HRP-503 - Template – Protocol

MICHIGAN STATE UNIVERSITY HUMAN RESEARCH PROTECTION PROGRAM

- Complete this template for new exempt, expedited, or full board studies.
  - Complete Section I for ALL studies (exempt, expedited, full board)
  - Complete Section II ONLY if your study does not qualify for exemption and requires an expedited or full board review. Contact the IRB office if you have any questions.
- CLICK™ IRB:
  - Include the template with a New Study Submission.
  - Upload the completed template to the Basic Information SmartForm page, Question 10.
  - When uploading documents to Click (e.g. consent documents, instrument), provide distinct file names.
- See the Click Quick Guides and the HRPP Manual for more information, available at hrpp.msu.edu

Study Title:	Caregiver Early Child Development Training for Preventing Konzo from Toxic Cassava in the DR Congo MSU IRB approval date: February 14, 2020
Click Study ID (if known):	2272
Sponsor (if applicable):	NIH
Sponsor ID (if applicable):	

Section I. IRB Protocol for <u>All</u> Studies

Section I is completed for ***all studies*** and includes questions to determine whether the study qualifies for exemption. Section II is <u>only</u> completed if the study does not qualify for exemption.

1. Hypothesis / Objective / Goals / Aims.

Briefly describe the study's hypothesis / objectives / goals / aims.

Konzo is a neurological disease associated with chronic reliance on poorly processed cyanogenic cassava as the main source of food. We found that school age children from konzo areas present with poor neurocognition compared to those from nearby non-konzo areas, persisting and worsening even 4 years after initial assessment. Our most recent work has extended these findings to children as young as a year in age, suggesting that the neurodevelopmental impact from cassava cyanide neurotoxicity may begin as soon as children are weaned from breast milk to cassava porridge. The "wetting method (WTM)" is a simple and effective method of detoxifying cassava flour prior to eating that is being taught to rural women in a clinical-trial study by our group in the Democratic Republic of Congo (DRC). The present proposal seeks to combine a curriculum of mediational intervention for sensitizing caregivers (MISC) with a WTM training program (MISC/WTM). MISC is an early childhood development (ECD) caregiver training program previously demonstrated in clinical trials by Boivin and colleagues to improve health, neurodevelopmental, and caregiver mental health outcomes in rural Ugandan HIV-affected households. Training 66 randomly selected moms from a cohort of 100 on MISC/WTM (while the remaining 34 get WTM only) will better sensitize mothers to their children's development, leading to better WTM adherence while providing practical ECD benefits.
The Aims for this study are:
1. To establish the feasibility of adding a biweekly 1-year MISC/WTM training program for mothers and their 1 through 4-year-old children, led by peer trainers from the community. MISC has been previously implemented for HIV-affected households in Uganda, but not for konzo communities in the DRC.

2. To document whether better adherence to WTM through MISC will lead to lower household flour cassava cyanogenic content and lower urinary thiocyanate (U-SCN) levels in the mother/child dyads. We will also test for improved child outcomes on the Fagan Test of Infant Intelligence (with automated eye tracking), Mullen Scales of Learning (MSEL), the Early Childhood Test of attention (ECVT; eye tracking), and the Color-Object Association Test (COAT). Caregiver depression/anxiety and corresponding functionality for activities of daily caregiving should also significantly improve.
3. To explore whether reductions in cyanogenic exposure from cassava and improved child's neurodevelopmental outcomes are mediated by improvements in caregiver emotional wellbeing and caregiving functionality immediately post MISC intervention and at 6-month follow-up. Overall Impact. Our DRC/USA partnerships will be the first to implement an evidence-based ECD program for at-risk children in the DR Congo, strengthening DRC Ministry of Health efforts to prevent konzo. If MISC strengthens the programmatic efforts to prevent konzo, the public health impact will be enormous, given the scope of risk in toxic-cassava dependent populations throughout central/western Africa. MISC could then also be used for children at ECD risk from other infectious diseases.

PUBLIC HEALTH RELEVANCE: Early childhood (1 through 4 yrs) is a period of dramatic developmental change that can be seriously compromised by exposure to toxic cyanogenic cassava (konzo disease), with potentially great impact throughout central and western sub-Sahara Africa in regions dependent on this food staple. In the face of ongoing economic instability and nutritional, medical and educational deprivation affecting communities at risk for konzo in the Democratic Republic of Congo, no programs exist for sustaining a favorable developmental milieu for young children. By establishing the viability of caregiver training intervention to enhance functionality among caregivers and improve caregiving quality while preventing konzo, this project can benefit neurodevelopment for tens of millions of at-risk children.

2. Procedures.

Describe the research procedures that involve obtaining information or biospecimens about a living person through interaction or intervention and/or by obtaining their identifiable private information or identifiable biospecimens. If subjects will participate in or undergo an intervention, fully describe the intervention. If the procedures are longer than 1 page, provide a summary and include the full procedures as an attachment.

Caregiver/child dyads will be randomized (by cluster) whereby 66 of the 100 households will be selected to randomly receive MISC/WTM caregiver training to enhance caregiver mental health and functionality and early childhood development. The remaining 34 households will receive WTM only (considered the recommended standard of care for the prevention of konzo disease in at risk communities). This is in order to see if adding MISC to caregiver training enhances adherence to WTM for flour detoxification, corresponding child neurodevelopmental and caregiver functionality mental health outcomes – as compared to WTM alone for similar households. To maintain concealment of MISC training allocation, the randomization sequence was generated by the trial biostatistician located in the USA, who also serves as our clinical methodologist and biostatistician for the R01 WTM konzo prevention non-inferiority clinical trial.
The WTM intervention. The intervention will implement the WTM cassava processing technique in participating households. Twenty women with leadership and communication skills have already been trained and are implementing WTM in the R01 trial and will do the training for our WTM-only households in this R21 study These are mothers who master the WTM technique and have been certified as trainers to train and support other small groups of other mothers. They have to been able to bring the cassava cyanogenic content to the lowest achievable level, which must be < 10 ppm as per the WHO recommendations.
The wetting method to remove cyanogens from cassava flour involves adding dry flour to a bowl and marking the level on the inside of the bowl. Water is then added with mixing, the volume of

