Upon clicking the "Finish" button below, this application **will not** automatically be submitted for review. It will instead appear under the "Presubmission" tab on your workspace, allowing further edits to be made to the application later if it is not yet ready for submission.

If this application is complete and ready to be submitted for review, you must click the "Submit Study" activity button, located in the left column of this application's workspace, to begin the Duke HRPP review process.

View: MultisiteCreateView
Complete detail form for each site:

Site Name and Location:

Name of Site:	ACE Africa
City:	Bungoma
State/Province:	
Country:	Kenya

Site Contact Information:

Primary Contact Name:	Augustine Wasonga
Primary Contact Phone or Email:	augustine@ace-africa.org

Site Details:

Does the site have an IRB?
(•) **Yes** ( ) No

Site IRB approval expiration date: 5/16/2018

If date not provided, explanation of why:

Has the site granted permission for the research to be conducted?
(•) **Yes** ( ) No

Does the site plan to rely on the DUHS IRB for review?
( ) Yes (•) **No**

Attach site approval letters or site personnel lists here:

Document Name	Date Created	Last Modified	Revision
KEMRI CBT2 Approval.pdf	3/15/2013 4:11 PM	7/5/2017 4:58 PM	0.05

View: MultisiteCreateView
Complete detail form for each site:

Site Name and Location:

Name of Site:	Tanzania Women's Research Foundation
City:	Moshi
State/Province:	
Country:	Tanzania

Site Contact Information:

Primary Contact Name:	Dafrosa Ithemba
Primary Contact Phone or Email:	dafrosakoku@gmail.com

Site Details:

Does the site have an IRB?
(•) **Yes** ( ) No

Site IRB approval expiration date:

If date not provided, explanation of why:
Site IRB approval was allowed to lapse after 2/6/2017, because data-related activities at the site ended on 1/31/2017. All study-related activities at the site ended on 2/28/2017. Please see attached study closure letter from TAWREF.

Has the site granted permission for the research to be conducted?
(•) **Yes** ( ) No

Does the site plan to rely on the DUHS IRB for review?
( ) Yes (•) **No**

Attach site approval letters or site personnel lists here:

Document Name	Date Created	Last Modified	Revision
KCMC CBT 2 IRB clearance certificate	3/15/2013 4:12 PM	3/18/2016 5:22 PM	0.03
NIMR CBT 2 IRB clearance certificate	5/21/2013 11:57 AM	6/22/2016 11:59 AM	0.04
TAWREF Site Completion Letter	7/6/2017 12:35 PM	7/6/2017 12:35 PM	0.01

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Name of Site:	University of Washington
City:	Seattle
State/Province:	Washington
Country:	U.S.A

Site Contact Information:

Primary Contact Name: Shannon Dorsey
Primary Contact Phone or Email: dorsey2@u.washington.edu

Site Details:

Does the site have an IRB?
(•) **Yes** ( ) No

Site IRB approval expiration date:

If date not provided, explanation of why:
University of Washington is willing to reply on Duke's IRB and enter into an IRB authorization agreement with Duke University

Has the site granted permission for the research to be conducted?
(•) **Yes** ( ) No

Does the site plan to rely on the DUHS IRB for review?
(•) **Yes** ( ) No

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Document Name	Date Created	Last Modified	Revision
UW cert insurance Psychiatry & Behavioral Sciences.pdf	9/5/2012 4:36 PM	9/5/2012 4:36 PM	0.01
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3. RESEARCH STRATEGY

3A. Significance

Over 143 million children worldwide are estimated to have experienced the death of one or both parents, and local, national, and international organizations struggle to meet their needs[1]. According to the 2010 UNAIDS report, HIV disease is estimated to be responsible for 16.6 million orphans; in Sub-Saharan Africa, the number of HIV-related orphans recently has doubled[3]. The well-being of orphaned children and their potential to become productive community members as adults are important factors for the future stability of their nations. Most of these nations are LAMICs that have both a high prevalence of HIV and high mortality among young parents[36]. In addition to these children's needs for basic necessities such as food, clean water, health care, and adequate shelter, their healthy development depends on effective mental health care [37,38]

A growing literature summarizes the high prevalence of unaddressed mental health needs of children orphaned by their parents, with a substantial proportion of the studies conducted in Africa[16,39]. Researchers and policymakers emphasize that providing food, clothing, and shelter is necessary but insufficient for children whose needs extend beyond basic physical needs to psychosocial care [40]. Being orphaned by a parent(s) is associated with mental health problems that last into adulthood [41,42]. Compared with non-orphaned youth, orphans have higher rates of childhood traumatic grief, posttraumatic stress symptoms (PTS), PTS Disorder, depression, suicidal thoughts, and anxiety[14,19,43,44]. In a qualitative study in Zimbabwe, researchers found that orphans were exposed to additional stressors from the major life changes associated with the death of the parent, including separation from siblings, child labor to provide extra income, and abuse in the new living situations [45]. Other stressors found to be commonly experienced include instability in living situations [46], loss of social support [47], and stigma associated with AIDS [48,49]. Various studies also demonstrate even greater mental health needs among HIV-affected orphaned, relative to other orphans, in the areas of PTS, depression, and conduct problems[15,50]. Mental health providers in the US reported that the death of a parent may be the most stressful event in the life of a child [51]. This finding is supported by our work developing the *Child Status Index (CSI*)[52], which involved interviews with guardians of orphaned children and village leaders in both KE and TZ. These interviews consistently pointed to child grief as the primary area of need. Our expectations were that food security would be prioritized; instead, adults described children whose "hearts were filled with worry," and reported concerns about their own abilities to help children overcome grief.

Childhood traumatic grief (CTG), also described as unresolved grief or complicated grief, can be caused by the loss of a loved one by death or abandonment, particularly under circumstances experienced as unexpected, shocking, or terrifying. In CTG, the individual shows a constellation of overlapping symptoms and reactions, which extend beyond normal grieving[53-55]. These symptoms include preoccupation with the deceased or manner of death, numbness, detachment from others, distress recalling positive memories of the deceased, and a sense of purposelessness about the future. CTG can interfere with effective coping and adjustment post-bereavement [56]. Studies focused on CTG indicate that although CTG is related to, and may co-occur with PTSD and depression, it is distinct[57]. CTG symptoms may create additional risk, as they have been found to predict persistent depression and PTSD one to three years later[58] .

For many children who are orphaned in LAMICs, the death of the parent(s) is only one of many potentially traumatic events. In our longitudinal study Positive Outcomes for Orphans (POFO), involving orphaned and abandoned children in five countries (*N* = 1,480), nearly all orphaned children experienced at least one additional potentially traumatic event (98%), with more than half experiencing 4 or more events (55%)[18]. Death of another family member (79%), physical and/or sexual abuse (70%), and witnessing family violence (50%) were the most commonly reported events for all children. One third of children reported a potentially traumatic event within the past year. The majority of double orphans had experienced physical and/or sexual abuse (79%), were more likely to have witnessed family violence (59%), and to have needed to leave home (42%). War, riots, or killings were experienced by one-quarter of the sample. The non-orphan sample, comparatively, experienced fewer traumatic events than both orphaned and abandoned children, further highlighting the greater vulnerability and need among orphaned children. In summary, in addition to having higher rates of mental health problems, children who have been orphaned are also at higher risk for chronic and cumulative exposure to potentially traumatic events and adversity[59,60].