the damp flour initially decreases and then increases as more water is added. No more water is added when the level of the wet flour comes up to the mark. The wet flour is then placed in a thin layer not greater than 1 cm thick on a mat and allowed to stand for 2 h in the sun or 5 h in the shade for the hydrogen cyanide gas to escape. The damp flour is mixed with boiling water to make the thick porridge (fufu) which is eaten with pounded, boiled cassava leaves (saka saka) or some other food to give it flavor.Colorfully illustrated and durable laminated posters depicting the WTM will be distributed to participating households as our previous experience indicate that they are kept for more than a year on walls in houses. The WTM approach is our chosen strategy for prevention, because it has been repeatedly demonstrated that it helps remove cyanogens in poorly processed cassava flour to safe levels, even if the flour is initially very toxic due to poor or limited processing.

Mediational Intervention for Sensitizing Caregivers (MISC) Training Intervention. The MISC/WTM trainers will be different from the WTM-only trainers (who will not be certified in MISC). The MISC/WTM training will be led by 10 women leaders in the Kahemba community (different than the WTM peer or professional trainers) who have already been trained by our Uganda MISC consultants in April 2018 and are presently implementing MISC training in Kahemba with 40 households with younger children as part of a pilot study funded by Michigan State University African Alliance Partnership program grant to Professor Boivin (http://aap.isp.msu.edu/research-funding/grant-program/scaling-grants/). Our two principal Ugandan MISC consultants led the MISC intervention teams in both of Boivin's R34 MH082663 and R01 HD070723 cluster RCT studies, and have already conducted a one-week training workshops with our 10 women leaders and worked with them in the initial adaptation and implementation of MISC in Kahemba for a one-week period (May 2018). The Ugandan MISC trainers will continue to train the community leader women responsible for MISC training at the Kahemba study site for the present R21 study until they are MISC-certified, and continue quality assurance follow-up for fidelity of MISC training in Kahemba every six months throughout the R21 study period. In the present pilot study phase, training session videos of the ten Kahemba community leader woman MISC trainers conducting individual training sessions are planning to upload videotapes of training sessions monthly to a highly secured Dropbox. These will be evaluated by our Uganda MISC expert consultants as part of a quality assurance evaluation for "fidelity of intervention" in Kinshasa and in Kampala Uganda, with the help of a DRC assistant working with us in Kampala and fluent in the local DRC languages of Kikongo and Chobwe

Fidelity of both interventions will be maintained through established methods outlined by the NIH Treatment Fidelity Workgroup on consistency in dose, providers, delivery, and receipt of the intervention

Questionnaires will be administered by an experienced interviewer with local language fluency and overseen by a study coordinator from the Congo Ministry of Health. The questionnaire seeks individual demographic data, occupation (mostly local farming), diet composition (mostly uniform cassava), cassava preparation method (including any changes resulting from prior intervention), 24- hour diet recall (composition, amount and number of meals), smoking history and practice (usually negative), prior family episodes of acute cassava cyanide toxicity (severe headache, vomiting, convulsions, coma, death), and onset date and course of any symptoms of konzo among household members.

All caregivers will complete these questionnaire, undergo on-site neurological screening and urine SCN and provide blood and urine specimens for the biomarker study at baseline, after six-months of caregiver training, and at one-year at the conlcusion of the caregiver training period. A sample of cassava flour originating from the subject's household will be collected on the same day prior to urine collection. Trained technicians from the Ministry of Health will measure the cyanogen content of the cassava flour using the picrate kit as in previous studies or interventions.

Children will be evaluated with a battery of non-invaisve, performace-based nueorcognitive tests at baseline, after six months and at one year after initiating trainings. These evaluations include the Modified Fagan Test of Infant Intelligence, the Mullen Scales of Early Learning, the ZEarly

CHildhood Vigilance Test. Caregivers will respond to the Home Observation for the Measurement of the Environment, the Hopkins Symptoms Checklist-25, and the caregiver functional impairment for daily activities.

Other caregiver/child assessments include video-taping of 15 minutes of child/caregiver interactions (5 minutes of caregiver feeding of child, washing of child, and work or play with child). These videos will be used on tablet as part of the MISC training, but also scored for observed mediational interactions in order to assess fidelity of MISC training and quality of caregiving. These video will be encrypted and password secured and will not be kept after the study, so as not to put the study identity of mothers and their children at risk. Mothers will consent to these videos as part of the informed consent process, and it will be a condition of eligibility for enrollment. This procedure with recording and scoring and management of videos was done for our Uganda-based clinical studies without adverse incidents or problems, and were clearly an important part of this type of caregiver training ECD intervention and assessment in a field-based clinical trial.

CLICK™ IRB: Upload instruments (e.g. surveys, interview questions, questionnaires, etc.), measures, variables, etc. to the Supporting Documents SmartForm page.

3. Subject Population.

A. Describe the subject population.

We will study 100 non-konzo mother/child dyads, and all household children 12 to 48 months of age. 34 mother/child pairs will receive 12-months of biweekly home-based personalized training sessions with wetting method (WTM) training only to detoxify cassava flour in the prevention of konzo, and 66 dyads will receive 12 months of MISC caregiver training to improve early childhood development (ECD) combined with WTM. These families represent a homogenous population of Congolese people living in the Kahemba district of the Bandundu Province, Democratic Republic of Congo (DRC) in southwestern Bandundu province. People in this rural district depend heavily on daily cassava root and leaves for food and cash income. A typical population of 100,000 cultivates about 5000 hectares of cassava per year. Traditional varieties of cassava, which are subject to the cassava mosaic virus, yield around 6 tons/hectare per year. Crop losses in the 1990s ranged from 5% to 95%, thereby resulting in severe food insecurity. Cassava dependency resulted in up to 5% of individuals in affected villages developing walking difficulties typical of konzo. A substantially larger percentage (estimated up to 10%) has neurological signs and symptoms of an earlier stage of konzo in which ambulatory difficulty is not overt. Our recent findings suggest that deficits in cognition may also be part of neurological picture. Therefore, this is an at-risk population.

B. Select the age range of subjects (select one):

- ☒ Adults who are 18 or older
- ☐ Specific Age Range: _____ (Enter Minimum) to _____ (Enter Maximum)

C. Study purposefully includes the following subject population(s) (select all that apply):

- ☐ Cognitively impaired adults
- ☒ Minors (children) (view information about the definition of a child)
- ☐ Minors who are wards of the state
- ☐ Pregnant women, fetuses, or neonates
- ☐ Prisoners
- ☐ Students

D. Study involves (select all that apply):

- ☒ Obtaining, using, studying, or analyzing biospecimens

☐ Funding, support, or other requirement to comply with U.S. Department of Justice regulations
☐ Incomplete disclosure or attempted deception of subjects
☐ Human subject research that will be conducted in the European Union (EU) or involve EU collaborators (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK - England, Scotland, Wales and Northern Ireland), if selected, please list the EU member state(s):

Procuring cassava flour samples and urine samples from villagers in Bandundu are routine activities for the INRB sub-contractor and the teams from the Congo Ministry of Health. They are experienced in collecting, processing, storing and shipping samples. Pre-printed labels with unique identification numbers are placed on each sample tube. Cassava flour and urine samples and their analysis are performed in the village setting, with results evident to both subject and investigator. The significance of the reagent-induced color change (density varying directly with SCN concentration) will be explained to the villager as part of the intervention. The SCN content and color of the urine sample will be entered into the questionnaire and the sample discarded. In the R01 study, additional urine, dry blood spots (DBS), and blood (serum/plasma) samples are being individually labeled for laboratory analysis of the different biomarkers (8.12-isop, pep1, pep2, and homocitrulline). Therefore, a good procedure is already in place in terms of securing the custody chain for handling specimens of this sort for our R21. Again, this information will be gathered before, at 6- and at 12-months following MISC training in coordination with the R01 study, and be made available for the proposed R21 study for co-enrolled caregivers and the very young study children in their households. In the present R21 study, urine samples are individually labeled with their unique ID numbers, flash-frozen or in a dry-ice refrigerated container as needed and transported to INRB Kinshasa. A transmittal slip (multiple copies) accompanies each sample, and a copy is retained in the study office chain-of-custody (COC) procedures ensure security of transportation from the origin (Bandundu villages) to destination (INRB, Kinshasa). The local study coordinator fills out a three-part check-in sheet using the sample tracking codes. The study number in combination with the sample number is identified as the key field, and all the information specific to the sample is referenced by the codes. The check-in sheet must be complete in order to track biological samples. After the check-in sheet is completed, the first copy is used to enter the information into the Sample Tracking Database and then filed with the laboratory liaison. The second copy is given to the Kinshasa project leader. The sample custodian compares each sample with its corresponding
COC, then signs and dates the COC showing receipt at the warehouse. A three-part check-out sheet is used to enter data into the Sample Tracking Database and track sample location. Comparable COC procedures will be used for the secure mailing of samples from the DRC to the USA, for delivery to MSU (R21) and OHSU (R01). Unique sample ID numbers will be used by the OHSU study coordinators to register the samples upon arrival, with crosschecking of each sample on a listing provided by the Kinshasa dispatcher.
Data are being entered into the secure database immediately after each batch of samples has been analyzed.

CLICK IRB: Upload the debriefing script, document, etc. to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

4. Estimated Study Duration.

Provide the time estimated to complete all human subject research, including analysis of the subjects' identifiable private information.

3 years

5. Reasonably Foreseeable Risks.

A. There are (select one of the following):

☒ No reasonably foreseeable risks to subjects
☐ Reasonably foreseeable risks to subjects

B. Explain the selection. *If you selected that there are reasonably foreseeable risks to subjects, describe the risks, considering physical, psychological, social, legal and economic risks.*

The major risk to enrolled subjects concerns misunderstanding of the purpose of the study, fear of the consequences of participating or not participating, stigma arising therefrom, and concern regarding study outcomes. Another potential risk is a failure to understand why a medical team is focused on prevention of konzo and cannot offer a treatment or cure for extant disease victims. Based on our prior experience in our preliminary research described in the research plan (Kashala-Abotnes et al., 2017) as well as in the Uganda MISC clinical trial studies, we have documented no adverse effects from neurodevelopmental testing of the younger children. The same is true for the caregiver functionality and depression/anxiety (mental health) questionnaires, and HOME evaluations specific to this proposal.

C. If you selected that there are reasonably foreseeable risks, describe the procedures for protecting against or minimizing potential risks and provide an assessment of their likely effectiveness.

Risks relating to misunderstanding will be minimized by the process of consenting as described above, with sequential explanations provided to tribal leaders, villager groups, and individual subjects. We have protocols in place to protect human subjects from the assessments we're using and report adverse events from the R01 study which this R21 study is occurring within its jurisdiction. Data confidentiality will be ensured by the procedures explained above, including the use of unique numbers to identify enrollees, and the secure storage of identifying personal biodata (including a photograph) on the front page of the questionnaire that has been separated from other data fields on the questionnaire. These procedures are expected to be effective since the INRB sub-contractor is experienced in the conduct of human research studies to international standards. Any subject with a condition that requires medical attention will be referred to the general hospital serving the area of interest.