Global mental health is an emerging priority in global health initiatives[23,24], with children who have mental health problems a particular focus[24 61]. In 2008, the WHO launched the mental health Gap Action Programme (mhGAP), designed to advance scaling up of mental health treatment for individuals with need in LAMICs. The burden of mental health disorders is high: "in all regions, neuropsychiatric conditions are the most important causes of disability, accounting for around one-third of YLD [Years Lived with Disability] among adults aged 15 and older"[24]. Depression, specifically, is the third leading global health threat (65,472,000

Disability Adjusted Life Year [DALY]). Despite the high prevalence and cost of mental health disorders, 90% of individuals with need do not receive treatment[62,63]. This is largely due to the scarcity of mental health professionals in LAMICs, particularly in the lowest income countries and in rural/low-income regions within countries[64]. Inequity of access is most notable for children with mental health needs, and only 0.16% receive care[65]. Given that nearly half of all lifetime mental health problems begin in childhood and adolescence, and the burden of adult disease, provision of effective interventions for child mental health problems presents a key component of closing the mental health treatment gap[24 66]. One large study in the US provides strong support for the associations among untreated trauma and life stress in childhood, adult risk behavior, and adult health problems, leading to early mortality[67]. Findings from POFO indicate that orphans were more likely than non-orphans to engage in high-risk sexual behaviors, and were less likely to engage in health promotion activities [68]. Taken together, studies from the US and LAMICs indicate the extreme importance of establishing effective and locally sustainable models for addressing the mental health needs of orphaned youth affected by HIV in countries. As stated in a commentary on *The Lancet* series on global mental health, "there can be no health without mental health"[69] (p. 109).

Need for evidence-based practices to address mental health needs of orphans.

Many NGOs, CBOs, and grassroots organizations have initiatives to provide psychosocial support to orphaned children [4]; however, few of these include specific, targeted mental health services. Although "*Children on the Brink*" [1] and other publications list strategic elements for protecting, caring for, and supporting orphans, EBPs in mental health which have been proven effective in high-income countries have yet to be included as standard of care for orphans (see Section 3C1. for our research), despite evidence that EBPs can be provided cost-effectively[65]. Children who have been orphaned and are experiencing CTG and other mental health difficulties need access to approaches that effectively address CTG, PTS, and commonly co-occurring symptoms (e.g., depression). US-based studies have shown that grief-specific treatments result in a better treatment response than more general, depression-specific treatments for children experiencing CTG (i.e., Interpersonal Therapy)[70]. Given the high rate of trauma exposure among orphans[18], treatment approaches need to include ability to address other trauma exposures, such as abuse and domestic violence, in addition to being grief-specific. Grief-specific approaches are even more critical in cultures that may have traditionally "protected" children from death (e.g. telling the child the parent has gone on a trip, or telling a child to forget that parent). As is often relatively universal, even in the US, individuals are often fearful of talking about past traumatic events, including the deaths of parents, directly with children. It is often felt that talking about such events only serves to remind the child of difficult times and worsens the child's emotional state. In a study focused on the experience of teenage AIDS-related orphans in Zimbabwe, youth reported that their guardians needed to know more about how to talk openly with them about death, specifically, and also how to talk to them about the changes that commonly occur subsequent to parental death [71].

Evidence for feasibility and effectiveness of EBPs in LAMICs.

Evidence for the feasibility and effectiveness of EBPs for mental health problems in LAMICs comes from a small, but growing number of RCTs and feasibility studies with a diverse range of cultural groups and populations (e.g., adults, adolescents, displaced persons, rural areas). Positive outcomes are notable for the range of LAMICs in which EBPs have been found to be effective, the different EBPs tested, and because the interventions were provided by local, lay counselors with little to no prior mental health training or experience[31]. The research includes promising findings from our own, ongoing feasibility field trial of TF-CBT focused on grief in TZ (see Section 3C1) and an additional TF-CBT feasibility study focused on abuse in Zambia with girls who are HIV-infected and have been sexually abused[30]. In a RCT of a trauma and grief-focused Cognitive Behavioral Therapy (CBT) intervention[72] with war-exposed teenagers in Bosnia, youth who received the intervention demonstrated greater improvements in PTS and CTG, compared to those who received a skills-only group[73]. In two RCTs conducted in Uganda, (one adult-focused; one adolescent), Interpersonal Therapy[74] was significantly more effective in treating depression than was a non-specific psychosocial intervention[33,34]. In a RCT of a collaborative stepped-care intervention[75] (i.e., MANAS) that also included provision of Interpersonal Therapy for adults with anxiety and depression in Goa, India, those who received the intervention were more likely to have recovered at 6-months than were those in an enhanced, usual care condition[32]. In rural Pakistan, a CBT intervention for maternal depression was effective in improving both depression and infant health[76]. In trials that included follow up assessments (e.g., 6 months), outcomes appear to be maintained[76,77]. Taken together, these studies demonstrate that EBPs can be adapted to LAMICs and that a task shifting approach, in which lay counselors deliver EBPs, is acceptable, feasible, and effective.

Improving outcomes for orphans: TF-CBT

TF-CBT holds considerable promise for improving outcomes for orphans as it: (1) has substantial evidence of effectiveness (i.e., 8 RCTs in the US); (2) specifically includes components for addressing CTG, PTS, and trauma exposure (e.g., parental death, abuse, violence); and (3) has been demonstrated to be feasible and culturally acceptable in two pilot trials in East African countries. In addition, TF-CBT includes substantial guardian involvement. For children who reside in family-based settings, family and guardian support is a potentially critical factor for improving mental health outcomes of orphaned children. In the *Lancet* series, mobilizing family support was recognized as an important factor for improving care[64]. In US-based research, guardian support following a traumatic event, like the death of a parent, is one of the factors that best predicts positive outcomes[78]. In Culver and colleagues' research on AIDS-orphaned youth in South Africa, high perceived social support, including that of family, was significantly associated with lower levels of PTSD symptoms following trauma exposure[50].

CBT approaches have the most evidence for treating traumatic exposure and stress in children[28,33,79,80]. Among these, TF-CBT has the most evidence of efficaciousness for reducing PTS symptoms and PTSD, CTG, depressive symptoms, shame, and trauma-related and general behavior problems for sexually abused and multiply traumatized children compared with non-CBT interventions (e.g., supportive or client-centered therapies, usual care)[78,81-87] (see Appendix D for TF-CBT overview). Follow-up studies of TF-CBT provide evidence of sustained benefit at 6 months, 1 year, and 2 years post-treatment[88-91]. Two pilot studies and one quasi-experimental trial focused specifically on grief and findings demonstrate improved symptoms of CTG, PTS, depression, anxiety, and behavioral symptoms[27,92]. In a large quasi-experimental trial of TF-CBT provided to children experiencing CGT after the terrorist attacks on September 11, 2001, children who received TF-CBT demonstrated similar improvements in CTG and PTS as those achieved in RCTs of TF-CBT for other types of trauma and exposure[93] Two TF-CBT studies (one RCT, one open trial) demonstrate the effectiveness of TF-CBT conducted in groups as comparable to that conducted individually[85,94]. Additional evidence for group interventions comes from two group-based CBT treatments with components that overlap with TF-CBT: Cognitive Behavioral Intervention for Trauma in Schools[95-97] and Multimodal Trauma Treatment[98,99]. Both demonstrated effectiveness in reducing PTS and related symptoms (depression, anxiety, behavioral difficulties). In TF-CBT and these other group CBT approaches, direct discussion of traumatic events (e.g., parental death, abuse) is done in adjunctive individual sessions (see 3C1 and Appendix B for our approach in TZ). All TF-CBT studies included active treatment comparison conditions, thereby largely avoid methodological concerns raised by Wampold and colleagues about biased effectiveness findings for trauma-focused interventions for PTSD when comparison groups were waitlist controls[100,101].

TF-CBT is rapidly being adopted by countries with diverse cultures and beliefs regarding trauma exposure, death, loss, and childhood. TF-CBT is currently being used in TZ (see 3C1), Zambia, China, Norway, Cambodia, Indonesia, Germany, Norway, Singapore, and the Netherlands. The book by the developers[102] has been translated into Dutch, German, and Mandarin, with translations into Japanese, Korean, and Polish underway. The web-based training for TF-CBT (http://tfcbt.musc.edu) and CTG (http://ctg.musc.edu) includes residents from over 70 countries. Our team receives regular requests for conducting training in other countries (e.g., South Korea, Northern Uganda, Japan). Given the high percentage of orphans in Sub-Saharan African, their high rates of CTG, PTS, and trauma exposure, it is critical to build evidence to guide the implementation of EBPs and TF-CBT, specifically. Our pilot study (see section 3C1) shows preliminary promising findings for TF-CBT used with orphaned youth in TZ, providing the foundation for the proposed RCT.