6. Conflict of Interest.

Do any investigators or research staff have a financial interest related to the research that has not otherwise been disclosed elsewhere in this submission? ☒ No ☐ Yes

7. Exemption Criteria. ☐ Not Applicable

A study may qualify for exemption when the only involvement of human subjects will be in one or more of the following categories (please view full exemption category / description here: https://hrpp.msu.edu/help/required/exempt-categories.html). ***(If the study does not qualify for the exemption criteria, do not complete this question and proceed to Section II.)***

A. Exemption Categories.

1. Select the category(ies) applicable to the study if the only involvement of human subjects in this study will be in one or more of the categories. Studies involving prisoners cannot be exempt UNLESS the research is aimed at involving a broader subject population that only incidentally includes prisoners *If your study is subject to U.S. Department of Justice requirements, do not complete this section; complete 7A2 below.*

☐ ***Exempt 1.*** Research conducted in established or commonly accepted educational settings, involving normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide

instruction. ***IF YOU SELECTED THIS CATEGORY, EXPLAIN WHY THE RESEARCH WILL NOT LIKELY ADVERSELY IMPACT STUDENTS' OPPORTUNITY TO LEARN REQUIRED EDUCATIONAL CONTENT OR THE ASSESSEMENT OF EDUCATORS WHO PROVIDE INSTRUCTION.***

☐ ***Exempt 2.*** Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (i) Information obtained is recorded by investigator in manner that identity of subjects cannot readily be ascertained, directly or through identifiers linked to subjects
- ☐ (ii) Any disclosure of subjects' responses outside research would not reasonably place subjects at risk of criminal or civil liability or be damaging to subjects' financial standing, employability, educational advancement, or reputation.
- ☐ (iii) **LIMITED IRB REVIEW REQUIRED**. Information obtained is recorded by investigator in manner that identity of subjects can readily be ascertained, directly or through identifiers linked to subjects, and responses could reasonable place subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation ***(LIMITED IRB REVIEW IS REQUIRED; YOU MUST ALSO COMPLETE QUESTION 7E TO DESCRIBE PRIVACY AND CONFIDENTIALITY SAFEGUARDS.)***

☐ ***Exempt 3.*** Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (i) Information obtained is recorded by investigator in manner that identity of subjects cannot readily be ascertained, directly or through identifiers linked to subjects.
- ☐ (ii) Any disclosure of subjects' responses outside research would not reasonably place subjects at risk of criminal or civil liability or be damaging to subjects' financial standing, employability, educational advancement, or reputation
- ☐ (iii) **LIMITED IRB REVIEW REQUIRED**. Information obtained is recorded by investigator in manner that identity of subjects can readily be ascertained, directly or through identifiers linked to subjects, and responses could reasonable place subjects at risk of criminal or civil liability or be damaging to subjects' financial standing, employability, educational advancement, or reputation ***(LIMITED IRB REVIEW IS REQUIRED; YOU MUST ALSO COMPLETE QUESTIONS 7E TO DESCRIBE PRIVACY AND CONFIDENTIALITY SAFEGUARDS.)***

☐ ***Exempt 4.*** Secondary research uses of identifiable private information or identifiable biospecimens. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ Identifiable private information or identifiable biospecimens are publicly available.
- ☐ Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects. ***IF YOU SELECTED THIS CATEGORY, CONFIRM THE FOLLOWING:***
  - ☐ Investigator and research team will not contact the subjects
  - ☐ Investigator and research team will not re-identify the subjects
- ☐ The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under the Health Insurance Portability and Accountability Act (HIPAA) 45 CFR parts 160 and 164.

☐ The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with specific federal privacy standards.

☐ ***Exempt 5.*** Federal demonstration projects.

☐ ***Exempt 6.*** Taste and food quality evaluation and consumer acceptance studies.

☐ ***Exempt 97***. ONLY applicable to research NOT FUNDED by a federal department or agency: Research involving the study of previously collected identifiable data (please view additional exclusions before selecting this category).

By checking the boxes below, you are confirming that the study will not include any of the following exclusions for the study's duration:

☐ Federal funding or federal training grants
☐ FDA regulated
☐ Sponsor or other contractual restrictions
☐ Clinical interventions (including clinical behavioral interventions)
☐ Receipt of an NIH issued certificate of confidentiality to protect identifiable research data
☐ Multi-site collaborative research study where another institution plans to rely or is relying upon MSU's IRB review

☐ ***Exempt 98.*** ONLY applicable to research NOT FUNDED by a federal department or agency: Prospective data collection with adults through verbal or written responses involving a benign intervention (please view additional exclusions before selecting this category).

By checking the boxes below, you are confirming that the study will not include any of the following exclusions for the study's duration:

☐ Federal funding or federal training grants
☐ FDA regulated
☐ Sponsor or other contractual restrictions
☐ Clinical interventions (including clinical behavioral interventions)
☐ Receipt of an NIH issued certificate of confidentiality to protect identifiable research data
☐ Multi-site collaborative research study where another institution plans to rely or is relying upon MSU's IRB review
☐ Children as research subjects

2. DEPARTMENT OF JUSTICE Exemption Categories. Complete this section ONLY if the research is subject to Department of Justice requirements.

i. Select the category(ies) applicable to the study if the only involvement of human subjects in this study will be in one or more of the categories. Studies involving prisoners cannot be exempt.

☐ ***Exempt 1.*** Research conducted in established or commonly accepted educational settings, involving normal educational practices.

☐ ***Exempt 2.*** Educational tests, survey procedures, interview procedures, observation of public behavior unless data is recorded in a manner such that subjects are identifiable and the responses could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation (research cannot involve children, except for educational tests or observation of public behavior where the investigator does not interact with the child).

☐ ***Exempt 3.*** Educational tests, survey procedures, interview procedures, or observation of public behavior not otherwise exempt that involves public officials or federal statute.

☐ ***Exempt 4.*** Collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if publicly available or information is recorded by investigator in a manner that subjects cannot be identified.

☐ ***Exempt 5.*** Federal demonstration projects.

☐ ***Exempt 6.*** Taste and food quality evaluation and consumer acceptance studies.

ii. Explain why the study presents minimal risk to subjects.

B. By checking the boxes below, you are confirming that the following are true and will remain true for the study's duration:

- ☐ Selection of subjects is equitable (considering the purposes of the research, setting in which research will be conducted, any vulnerable populations).
- ☐ If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
- ☐ There are adequate provisions to maintain the privacy interests of subjects.
- ☐ Safeguards are or will be put in place to protect against any coercion or undue influence if you or members of your study team are or may be associated with the subjects at any point in the study (e.g. students, employees, colleagues, patients).

C. Consent

i. There will be a consent process for the study's duration that will disclose information such as that the activity involves research, a description of the procedures, that participation is voluntary and withdrawal is without penalty, and the name and contact information for the researcher (select appropriate option below):

- ☐ For All Subjects
- ☐ For Some Subjects
- ☐ For None of the Subjects (consent will not be obtained)

CLICK IRB: Upload the consent document to the Consent Forms and Recruitment Materials SmartForm page.

ii. Please explain your selection.

D. Please acknowledge that you may not begin the research at non-MSU institutions (regardless of engagement), until you receive the appropriate approvals/permissions from the sites (e.g. IRB review/exempt determination from non-MSU sites, data use or research agreements, other regulatory approvals). An MSU exempt determination does not provide approval/permission for a non-MSU site, including sites with reliance agreements with MSU. Please note that non-MSU sites may have requirements that differ from MSU for exempt research. Note that this also applies to sites added after the MSU exempt determination.

- ☐ Acknowledged

E. LIMITED IRB REVIEW. If the exemption(s) require limited IRB review (if you selected Exemption 2(iii) or 3(i)(C) in Question 7A), complete questions 1 and 2 to describe privacy and confidentiality.

1. Privacy of Subjects.

How will subjects' privacy be protected? Consider the number of individuals interacting with the subject or subject's records, location of consent process and study, presence of individuals not associated with the study, sensitivity of the research.

2. Confidentiality of Data.

i. Select the appropriate option:

- ☐ Identifying or coded information will not be stored with the information and/or biospecimen(s)
- ☐ Identifying or coded information will be stored with the information and/or biospecimen(s)

ii. Please explain your selection. If you are storing identifying or coded information with the information and/or biospecimen(s), explain why identifiable or coded information and/or biospecimen(s) needs to be maintained and how long it will be necessary to maintain it.

iii. Describe the procedures and safeguards you will use to secure the information and/or biospecimen(s), including during transport of information and/or biospecimen(s).

Other Click IRB Documents to Upload As Appropriate (Applicable to All Studies)
• *Upload this completed protocol to the Basic Information SmartForm page, Question 10.* • *Upload any funding materials not accessible in Kuali Coeus in the Supporting Documents SmartForm page.* • *Upload the HRP-537 - Template - Use of Protected Health Information Application to the MSU Additional Study Information SmartForm page.* • *Upload the HRP-538 - Template - MSU Authorization to Use or Disclose Health Information for Researchers to the MSU Additional Study Information SmartForm page.*

IF THE STUDY MAY QUALIFY FOR AN EXEMPTION (INCLUDING THOSE THAT MAY REQUIRE LIMITED IRB REVIEW), STOP HERE AND DO NOT COMPLETE SECTION II.

CONTINUE ONLY IF THE STUDY DOES NOT QUALIFY FOR AN EXEMPTION. COMPLETE QUESTIONS 8-24 FOR AN EXPEDITED OR FULL BOARD STUDY.

Section II. Additional Questions for an Expedited or Full Board Study

Not all questions or sections are applicable to every study. If the question or section is not applicable, check the "Not Applicable" box. All other questions are required.

8. Expedited Categories.

A. Please select the Expedited category(ies) and sub-categories as applicable to the study if the only involvement of human subjects in this study will be in one or more of the categories. If the study involves more than minimal risk or none apply, select "The study involves more than minimal risk OR none of the expedited category(ies) apply."

☒ ***The study involves more than minimal risk OR none of the expedited categories apply. IF THIS OPTION IS SELECTED, DO NOT SELECT ANY OF THE EXPEDITED CATEGORY(IES).***

☐ ***Expedited 1.*** Clinical studies of drugs and medical devices only when condition (a) or (b) is met. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- ☐ (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

☐ ***Expedited 2.*** Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
- ☐ (b) from other adults and children [2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week

☐ ***Expedited 3***. Prospective collection of biological specimens for research purposes by noninvasive means.

☒ ***Expedited 4***. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

☐ ***Expedited 5***. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

☐ ***Expedited 6***. Collection of data from voice, video, digital, or image recordings made for research purposes.

☐ ***Expedited 7***. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

B. **For Studies Regulated by the U.S. Food and Drug Administration or the U.S. Department of Justice**. If you selected an expedited category, explain why the study presents minimal risk to subjects.

9. More than Minimal Risk Research. *Complete the following question if you selected "The study involves more than minimal risk OR none of the expedited categories apply" in Question 8A (Expedited Categories).*

A. Describe the relevant prior experience and gaps in current knowledge, relevant preliminary data, if any, and the scholarly background for, and significance of, the research based on existing literature and how it will add to existing knowledge.