3B. Innovation

The proposed study is innovative in five ways: 1) it represents the first RCT of a mental health EBP for orphans with CTG in LAMICs; 2) it incorporates and builds on local experience and expertise developed during our pilot study, adding to the potential sustainability of the intervention (see 3C1); 3) the study examine both clinical (CTG, PTS, depression) and broader outcomes, including any improvement in child daily functioning as well as implementation factors (e.g., TF-CBT fidelity, supervisory relationship); 4) the RCT includes regions within two countries (TZ and KE) that allow for testing TF-CBT in urban and rural settings, with diverse political histories and usual care services and supports; and 5) as the TF-CBT model appears to have relevance in a wide range of cultural settings, and if found effective in this trial, it would be an excellent candidate for broader dissemination and implementation to improve outcomes for orphans in LAMICS internationally.

To our knowledge, we are among the first to include already trained lay counselors in the training of the subsequent generation of lay counselors, thereby taking a systematic step toward building local expertise and sustainability. According to the Lancet series, "flexibility and creativity [is] needed to diversify the workforce"[64]

(p. 81). A shortage of trained mental health professionals is "the main limiting factor" for mental health care in LAMICs[65] (p. 881), creating the necessity for task-shifting approaches[31]. Pending results from this RCT, our team plans to take additional, systematic implementation steps that increasingly build upon local expertise and decrease expert involvement to examine impact on clinical outcomes and implementation factors (e.g., fidelity). Our team intentionally selected a second country (KE) that is predominantly Kiswahili-speaking. Should this RCT support effectiveness of TF-CBT, successive implementation phases can include training in Kiswahili by local trainers, increasing the ecological validity of the training.

These innovations are explicitly included to increase practical findings from this trial[103]. Therefore, our goal is that findings will enhance the capacity of international, national, and local agencies to have a substantial public health and policy impact on services for orphaned children, especially those affected by HIV. Current orphan support predominantly has focused on nutritional, educational, and shelter-related resources. If TF-CBT is effective relative to usual services, we will take advantage of our ongoing communication with major orphan policymakers and funders in individual LAMICs as well as national policymakers such as UNICEF and USAID, as facilitated by the International Sector of the Center for Health Policy and Inequalities Research to disseminate the findings and the intervention. The POFO study team currently meets regularly with UNICEF and UNAIDS officials in the US and in study countries to receive input and to present new results. Orphan study results are disseminated to national orphan officials in LAMICs with high rates of orphans. Results from the proposed study would be similarly disseminated.

3. RESEARCH STRATEGY

3C. Approach

Members of our core research team have been conducting research designed to improve the physical and mental health of persons living with or affected by HIV in LAMICs for more than 25 years. Collectively, we have 4 NIH funded research projects in 6 LAMICs; one is a longitudinal study of orphans and abandoned children (OAC) with 6 research hubs in 5 countries for which we recently received a competing continuation for an additional 4-5 years, to follow children into young adulthood. The study most relevant to this proposal is a NIH-funded study testing the feasibility of a group TF-CBT for orphaned children in TZ. We also have implemented and tested CBT approaches in a wide range of countries (e.g., Iraq, Cambodia, Thailand). The investigators from the US, KE, and TZ have been collaborating for a decade. Our LAMIC partner organizations and investigators were chosen for their professionalism, understanding and success in carrying out complex research, and ease of communication and collaboration with distant partners (see Biosketches & Facilities/Equipment section). Our collective experience conducting research involving orphaned children and their guardians in LAMICs, experience implementing CBT internationally, history of collaboration with partner organizations, and our specific experience with implementing and studying TF-CBT in TZ (e.g., ability to train lay counselors, enroll children and guardians, acceptability, instrument appropriateness, and promising child outcomes) provides a strong foundation for the proposed study.

3C1. Feasibility Study of TF-CBT: Adaption, Training, Supervision & Acceptance of Survey Questions.

Since 2008, our US team has been collaborating with TAWREF on a feasibility study of TF-CBT for orphans with CTG and PTS. To date (study is ongoing; completion date: December, 2011), TZ lay counselors have provided TF-CBT to 48 children, ages 7-13 and one of their respective guardians (32 children have completed treatment and end of treatment assessment; 16 are in the end of assessment phase; predicted total $N = 64$). Implementation outcomes at this stage are promising—the lay counselors demonstrated high levels of fidelity to TF-CBT and child and guardian participation, report of acceptability, and satisfaction were positive (See Appendix B for TZ TF-CBT intervention guide and end of treatment exit interview summaries).

3C1a. The feasibility study of TF-CBT in TZ was proposed in response to findings of high mental health needs and trauma exposure among orphans from the literature, our POFO study, and interview findings during the development of the *Child Status Index* in TZ, KE, and Ethiopia in which guardians of orphans identified child grief as one of their primary difficulties in caring for them. To ensure cultural relevance of our planned approach to address these needs (i.e., TF-CBT), we conducted focus groups with guardians of orphans and with adolescent-age orphans (ages 15 and older) in the first phase of our feasibility study. The goal of the focus groups was to: 1) identify emotional and behavior problems experienced by orphans, including local terms for these symptoms; 2) identify local concepts of death and grief, particularly as they pertains to children; and 3) obtain feedback on the TF-CBT intervention content and delivery mode.

3C1b. Focus group findings indicated that: group delivery was appropriate; guardians were likely to participate actively; groups should be gender-specific and limited to 8 children and their 8 guardians (versus

our originally proposed 12 per group); and that the groups should be divided by age (primary school age groups; young adolescent groups). Further, focus group members indicated that although it might be hard at first, children could, and needed to, talk about parental death and that guardians needed support and skills for both how to talk with children about the parent who has died and how to support children with a continuum of mental health problems, including CTG and PTS related to parent death.

3C1c. Following the focus groups, 3 lay counselors hired by TAWREF were directly trained by Drs. Dorsey, an international TF-CBT expert, and O'Donnell, an expert in clinical issues of orphaned youth and their guardians in LAMICs (see Biosketches). Following the training, Dorsey, O'Donnell, the lay counselors (Gali, Joseph, and Kitomari) and the local Lead Investigator, Itemba, collaboratively revised the existing 12-session, individual TF-CBT protocol for CTG[92] to: (1) be appropriate for group delivery; and (2) apply to the local population. Adaptations for group delivery included group sessions for psychoeducation, skills-based components and joint child-guardian work; and individual sessions (at a community center or the child's home) for the trauma narrative component (i.e., gradual exposure), in which the child discusses the parent(s)'s death, other traumatic experiences, and their associated thoughts and feelings. Minor adaptations to fit the local population included adding local analogies, sayings and examples, as well as thoughts, feelings, and behaviors specific to orphans in TZ. The resulting protocol (see Appendix B) includes 12-group sessions and 3- individual sessions, delivered over 12-weeks. Dr. Dorsey provided day-to-day supervision in TZ on the trauma narrative component of the intervention for the first set of groups. Gali, Joseph and Kitomari were supervised through weekly Skype calls with Dorsey and O'Donnell. Prior to the call, the lay counselors submitted self-reports of fidelity and individual child and guardian treatment response and needs for review (see Appendix A). Supervision calls involved discussion of the past group/individual visits and planning for the upcoming session(s), with attention to both TF-CBT fidelity and individual child and guardian needs. Enrolled children and guardians participated in assessment interviews prior to the intervention, at the end of the intervention, and 3-months post-intervention.

This pilot study represents the initial stage of implementation: Feasibility Testing with Expert Oversight, in which PhD-level, mental health experts were responsible for all aspects of counselor training and supervision throughout implementation, testing both new study instruments (many were already used in POFO), and feasibility of the intervention**.** Survey instruments were found to be acceptable and able to detect change.