Many chronic degenerative diseases, including those affecting the nervous system, are expected to have etiologies that result from yet-to-be-understood environmental exposures. Biomarkers of disease as well as pathways involved in their pathogenesis have yet to be uncovered. The propose study will shed light on the specifics of cyanide/cyanate-associated neurodegeneration. Our research findings as applied to early childhood development in konzo at-risk households will provide a strong basis for bench studies to reveal pathways involved in the death of motor neurons under exposure to cyanogenic compounds and propose drug candidates to either prevent or reverse symptoms that would arise from such exposure. For the study subjects, knowledge of how to prevent konzo (WTM), how to enrich the early learning environment of their children (MISC), with concurrent ECD-based understanding of how to promote brain development, greatly outweighs the minimal risks of bruising and/or adverse emotional effects for out maternal evaluations. For the community, the public health professionals, and the governments of countries with a cassava-dominated diet, this study is expected to provide information of markers that can be used to monitor risk associated with dietary dependency on poorly processed bitter cassava. In the present R21 proposal, we also hope to lay the foundation for partnership that can continue to build capacity for the implementation of caregiver training in practical strategies to protect and enrich the learning and neurodevelopmental environment of their at-risk very young children. The findings of the proposed studies are of high translational potential as they may be applicable to all manner of children at risk in the DRC neurodevelopmentally from poor or toxic nutrition, chronic and infectious disease that puts the caregiver and/or child at significant risk. Finally, our findings will help understand the type of risks and markers of neurological disease in very young children, associated with cyanogenic exposure that may arise under other circumstances such as exposure to cyanogenic compounds under environmental contamination during mining operations as occur throughout the DRC. MISC may provide practical tools for moms with which to intervene on behalf of their disabled children, while encouraging their mental health and functionality as it relates to caregiving quality.

B. Sample Size.

i. Total number of subjects who will be approached (including screen failures, controls and subject withdrawals) to reach enrollment numbers for the lifetime of the study at this investigator's sites.

140 households

ii. Total number of subjects who will be enrolled in the study at this investigator's site.

This study will enroll 100 households without a konzo individual (based on neurological exam) in the family and where the mother of one of more children under 4 yrs of age is the principal food preparer.

iii. Describe the statistical justification or rationale for the proposed sample size. Considerations for sample size may include the acceptable level of significance, power of the study, expected effect size, underlying event rate in the population, standard deviation in the population, saturation of themes, and/or have a theoretical basis.

This exploratory developmental R21 project aims to generate hypotheses for subsequent formal testing in an R01-supported larger trial. Therefore present sample size considerations are based

on project timeline and resources. With n=66 in MISC+WTM arm and n=34 in WTM only arm. Based on our clinical studies with a biweekly MISC caregiver training with mothers with HIV in rural eastern Uganda, we expect an over 90% retention rate for the full year. With this retention rate, the unadjusted effect size of 0.60 is detectable as statistically significant with power of 0.80 and 0.05 level of significance in two-tailed tests, that is differences between trial arms of 0.6 of the standard deviation or greater will be captured with statistical significance. For the main trial arm effect (differences between arms over time) from two repeated measures at 6 and 12 months with the planned covariance adjustment for baseline, the adjusted standard deviation is smaller than the unadjusted due to the reduction in error variance. Assuming correlation of 0.4 between pairs of repeated measures seen in past testing of MISC, the adjusted detectable effect size is 0.44. This effect size is consistent with past testing of MISC in HIV-affected households that produced effect sizes ranging from 0.35 to 0.53, and is below the threshold of 1/2 of the standard deviation for clinical significance. Thus any meaningful differences between arms will be captured with the proposed sample size. If the differences between trial arms correspond to the adjusted effect size smaller than 0.44, the effect size will be estimated in this study and used to power future clinical trial studies.

10. Minimal Risk Research. *Complete the following question if you selected an expedited category in Question 8A.*

A. Briefly describe the background for conducting the research. (1-2 sentences)

B. Sample Size.

i. Provide an estimated sample size for the lifetime of the study at this investigator's sites.

ii. Describe the basis for that estimate.

11. Benefits.

Describe any potential direct benefit(s) to subjects in this study, if any and the importance of the knowledge that may reasonably be expected to result. Within the description, do not include payment to subjects as a benefit.

The proposed research is designed to evaluate the value-added benefit of embedding WTM caregiver training within a more comprehensive MISC ECD program so as to better prevent the toxic effects of cassava on the developing brain in very young children. Also, we hope to identify key biomarkers of early childhood neurodevelopment that can be utilized to monitor the health risks associated with the consumption of poorly processed cassava. Finally, for the present mothers in konzo-affected communities in the DRC, we hope to see whether MISC can provide the same mental health benefits and the caregiving functionality in activities of daily living, and diminished depression and anxiety mental health benefits as evidenced in its application with Ugandan mothers with HIV. Throughout the recruitment process and the course of the study, villagers will learn that they need to correctly process cassava prior to its consumption and also, diversify their diet. This type of information is already given to the population by the PRONANUT team and will be just emphasized during interviews with villagers. The long-term benefit for healthy subjects is a reduced risk for konzo. For individuals at risk for konzo (mothers and even very young children; Kashala-Abotnes et al., 2017), the long-term benefit is a reduced risk for advancement of spastic paraparesis and associated neurodevelopmental disability. Reduced exposure of pregnant women and children to cyanogens should also promote brain development by reducing the risk for thiocyanate-induced hypothyroidism and/or cyanate-induced neurotoxicity.

Prevention of the risk of spastic paraparesis (konzo) in children and adults reduces chances of lifelong disability and societal stigma. This greatly outweighs the minimal risk of bruising or infection following phlebotomy. Automated eye tracking data will be gathered for two of the neurodevelopmental assessments (Fagan Test of Infant Intelligence working memory for human faces; Early Childhood Vigilance Test of attention). These data can be explored and evaluated for what they can provide in terms of additional neuro-ophthalmological and eye motility indicators of pre-clinical or early onset konzo disease in very young children. This has not been done before with pediatric konzo disease, and is a highly innovative feature of the present study proposal.

12. Screening, Recruitment, and Determining Eligibility.

A. Describe the criteria for who will be included or excluded from the study, including how subjects will be screened for eligibility

The proposed study will enroll 100 households from villages not presently enrolled in the R01 study. Eligible households must have at least one child less than 4 years of age, and the biological mother of the child must be the primary caregiver and food provider for the child.Eligible households may NOT have an older child or other family member already affected by konzo, thus the results will be generalizable to a broader population. Enrollment and randomization will occur at the village level. After 100 households with children 1-4 years of age complete baseline assessments, 66 of them will be randomly selected to undergo individualized MISC+WTM training sessions by peers trained in the MISC+WTM curriculum, who will come to their homes for a 1 to 2 hr. session on a biweekly basis.
Exclusion Criteria. At pre- study medical examination we will exclude children with a medical history of serious birth complications, severe malnutrition, bacterial meningitis, encephalitis, cerebral malaria, or other known brain injury or disorder requiring hospitalization. Also children with seizure or other neurological disability will be excluded. Serious CNS neurodisabilities would prevent such children from completing the MISC intervention, and possibly significant portions of the neuropsychological test battery.

B. Describe how subjects will be identified and recruited, including who will perform the recruitment.

This study will enroll 100 households where the mother is the principal caregiver and food preparer for one or more children from 1 to 4 yrs of age. If multiple biological children for a study mother are in that age range, they will all be enrolled and assigned as a household to the same caregiver training trial arm (either MISC/WTM or WTM only). However, the mother cannot be diagnosed with konzo following a full neurological exam at study enrollment, so that she is able to full implement MISC and/or WTM training. Randomization occurs by geographic location (i.e. village) rather than individually to minimize the likelihood of contamination and diffusion effects within a community. Our MISC biweekly year-long caregiver training with rural Ugandan HIV mothers using MISC training resulted in a pre- to post-year retention rate of over 90% in our dyads, and we anticipate at least that retention rate given the fact that our mothers and children are not affected by HIV and those health and motivational issues.

We will randomly select our eligible households from a health zone census already established by the PRONANUT for Kahemba district in preparation for the R01 peer- versus professional-led non-inferiority clinical trial for teaching small groups of mother the use of WTM to detoxify their cassava flour before eating. The present study will stratify its sample selection so that half of the participating households will be from peer- and half will be from professional-led health zones. Ho Also, the mothers of the study children are responsible day-to-day for cassava flour preparation. Mother and child have no prior history of severe medical condition or brain infection, accident, or injury which may preclude the ability to learn WTM and/or MISC and benefit from it in terms of functionality (maternal) or neurodevelopmental (child) outcomes. Once enrolled, they will be

cluster randomized to either the MISC/WTM or WTM-only peer-led training standard of care. Randomization will occur by geographic location (i.e. village) rather than individually to minimize the likelihood of "spillover" (contamination and diffusion) effects within a community, whereby caregivers receiving training by a specialist provider might share aspects of their experience with caregivers receiving training from a peer-provider. Therefore villages participating in this study will be randomly assigned to peer- versus specialist-led group training intervention (randomized cluster technique). To maintain concealment of allocation, the randomization sequence will be generated by the trial biostatistician who is a full professor at MSU and very experienced at the clinical methodology and the statistical assessment of our study outcomes. She is the clinical methodologist and biostatistician for the konzo WTM non-inferiority R01 study, and will serve the same role in this study. Child neurodevelopmental and urinary thiocyanate and quality of home environment and evaluation of observed MISC interactions using the caregiving videos will be done by research assistants blinded to caregiver training intervention arm in the present study.

C. Identify materials that will be used to recruit subjects (select all that apply):

☒ None
☐ Letter, email, flyer, postcards, CD, DVD
☐ Newspaper, television, or radio advertisements
☐ Use of websites or Apps (e.g. Facebook, ResearchMatch)
☐ Other, *describe if other is selected:*

CLICK IRB: Upload the recruitment materials to the Consent Forms and Recruitment Materials SmartForm page, Question 2.

D. The study team will obtain for the purpose of screening, recruiting, or determining the eligibility of prospective subjects (please select the appropriate option(s)): ☒ Not Applicable

☐ Information through oral or written communication with the prospective subject or legally authorized representative. Before the information is obtained for the purpose of screening, recruiting, or determining eligibility, consent: ☐ will be obtained. ☐ will not be obtained. *Please describe screening consent procedures in Question 13.*

☐ Identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens. Before the information is obtained for the purpose of screening, recruiting, or determining eligibility, consent: ☐ will be obtained. ☐ will not be obtained. *Please describe screening consent procedures in Question 13.*

Note: The revised Common Rule permits an exception from informed consent for screening, recruiting, or determining eligibility when certain criteria are met; this exception does not apply to studies subject to the Pre-2018 Common Rule Requirements and/or studies regulated by the U.S. Food and Drug Administration (FDA).

1. Please explain your selection(s).

Participation also requires receiving information on how to process cassava so that it is safe to eat. If and when the village tribal leader grants permission, groups of villagers will be invited to assemble and learn why the team has visited their village. The Kinshasa study team will repeat to the villagers the information previously provided to the tribal leaders. They will be encouraged to ask questions to which answers will be provided. Konzo will be familiar to the villagers, but they may not understand the causal connection between the consumption of cassava and the induction of walking difficulty. In particular, since cassava is a staple that provides a major source of nourishment that keeps them alive, there may be disbelief that a causal connection with disease could be possible. Other explanations for walking difficulties may be offered by the villagers, including punishment for undefined wrongdoing, a curse placed upon villagers by another tribal group, or the result of a natural event such as a flood or

a drought. Explanation that studies have shown that other people both near and far also develop “tied legs” if they do not wash their cassava roots for a sufficient period of time usually overcome doubts and focus attention on the principal cause of konzo. Great care must be taken to explain that cassava is an important and healthy food for the community provided it is properly prepared for human consumption. Since women of the village have major responsibility for food preparation and take pride in providing adequate nutrition for their family members, optimal food preparation is a subject of considerable interest and pride. Villagers will be familiar with the fact that children and women of childbearing age are the most heavily affected by konzo (relative to adult men), and it will therefore be logical that women and children are subjects of special importance to the study team.