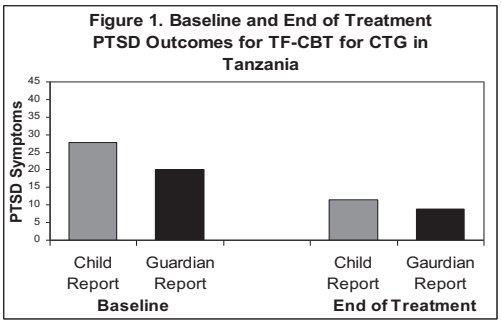
3C1d. Findings. Attendance for the 12-group sessions was high; guardians attended an average of 10.5, and children attended an average of 11. Even fewer absences occurred for the 3 individual visits. Children who participated in the group had parents who died, on average, 4.69 years (range = 4-12) prior to participating. Guardians who participated were most often a grandparent (31%), surviving parent (19%), or aunt (19%) but also included other relationships (e.g., uncle, family friend). As displayed in Figure 1, significant reductions in PTSD symptoms were reported by both children and guardians at the end of the intervention (n = 32; child-report: t = 9.57, p < .001; guardian-report: t = 9.97, p < .001). Symptom decreases appear to be continue to improve 3-months post-intervention (child report: t = 2.9, p < .01; guardian report: t = 2.83; p < .01). Reports of CTG and depression follow a similar pattern of symptom reduction over time (see Table 1). For depression (child report), 16 children (50%) had clinically significant depressive symptoms at the start of treatment (i.e., scores > 11), with only 4 children in the clinically significant range at the end of treatment.

3C1e. Feasibility Study Limitations. The feasibility study demonstrates the acceptability and appropriateness of TF-CBT; however, as it did not include a control condition, it does not rigorously test the effectiveness of TF-CBT. In addition, the lay counselors conducted the assessment interviews pre and post-intervention. Therefore, although these clinical outcomes are promising, the lack of a comparison condition and the interviewer dual role (i.e., interviewer & counselor) make it difficult to determine if outcomes are due to the intervention, respondent desire to please the interviewer/lay counselor, or other variables (e.g., natural decrease in symptoms over time, other services/supports). This pilot study met our goals of initial development and feasibility testing. The next research step involves a rigorous test of the effectiveness of TF-CBT with orphaned children experiencing CTG, PTS, and other related mental health problems.

Table 1. Baseline and End of Treatment Scores for TF-CBT

Symptom Area	Baseline Mean (SD)	End of Treatment Mean (SD)
Traumatic Grief (C)	19.28 (4.97)	11,44*** (9.66)
Depression (C)	11.63 (5.79)	4.66*** (5.30)
SDQ Total Difficulties (G)	13.59 (6.64)	8.75*** (6.28)

*p < .05; **p < .01; *** p < .001



3C2. Overview of the Proposed Study.

We propose a RCT of TF-CBT that builds on our feasibility study, with the goal of testing the effectiveness of an intervention that is locally feasible, acceptable, and holds promise for improving mental health outcomes and functioning of orphaned children. Although 8 RCTs of TF-CBT have been conducted in the US, there has never been a RCT of its effectiveness in LAMICs with high prevalence of HIV. The proposed trial, to be conducted in both Moshi, TZ and Bungoma, KE (*N* = 640, with 20 TF-CBT groups provided in each region), includes: (1) a usual care control group in each region, (2) independent research interviewers; and (3) enhanced ecological validity and local responsibility by including the lay counselors from the feasibility study to assist Dorsey and O'Donnell in training and supervising the lay counselors.

3C2a. Outcomes Examined. We plan to examine clinical outcomes, which include CTG, PTS, PTSD, depressive symptoms, behavioral problems, as well as any effect on the child-guardian relationship and the child's overall daily functioning (the last of these is a tool to be developed locally in the first quarter of the study; see Tables 3 & 4). We also plan to describe and examine the impact of implementation factors (e.g., TF-CBT fidelity, lay counselor knowledge gain, guardian and child attendance) on clinical outcomes. With the increasing attention given to task-shifting approaches[32] and their promise for reducing the mental health treatment gap, implementation efforts that incorporate feasible methods for building greater local responsibility and sustainability are needed.

The proposed study is a rigorous test of clinical outcomes building on a training and supervision approach employed by Bolton (consultant on this study)[33,34], Dorsey[35,76], and others[35] in RCTs in other LAMICs. This approach involves local, trained lay individuals (i.e., our feasibility study lay counselors) who act as the direct treatment model supervisors, under supervision themselves, by TF-CBT and mental health experts (i.e., Dorsey & O'Donnell). Our team views this RCT as the first step in a broader research plan to test the effectiveness of TF-CBT in successive implementation stages that systematically increase local expertise and responsibility and decrease expert involvement, with the goal of enhancing our knowledge around effective, feasible, and sustainable implementation strategies in LAMICs. As stated in the recently released NIH/PEPFAR RFA, focused on HIV/AIDS specifically (i.e., RFA-AI-11-003): "scientific advances regarding the implementation of effective interventions have not kept pace."

3C2b. The comparison group for the RCT is a "usual care" (UC) condition (i.e., existing orphan support services; (see Section 3C3c for our preliminary studies on UC in TZ & KE; also see Human Subjects). We enroll 320 child-guardian dyads in each of the two conditions (TF-CBT & UC; 640 total), with half of the participants enrolled in TZ and half in KE (see Table 2). Both sites are mixed urban and rural areas, allowing testing of TF-CBT in both settings to examine any impact of setting variables (i.e. differences in UC; urban vs. rural) on clinical outcomes or implementation (e.g., fidelity, attendance). Equal numbers of males and females, and children in age groups 7-10 and 11-13 will be recruited for both TF-CBT and UC. In the POFO study we easily recruited nearly twice this number (e.g., 560) in each region, indicating that the population of OAC in the areas in which we plan to recruit are high enough to support the proposed sample.

Table 2. Enrollment Plan

	Moshi, TZ		Bungoma, KE	
	Urban	*Rural*	*Urban*	*Rural*
TF-CBT	80	80	80	80
Usual Care	80	80	80	80
Total by Country	320		320	
Total	640			

Sample size estimates for the RCT were determined using effect sizes from TF-CBT RCTs conducted in the US[81,104], from outcomes obtained in our TZ feasibility trial, and data from the Zambia TF-CBT feasibility trial (see Section 3C5b; for Power Analyses). Each site has a local UC group to enhance internal validity, given unique cultural, historical, political, religious, and ethnic differences, including relatively recent election riots experienced in KE.

3C3. Study Conditions

3C3a. TF-CBT Condition. Children will receive the TF-CBT treatment protocol as tested in the TZ feasibility study and modified for KE (see 3C1c). Dorsey, the KE-lay counselors, KE-based investigator (Wasonga), and the local trainers (Gali, Joseph, & Kitomari) will oversee iterative modifications of the 12-week protocol that maintain fidelity and are culturally responsive and appropriate. A thorough overview of TF-CBT (Appendix D) and the TZ TF-CBT protocol (Appendix B) are included with this proposal and briefly described here. The intervention is delivered in 12 1.5-hour group sessions and 3 1-hour individual sessions, provided over 12 weeks. During weeks 1-8, guardian and child groups (8 participants in each) are run separately and concurrently with guardians and children earning the same skills. In the final 4 groups (groups 9-12) they participate in conjoint child-guardian activities. The trauma narrative, gradual exposure component is conducted in individual visits with the child (which are weekly and begin after group 4; see Appendix B), so that

the child can talk privately, one-on-one, with a counselor about the details, thoughts, and feelings related to their parent(s) death(s) and other traumatic events and so that other children are not triggered or traumatized by another child's narrative details. In groups 5-8, the children review, with counselor support, what they have done in the individual sessions (e.g., draw the picture again, write the story again), but no details are shared in the group. The group intervention is efficient (e.g., can provide treatment to 8 children-caregiver dyads with 3 counselors), culturally responsive (e.g., group delivery, modified analogies), and normalizing, as it includes other children/guardians with similar problems. The inclusion of the 3 individual sessions after trust is built, as with other group-based trauma treatment models [95] allows for individualization and privacy around specific trauma narrative details.

3C3b.Training and Supervision of Lay Counselors. The proposed trial uses an apprenticeship model [33-35] of implementation in which "local trainers" (i.e., the experienced lay counselors from the TZ feasibility study: Gali, Joseph, & Kitomari) apprentice to the TF-CBT and mental health experts in training and supervising lay counselors. Our team will train 9 counselors in TZ and 9 counselors in KE (18 total), who will deliver 20 TF-CBT groups (10 urban; 10 rural) to 160 children in each region. Lay counselors within each region will be randomly assigned to groups (3 counselors per group; 2 lead the child group, 1 leads the guardian group), so that counselor effects are balanced across groups and setting (urban, rural). In preparation for the training, Dorsey and O'Donnell will work with the local trainers to establish a training plan that allows the local trainers to pair with the TF-CBT and mental health experts in providing didactic information, modeling TF-CBT skills, and overseeing lay counselor role plays during the training. As in the feasibility study, the training will be 10 days and will include substantial opportunities for lay counselors to practice skills while receiving coaching and feedback. The training will be provided in Moshi, TZ at the end of year 1 (see Table 3), with the KE-based lay counselors and Wasonga travelling to Moshi to attend the training.

Lay counselors are supervised directly by the local trainers, who receive supervision and direction themselves, from Dorsey and O'Donnell. Following the in-person training, the TF-CBT and mental health experts will provide training in how to set up and structure practice in supervision (during year 1) and supervision of groups (during year 2, when the intervention begins) for the lay counselors in both TZ and in KE. We will be following established procedures used in other CBT trials that employ an apprenticeship model of CBT implementation [33,34]. Local trainers will then provide supervision to the 18 counselors (9 in TZ, 9 in KE), while receiving weekly supervision themselves. Both the local trainers and the TF-CBT experts will review baseline assessment data for children randomized to the TF-CBT condition as well as the lay counselors' self-reports of fidelity and the week-by-week qualitative assessment of individual child and guardian response to the intervention and attendance (see Appendix A). Review of these data will guide the local trainer supervision calls. In this way, the local trainers are apprenticing to the TF-CBT and mental health experts in learning to direct both training and supervision of lay counselors, under close supervision. Lay counselors also have access to local mental health professionals who can be called upon when concerned about child safety (e.g., suicidal thoughts, abuse) (see Human Subjects).

Table 3. Study Activities Timeline

ACTIVITIES	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5
Hiring					
Refine Coding Measure					
Functioning Measure Dev.					
Translation & IRB Sub					
Interviewer Training					
Local Trainer Preparation					
Lay Counselor Assessment					
Lay Counselor Training					
Lay Counselor Supervision					
Local Trainer Supervision					
Youth Enroll. & TF-CBT Groups					
Interviewer Supervision					
Youth & Guardian Assess.					
Data Entry and Transfer					
TF-CBT Fidelity Coding					
Data analyses; Manuscripts					

3C3c.UC Comparison Condition. Both TAWREF and ACE Africa include orphan support in their programs and are linked to other NGOs and government agencies in their regions that provide support for orphans in need and their families. Services range from assistance with school fees, nutritional support, family income support, to some psychosocial support (e.g., one to two general counseling or support sessions; see Appendix C; Bungoma, KE example Standard of Care Document). Our team will capture services received during this period using a services and support measure that combines items from POFO and services items from the Record Form of the *Child Status* Index[52]. These questions were all developed specifically for, and are already used, in both KE and TZ (see Table 4). All children screened and entered into the study are eligible for

the existing local services and will be referred to them, including those randomized to TF-CBT. Therefore, we are testing the additive benefit of TF-CBT, compared to UC only.

Preliminary Studies Examining Usual Care Services. We examined supports and services received by orphans in TZ and KE using our longitudinal data from POFO. At baseline, nearly half of all POFO study participants in the Bungoma, KE (49%) and Moshi, TZ (42%) regions received at least some support in the form of food, clothing, educational assistance, money, childcare, counseling/emotional support, medical care, and/or transportation. At 36-months, rates of support remained stable in TZ (48%) and increased dramatically in KE (91%), mostly due to the influx of services following political violence (although anecdotal evidence indicates that this high level of support is has not been maintained). Support services were received from community, religious, and government organizations, as well as from friends and family. At the 36-month POFO follow-up, 31% of the KE respondents and 15% of the TZ respondents reported that they were receiving counseling/emotional support. The POFO children in KE also had higher rates of emotional and behavioral needs following the political violence than did those in TZ. Preliminary results from POFO indicate that recipients of support were those with higher emotional and behavioral needs (identified via Strengths and Difficulties Questionnaire, also used in the proposed study, see Table 4) and in worse physical health, suggesting that children with greater needs receive more services. The effectiveness of UC services in improving outcomes is unknown. ACE Africa and TAWREF are aware of the local support services to which participants can and will be referred (in addition to those provided by their own organization), and each have established a local Standard of Care document (see Appendix C for Bungoma, KE example).

3C4. Assessment and Data Collection Procedures

3C4a. Assessment: Children and Guardians. Clinical outcomes are assessed by child and guardian report at baseline, 12-14 weeks post-baseline (i.e., end of treatment for the TF-CBT condition, with a 2-week window), and at a 6- and 12-month follow up, to assess maintenance of any gains. Two trained interviewers at each site conduct all interviews. Interviewers will have minimal contact with lay counselors and will not attend the TF-CBT groups, so the intervention is not contaminated nor are the interviewers biased. The clinical assessment battery reflects what was used in the feasibility study (therefore many of the measures for this proposal have already been translated, back-translated, and approved by the Duke IRB and Kilimanjaro Christian Medical Center, for Moshi, TZ). One change that we believe enhances the assessment battery is inclusion of a locally derived tool to assess daily functioning activities, as other studies have demonstrated functional impairment resulting from CTG[53]. The locally derived tool will be developed during the first year of the project, in both regions, following standardized qualitative measurement development procedures[105]. An interview guide for development of the functioning tool was created during the feasibility study and is approved by the Duke IRB for use in Moshi, TZ (see Table 4 and Appendix A, for the interview guide and an example functioning tool from Bolton & Dorsey's other research).

3C4b. Assessment: Lay Counselors. In addition to clinical outcomes, we examine implementation factors that may affect clinical outcomes and, by measuring them in this RCT, we establish a benchmark for future implementation efforts. Implementation outcomes, as detailed below, include child and guardian attendance at groups (which may vary across countries; urban vs. rural settings), lay counselors' knowledge and fidelity to TF-CBT, and the lay counselor-supervisor relationship. Lay counselors will complete measures assessing knowledge and the supervisory relationship with the local trainers (see Table 4). These measures are administered to the lay counselors by the project coordinator (PC) in each site via paper and pencil self-report format and will be returned to the PC in a sealed envelope. Self-report fidelity data will involve lay counselors completing the group reports after each TF-CBT group session and emailing these reports to the local trainers and to Dorsey and O'Donnell, within two days of the group. Lay counselors audiorecord all sessions digitally. The electronic files are collected by the PC on a jump drive. Three child and 3 guardian sessions (6 total) will be randomly selected from each group by Dr. Dorsey (remotely) and will then be coded by the data entry person, who also serves as the independent coder and will be trained by Drs Dorsey and Cohen in TF-CBT coding procedures.

3C4c. Data Collection from Children and Guardians. As in our other research, interviewers who have experience in working with children and a college degree in a field related to data management or social services are selected. Interviewers will undergo one week of training. Interviewers receive training in issues of research confidentiality, protocols, ensuring common understanding of questions, and standard ethical procedures (see Human Subjects for more information and Appendix C for example training documents). Interviewers will not be allowed to begin interviewing until they have been certified by Whetten and O'Donnell on all procedures and passed practice interviews (see Appendix C: Interview Training Log).

Our team has established procedures for monitoring interviewers during the RCT that decrease interviewer bias and drift (see Appendix C, Example Shadowing Log). The local PC in each site will shadow each interviewer for at least one child and one guardian interview each month. Interviewers will also be required to shadow a colleague's interview once per month. Both interviewer and "shadower" independently complete the assessment forms to allow examination of adherence to the protocol. In each case, the "shadower" and interviewer debrief about the interview within 48 hours. Shadowing logs are maintained and reviewed monthly during the M-PI and PC calls.

The primary offices of interviewers and the data entry person and the lay counselors are physically separate so that they do not inadvertently discuss participants, the study condition, or an interview. This physical separation, along with training on the importance of maintaining confidentiality and clear communication of confidentiality to guardians and children, helps ensure non-biased study results. The Lead Investigators in both countries understand the importance of maintaining confidentiality and not contaminating either the intervention or research data by allowing interviewers and counselors to discuss, even casually, their work with participants. Investigators research teams will hold weekly calls with the interview team (via Skype) that are separate from the TF-CBT supervision calls with the local trainers.

3C4d. <u>Recruitment and Screening.</u> All child/guardian participants will be identified by the two partner agencies in Moshi, TZ (TAWREF) and Bungoma, KE (ACE Africa). Children who are orphaned come to their attention through their existing support services (e.g., NGOs, church), from schools, or from other local groups. Staff from the partner agency make the initial contact with any potential participants and ask about willingness to receive information about the study. Children and guardians who are interested participate in a 2-level consent process conducted by the interviewers (see Human Subjects for additional information on recruitment, screening, and consent procedures). The two-level consent is similar to that used in our feasibility study, with added details on randomization, with the first level for screening (e.g., brief assessment of CTG and PTS). **Eligibility criteria** for study participation include: 1) child age between 7-13; 2) single or double orphan; 3) guardian adult (<u>≥</u> 18 years old) who is willing to participate in either arm of the study and understands the randomization process ; 4) child's parent(s) died <u>*after*</u> the age of 4 years (to ensure the child remembers the parent) and <u>*before*</u> the last 6 months (to avoid normal distress immediately post-death); and 5) a score of 10 or higher on the CTG measure or a score of 15 or higher on the PTS measure, by either child or guardian report. The inclusion criteria are designed to be broad, include even mild symptoms, but not to include children who do not need intervention. **Exclusion criteria** are few and include: 1) known developmental or cognitive disability, 2) the unwillingness of the child or guardian to be randomized, and 3) the unwillingness of the guardian to attend a 12-week group if randomized to the TF-CBT condition.

If children are eligible and assent and consent are provided, remaining baseline assessment measures are administered (see Table 4) and participants are randomized. Randomization procedures occur prior to the screenings by the local PC and Drs. Whetten and Dorsey, reducing any randomization bias. Interviewers have a numbered stack of consent forms that are used in numerical order. Each consent form includes an attached envelope with randomization status (see Human Subjects for more information). Guardian-child dyads randomized to TF-CBT begin the 12-week group protocol within 2 weeks. All dyads are assessed again at 12-14 weeks post-baseline, 6-months, and 12-months post baseline. For all assessment meetings, children and guardians receive a small incentive for participation costing <$2.50, (e.g., bag of sugar, laundry soap, pen).

<u>Table 4. Study Measures (All Measures are included in Appendix A</u>

Domain; Respondent^		Measures & Indicators	Interval*
	Demo-graphics; G	*Demographic Survey*. We assess pertinent demographic information (e.g., guardian characteristics, years caring for child, home situation) using an established demographics measure from POFO, also used in the feasibility study. † +	BL, 12w, 6M, 12M
Clinical Outcomes	Posttraumatic Stress; C, G	*UCLA PTSD Index for DSM-IV*[106] (UCLA PTSD-RI). The 38-item UCLA PTSD RI assesses trauma exposure and PTS symptoms. Response choices for PTS items are 0 - 4. The UCLA PTSD RI demonstrates good convergent validity and good to excellent test-retest reliability. Cronbach's α in the range of .90. †	BL, 12w, 6M, 12M
	Behavioral Difficulties; G	*Strengths & Difficulties Questionnaire*[107] (SDQ). The SDQ is a brief behavioral screening survey (ages 3-16) with 25 items on 5 scales (Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Relationship Problems, & Prosocial Behavior). Response choices are from 0-2. The SDQ has been shown to have good discriminant validity and acceptable levels of test-retest reliability[108] and a Cronbach's α of .73[109]. †	BL, 12w, 6M, 12M
	Childhood Traumatic Grief, C	*The UCLA Trauma Psychiatry Service Grief Inventory*, (TPSG) is a 10-item measure that includes a subset of the items on the Expanded Grief Inventory[110] and is used to assess CTG symptoms. The scale has demonstrated moderate - high levels of internal validity, and has been used successfully with children aged 6 and older. †	BL, 12w, 6M, 12M
	Depression, C	*Short Mood and Feelings Questionnaire*[111] (SMFQ). The MFQ has 13 items and assesses depressive symptoms over the past 2 weeks. Each item is assessed on a 0 – 2 scale. Scores over 11 are considered clinically significant. The SMFQ has acceptable psychometric properties with a Cronbach's α of 0.87. †	BL, 12w, 6M, 12M

	Child-Guardian Relationship; G	*Child-Parent Relationship Scale*[112] (CPRS). The CPRS is an unpublished measure that includes 15 items that assess the warmth of the child-guardian relationship from the guardian's perspective. It has been used successfully in the POFO study with acceptable levels of reliability and validity. Items are scored from 1-5. +	BL, 12w, 6M, 12M
	Child Functioning; C	*Child and Adolescent Functioning.* This locally derived tool will be developed during year 1 of the project, following established procedures[113]. As in Bolton's other work, our team will conduct free list interviews to identify common areas of functioning for children in KE and in TZ (see Interview Guide and example measure in Appendix A). These qualitative interviews result in a list of approximately 10 -15 common activities/tasks (1 for boys, 1 for girls, for each country).Interviews will be conducted by study interviewers.	BL, 12w, 6M, 12M
Other	Services Received; G	*Receipt of Support Services*. To measure services received by both conditions, we utilize a set of questions from POFO that have been validated and used in both Moshi, TZ and Bungoma, KE to assess potential supports for children and guardians from a range of formal and informal sources and an interview format adapted from the *Child Status Index* (CSI) to query the guardian about all services received in the 12 CSI factors. +	BL, 12w, 6M, 12M
Implementation Outcomes	Objective Fidelity; RC	*TF-CBT Checklist Scoring Sheet—TZ Group Version*. The original TF-CBT Checklist Scoring Sheet, used in prior TF-CBT studies and has a well developed coding manual [114]. The intraclass correlations for the parent and child sessions were .80 and .79, respectively. Our team has revised this coding measure for coding group delivery of TF-CBT, based on the 12-week protocol used in the feasibility study. The coding measure has been piloted by the feasibility study lay counselors. Inter-rater reliability was acceptable. Our team is currently refining and testing this measure (to be completed 9/2011). As this measure is under revision, the original is included in the Appendix.	3 random selected sessions/ group
	Self-report of Fidelity, Attendance; LC	*TF-CBT Group Report—Child and Guardian Forms*. These group report forms were developed for lay counselor self-report of fidelity to TF-CBT. It allows for self-report of (1) components covered for each group; (2) time spent on each topic; (3) notes on each component; (4) participant attendance; (5) short subjective report on response of each i participant (child or guardian, depending on the form). Examples of 6 groups are included in Appendix A. †	Each TF-CBT group
	Acceptability; G	*Exit Interview Guide.* We plan to use the exit interview that was used in the feasibility study to assess acceptability and appropriateness. The exit interview solicits guardian feedback about the TF-CBT intervention. †	12w, TF-CBT only
	Counselor Knowledge, LC	*TF-CBT Knowledge Test.* In collaboration with Dr. Cohen, our team has developed a short TF-CBT knowledge test that asks about specific TF-CBT components in which lay counselors are trained and are provided in the TF-CBT group. This test was piloted by the feasibility study lay counselors (*N* =3), who performed at 95%, collectively, on the test.	Post-T#; Post C1
	Supervisory Relationship , LC	S*upervision Alliance Scale*[115] (SAS). The SAS has 12 items; drawn from two scales[116] [117]. The 12-item measure assesses the counselor-supervisor relationship and has demonstrated predictive value for burnout and turnover intention and has a Cronbach's α of .95[115].	Post C1; Post C2

^ C= Child, G=Guardian, LC=Lay Counselor; RC: Research Coder (i.e., Data entry person)
* BL = Baseline; 12w = 12-14 weeks; 6M = 6 months; 12M = 12 months
# Post-T = Post-Training; Post C1: after delivery of one 1 cycle of groups (2 groups); Post C2: after delivery of 2nd cycle of groups
† Measure used in the TF-CBT for CTG Feasibility Study
+ Measures used in POFO (both TZ and KE)

3C5. Data Analysis Plan

Basic data screening procedures will be conducted (e.g., means, standard deviations, skewness, plotting relationships) to screen for errors and explore normality, linearity, form, and outliers. Data will be transformed as appropriate. We will confirm the assumption of randomization at baseline by testing cohort differences in outcome variables (i.e. symptoms), history of traumatic events and basic demographics (i.e. gender and age). Minor differences will be controlled for in statistical models as described below. Statistical analyses for the main aims will be conducted using the SPSS[118], Stata[119] and Multilevel/Hierarchical Level Modeling[120] (MLM/HLM) software programs. HLM allows for the presence of missing data at Level 1 (such as when participants are lost to follow-up) appropriately adjusting for data missing at random, particularly when covariates associated with missingness are included in the statistical model[121].

3C5a. Overview of Modeling Approach. Hypotheses related to Aim 1 will be tested using MLM (i.e. HLM, random coefficient models, mixed effects models), which are a powerful and flexible class of analytic approaches that allow for the analysis of non-independent data. MLM allow researchers to account for nesting within different data structures and to explicitly model effects across nested groups. For the current study, the outcome data will be observations of clinical outcomes at multiple time points, nested within children, who are also nested within TF-CBT groups (for the TF-CBT condition). Not accounting for the fact that some children are treated in the same treatment group, for example, could lead to biased estimates. The MLM approach reduces Type I errors caused by violating assumptions of independence, allows time-varying assessments and increases power by utilizing information from multiple time points in a single model.

We will test hypotheses through a standard approach to model-building, focusing on creating parsimonious explanatory models through progressive taxonomies as follows[122,123]. An unconditional model (i.e. one without predictors) of the outcome will be fitted first, which allows specification of the random effects, which in turn provides an estimation of the amount of interdependence at each level of clustering. For longitudinal models including multiple time points (i.e. client outcomes from baseline to follow up assessments), an unconditional growth model will be fit to identify time trends and inter-individual variance in trends. We will next test the effects of the primary variable of interest (e.g., condition assignment, or therapist fidelity to treatment model) on the outcome in a conditional model (i.e., one with predictors). Finally, theoretically relevant covariates will be

added to determine the robustness of the main effects. Relative goodness-of-fit for each successive model will be evaluated using likelihood ratio tests and deviance statistics.

3C5b. Primary Analyses

Aim 1. Test the effectiveness of a group model of TF-CBT for orphaned youth in two East African countries, including any variation by child age and gender.

Hypothesis 1: Children in the TF-CBT condition will demonstrate greater reductions in symptoms and greater improvement in overall functioning and the child-guardian relationship.

These analyses focus on whether TF-CBT produces significant reductions in symptoms (i.e. CTG, PTS, depression, behavioral problems) or improvement in functioning, or the child-guardian relationship compared to UC. Hypotheses will be tested in two ways using MLM. First, we test whether the TF-CBT condition differs from the UC condition at 12-weeks (i.e., end of TF-CBT). This hypothesis will be tested with a simple 2- level MLM, predicting the observed outcome (by child or guardian report) at 12-weeks, while accounting for clustering of individuals within TF-CBT groups, for the TF-CBT condition. The general Level 1 equation, which models individual differences in symptoms at 12-weeks, would be as follows:

Level 1:	$Symptoms_{ig} = B_{0g} + B_{1g}PreSx + B_{2g}Cov + e_{ig}$
Level 2:	$B_{0g} = \pi_{00} + \pi_{01}Treatment + r_{00}$ $B_{1g} = \pi_{10} + r_{00}$ $B_{2g} = \pi_{20}$

For example, where the outcome is the level of symptoms for a given client *i* in group *g;* B_{0g} (the intercept) represents the average 12-weeks level of symptoms for all children in a given group *g*, B_{1g} is the effect of pre-treatment symptoms, B_{2g} is the effect of child/guardian-level covariates (such as demographics: child age, gender), and e_{it} represents residual variance in the outcome for individual *i* in group *g*. If randomization was effective, the effects of pre-treatment symptoms may be ignored. The Level 2 equations represent how the coefficients at Level 1 are distributed across treatment groups. Both the intercept and the effects of pre-treatment symptoms (if needed) would be specified as random variables, which would allow their effects to differ across treatment groups. The level 2 equation would follow the general form of $B_{0g} = \pi_{00} + \pi_{01}Treatment + r_{00}$, which uses condition-level variables (such as assignment to TF-CBT or UC) to predict how effects differ. Thus the hypothesis that group-based TF-CBT produces significant improvements in symptoms over the UC condition would be tested by evaluating the significance of π_{01} above, which tests the effects of condition assignment on 12-week symptoms.

To test how TF-CBT influences trajectories of symptoms over time (e.g., 6-months, 12-months), analyses may be expanded to incorporate multiple times of assessments by adding a third level to the above model to test a growth curve model in the MLM framework. Because there are expected to be no differences across conditions at pre-treatment, the intercept could be fixed to the final time point (12-months), allowing two related but distinct questions to be tested: (1) does TF-CBT predict lower levels of symptoms at 12-months; and (2) does TF-CBT produce greater changes (reductions) in symptoms over time than receipt of usual care? The general Level 1 equation would then represent an individual's level of symptoms at a given time point, Level 2 equation would represent individual differences in the Level 1 equation, and Level 3 would represent group differences in the Level 2 equations. Thus the new Level 1 equation would be: $Symptoms_{tig} = B_{0ig} + B_{1ig}Time + e_{tig}$, representing Symptoms at time *t* for individual *i* in group *g*, B_{0ig} being the level of symptoms at Time 0, and B_{1ig} being the effects of Time on symptoms (i.e. the rate of change in symptoms over time). Both the intercept and slope would be allowed to randomly vary across individuals, allowing their prediction from individual level variables (such as pre-treatment symptoms or covariates). For example, the Level 2 equation for the effects of Time would be $B_{1ig} = \pi_{00} + \pi_{01}Cov + r_{00}$. Finally, effects at Level 2 would also be allowed to randomly vary across groups, allowing us to model the effects of condition on the level of symptoms at the final time point, and on the rate of change over time.

It may be that there are significant individual differences in symptoms at 12-weeks, but that these differences do not continue to increase or are not maintained. The hypothesis of decreasing gains for the TF-CBT condition would be tested by adding a quadratic component to the linear growth model. Specifically, the quadratic effect (of time, represented as $time^2$) would test whether there are decelerations in the rate of change in symptoms from baseline to the 12 month outcome, and whether there are individual differences in those decelerations.

Aim 2. Examine any differences in clinical or implementation outcomes for country (TZ; KE) or setting (urban, rural), including differences in receipt of usual care.

These aims would be tested by adding country and rural or urban setting as predictors at Level 2. These analyses would test whether country or setting explain between-condition differences in treatment outcomes at

a specific time point, and for the growth models, whether they explain differences between conditions in the rate of change over time.

Aim 3. Examine the impact of implementation factors (e.g., TF-CBT fidelity, lay counselor-supervisor relationship, child/guardian attendance) on outcomes.

Analyses for Aim 3 will focus on how implementation variables (such as attendance, fidelity, provider knowledge) are related to outcomes at 12-14 weeks (end of TF-CBT) and at the follow-ups. These analyses will be restricted to those in the TF-CBT condition. These Aims are tested by expanding the models described in Aims 1 and 2, above, to include implementation variables at both the individual level (such as attendance) and the group level (TF-CBT fidelity). For example, MLM equations that look at implementation effects on post-treatment levels of symptoms could be:

Level 1:	$Symptoms_{ig} = B_{0g} + B_{1g}PreSx + B_{2g}Cov + B_{3g}Attendance + e_{ig}$
Level 2:	$B_{0g} = \pi_{00} + \pi_{01}Fidelity + r_0$ $B_{1g} = \pi_{30}$ $B_{2g} = \pi_{30}$ $B_{3g} = \pi_{30} + r_2$

These models test how attendance during treatment and fidelity of the treatment provider influence symptoms at 12-weeks and at follow-ups, treating the intercept and the effects of attendance as random effects, and the effects of pre-treatment symptoms and covariates as fixed effects.

3C5c Power. Power analyses were conducted using Optimal Design 2.0[124]. A primary concern when estimating power in HLM focuses on the Interclass Correlation Coefficient (ICC) for providers, as providers are nested within conditions. Higher positive ICCs result in less statistical power, and few estimates of provider ICCs for fidelity to treatment are available. A review of 20 studies predicting client functioning found provider ICCs clustering from -0.1 to .06[125]. Because precise estimates for ICCs are unknown, we examined ICC thresholds within a range of effect sizes (with .05 Type I error rate, power of .80, 8 children per TF-CBT group; 320 children total). Estimates did not include the effect of covariates which, if moderately correlated with the outcome variable, will increase statistical power. Therefore, these estimates present a conservative estimate. Our primary hypothesis test (i.e. differences at 12-weeks between TF-CBT & UC) is sufficiently powered ($1-\beta$ = .80) to detect small effects (.35) with ICCs up to .15, moderate effects (.50) with ICCs up to .30, and all conceivable large effects. For detecting condition differences in terms of the linear or quadratic slope, analyses suggested that the proposed *N* has power ($1-\beta$ = .80) to detect effects as small as .29 on slopes. Finally, for Aim 3, the current sample of 320 individuals in the TF-CBT condition, the current study is sufficiently powered to detect small (.21) effects of individual implementation variables on outcomes, but with only 20 clusters (i.e., groups) the study will have less power to detect all but large effects of group-level variables (e.g., fidelity).

3C6. Rationale of Choices Made in the Research Design. Our team carefully considered various design and methodological challenges, our rationale for various decisions is discussed here.

Comparison Condition. Our team considered a range of comparison conditions, including another active treatment arm (12-week social support group) to control for intervention time and a waitlist control. We decided to use a UC comparison group to test differences from services usually received in LAMICs, given scarcity of resources. We considered allowing children and adolescents in the control group to receive the TF-CBT intervention at 6 months (which would preclude examining outcomes at 1-year), but decided against this so that we could examine whether provision of TF-CBT (short-term, but still time-intensive; 12-weeks, 15 sessions) has a lasting impact on clinical outcomes, the child-guardian relationship, and child functioning.

Training and Supervision of Lay Counselors. The counselors in our pilot study were directly trained and supervised by TF-CBT and mental health experts. We decided not to replicate this model of training and supervision in the proposed RCT because (1) there are sufficient findings supporting the ability of local, lay supervisors to supervise lay counselors and (2) our interest is in moving towards increased local responsibility. Therefore, it is necessary to examine effectiveness of TF-CBT, and other mental health interventions, under conditions that are more likely to build sustainability.

3C7.Hazardous Procedures/Materials. None are planned or expected.

3C8. Implications. If effective, TF-CBT offers an EBP that can improve outcomes for high-need orphans in LAMICs. In addition, our research contributes to the growing body of literature on EBPs in LAMICS and extends other work in the task shifting area by incorporating trained lay counselors into both the training and supervision of a subsequent generation of lay counselors to increase local responsibility and sustainability.

A. Specific Aims

Worldwide, 143 million children are estimated to have lost one or both parents, 16.6 million of these to HIV/AIDS.[1] In Sub-Saharan Africa, the number of orphans due to HIV/AIDS has doubled in the past 10 years[2]. Orphaned children in Africa and in other low and middle income countries (LAMICs) are vulnerable to nutritional, medical, educational, and mental health disorders and problems[3-13]. Relative to their non-orphaned peers in LAMICs, orphans have higher rates of mental health problems that include traumatic grief, posttraumatic stress, depression, and anxiety[14-18]. When parents die from HIV, children are faced with the sickness and death of one or both parents, the stigma of HIV, and their own possible infection. Among orphans, those orphaned by HIV have even higher rates of mental health problems, with childhood traumatic grief particularly prominent [14,19]. Previous work by our team and others indicates that trauma exposure among orphans is not limited to parental loss but also includes higher rates of exposure to other potentially traumatic events, including abuse, exploitation, and community and domestic violence[18]. Children who have been orphaned are less likely to complete school, have higher rates of sexual risk-taking, and lower levels of health-seeking behaviors [18,20,21]. These effects result in high costs to society and threaten the achievement of many Millennium Development Goals[22].

Despite high mental health needs among orphaned children, only 0.16% of any children with need receive even basic treatment[23] due largely to the substantial mental health treatment gap in LAMICs[24]. Policy makers clearly recognize the importance of addressing the needs of orphans; through PEPFAR, the US alone committed $4.3 billion over five years to services for orphans.[25] The National Institutes of Health (NIH) recently requested applications to: 1) advance the science on effective services for orphans (RFA-HD-10-017) and 2) to identify "effective and efficient methods…and strategies to disseminate and implement" health and mental health interventions (PAR-10-038; RFA-AI-11-003). To date, few initiatives focused on orphans have included mental health interventions beyond basic psychosocial support. Empirical guidance is needed to inform both effective service options for orphans ***and*** to inform implementation and sustainability of interventions found to be effective. As stated in the recently released NIH/PEPFAR RFA, focused specifically on HIV/AIDS (i.e., RFA-AI-11-003), "scientific advances regarding the ***implementation*** of effective interventions have not kept pace."[26]

To address these gaps, we propose a randomized clinical trial (RCT), to be conducted in Moshi, Tanzania (TZ) and Bungoma, Kenya (KE) of Trauma-focused Cognitive Behavioral Therapy (TF-CBT), an evidence-based mental health treatment with a strong body of evidence in the US[27,28] and promising findings of feasibility, acceptability, and potential positive child outcomes in two East African pilot studies[29,30]. The proposed RCT builds on our team's NIH-funded feasibility study (MH081764) of TF-CBT in TZ. A growing body of evidence suggests that brief Evidence-based Practices (EBPs) are both feasible and effective in LAMICs and can be delivered using a task shifting approach, in which lay counselors deliver EBPs when trained by and under the supervision of mental health professionals [31-34]. Using this approach, lay counselors in TZ provided a 12-week group-based TF-CBT intervention to orphaned children with childhood traumatic grief and posttraumatic stress and their primary guardians. To date, six of eight TF-CBT groups have been completed (8 children per group; 2 rural; 2 urban; *n* = 48). TF-CBT has proven acceptable and feasible, with high levels of reported satisfaction from children and guardians and promising clinical outcomes (e.g., improvements in grief, posttraumatic stress, and depression). However, a RCT of TF-CBT in LAMICs has not been conducted.

In the proposed RCT, we plan to enroll 640 children (ages 7-13). In each country, half are randomized to receive TF-CBT and half to receive usual care orphan supports (*n* = 320). The sample includes children from urban and rural areas. In addition to assessing clinical outcomes (e.g., traumatic grief, posttraumatic stress), our proposal includes enhanced local involvement and responsibility, in which the lay counselors from our feasibility study are included as co-trainers and supervisors of lay counselors, following established training models[33-35]. Further, we will assess the impact of implementation factors (e.g., TF-CBT fidelity) on treatment effectiveness to advance our understanding around effective implementation.

The primary Aims of this R01 are to:

*Aim 1.*Test the effectiveness of a group model of TF-CBT for orphaned youth in two East African countries, including any variation by child age and gender.

Hypothesis: Children in TF-CBT condition will demonstrate greater reductions in symptoms as well as greater improvement in overall functioning and the child-guardian relationship, compared to Usual Care.

Aim 2. Examine any differences in clinical outcomes or implementation factors for country (TZ, KE) or setting (urban, rural), including differences in receipt of usual care services.

Aim 3. Examine the impact of implementation factors (e.g., TF-CBT fidelity, lay counselor-supervisor relationship, child/guardian attendance) on clinical outcomes.