13. Consent Process.

A. If the study involves adults, consent will be obtained from (select appropriate option(s)): ☐ Not Applicable

☒ All subjects
☐ Some subjects
☐ No subjects (consent will not be obtained)

CLICK IRB: Upload the consent document, script, etc. (including translations) to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

B. If the study involves children, parental permission will be obtained from (select appropriate option(s)): ☐ Not Applicable

☐ Both parents or guardians (unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child)
☒ One parent or guardian
☐ Will not be obtained

CLICK IRB: Upload the parental permission forms to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

C. If the study involves children, child assent will be obtained from (select appropriate option): ☐ Not Applicable

☐ All children
☒ Some children
☐ Will not be obtained

CLICK IRB: Upload the child assent form to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

D. Describe the consent process, including an explanation of your selection(s) above. If the study involves screening activities, please describe whether consent will be obtained and if consent will not be obtained, explain how the screening data will be used. If only some subjects will provide consent, explain who will or will not provide consent. If only some children will provide assent, explain which children will and will not provide assent.

Consenting will be performed by a member of the Kinshasa team on an individual basis after subjects have participated in the group meeting. Each subject will be asked to explain the purpose of the study: correct answers will be reinforced, and incorrect answers will be corrected with further information until the subject has a clear understanding. The subject will be informed they are free to accept or decline the invitation to participate and, if they choose to accept, they may withdraw at any time without recourse or penalty. Before making a decision whether to accept or decline, they will learn that participation in the study means the following: the study will have

access to the information being provided, as they provide a sample cassava flour, urine, and caregiver mental health/functionality and child neurodevelopment outcomes, for the study each time the research team visits the village over the course of the study period; answer some questions and provide a urine sample; be willing to learn about the MISC caregiver training intervention if chosen for that intervention arm in the study.
They are being told that their flour and urine samples will help the study team understand how to advise them on the best cassava preparation and risk for the disease konzo. They are also being informed that information collected from their blood/urine may be used in additional future studies of other diseases and their treatments. Participants will be encouraged to ask questions and, if necessary, take the necessary time to consider whether to participate or not. As noted in the research plan, after the first month of MISC training (under the supervision of experienced and Uganda certified MISC trainers at the Kahemba study site), the ten community women leaders trained to do the MISC trainers will continue to do bi-weekly personal MISC training sessions in the homes of the mothers to whom they have been assigned. One monthly encrypted and password protected videotaped MISC training session for each trainer will be uploaded to a secured DROPBOX for the remainder of the six-month MISC intervention period. These will be evaluated at our assessment center in Kampala Uganda for quality assurance and corrective feedback of the MISC training. We have used a similar procedure before for MISC training QA at our satellite study sites in rural areas of eastern Uganda, and the process worked well. A separate consent to video will be obtained from the mothers before the videotaping of any sessions, and the videotape will be available in a DROPBOX site that is only accessible to the trainers and the Ugandan MISC supervisors. Co-investigators Drs. Esperance Kashala-Abotnes and Itziar Familiar-Lopez, who have oversight for the MISC intervention portion, will also have access. All videotapes will be removed from the DROPBOX site and deleted within two weeks following evaluation for QA by the Ugandan MISC supervisors. This will all be explained in the separate consenting process of the mothers selected for the MISC training session videotaping with a given trainer for that month.
Agreement to participate will be taken if the child makes a clear statement of assent relevant for the present study, since all study children are under 7 yrs of age. The consent document will explain the purpose of the study, why questions will be asked, why flour and urine information is needed to be obtained for the study, the benefits and risks to the subjects, the payment schedule and amount, and the possibility of accepting or declining without consequence. There will be a clear statement that treatment of the disease will not be attempted and prevention of the disease cannot be assured. However, information will be provided in relation to the importance of knowledge to be gained and future intervention studies to prevent further cases of konzo. Subjects who agree to participate in the study will be asked to mark the consent document with an “X” by the side of the individual’s name, as witnessed by the signature of the research assistant obtaining consent. They will also be asked for permission to record their face and their children(s) face photographically for the purposes of verification of the enrollee in future years. Whether permission for a photograph is granted or not, a unique number will be assigned to the enrollee and the number written on the document and photograph. Subjects who decide not to participate will not be asked to mark the document or to be photographed.

E. If consent will not be obtained, explain why. Describe why the research could not be practicably carried out if consent was required. If the research involves identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format. ☒ Not Applicable

F. If your study involves use of a consent form, complete i, ii, and iii. ☐ Not Applicable

i. Select the appropriate option(s) below for the documentation of consent.
- ☒ Will use a written consent document signed by subjects
- ☐ Will use a short form written consent document signed by subjects
- ☐ Will not obtain a signed consent document for some subjects
- ☐ Will not obtain a signed consent document for all subjects

ii. Describe when and how the subject will receive a copy of the consent form.

A copy of the consent will be given to the caregivers after signatures are completed

iii. If subjects will not be signing the consent document, please explain why. If some subjects will not sign the consent document, explain who will and will not sign the consent. ☒ Not Applicable

G. If the study involves cognitively impaired adults, explain the process to determine whether a subject is capable of consent, use of any legally authorized representative(s), and any assent process. ☒ Not Applicable

CLICK IRB: Upload any assessment tools to the Supporting Documents SmartForm page.

14. Coercion or Undue Influence.

A. If some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, describe additional safeguards that have been included in the study. ☒ Not Applicable

B. If you or your study team are associated with the subjects (e.g. your students, employees, colleagues, patients), explain the nature of any association and measures taken to protect subjects' rights, including safeguards against any coercion or undue influence (e.g. pressure a subject might feel to participate based on the association). ☒ Not Applicable

15. Privacy.

How will subjects' privacy be protected? Consider the number of individuals interacting with the subject or subject's records, location of consent process and study, presence of individuals not associated with the study, sensitivity of the research.

The potential for loss of confidentially is a serious threat that will take several training and procedural steps to minimize. The requirement of treating health information as confidential will be strictly emphasized for all staff as part of training prior to study initiation. All staff will be required to undergo certified training on human subjects' protection including the imperative of strictly adhering to confidentiality enhancing measures. All staff will be specifically trained to know that no one involved in this study is authorized to ever reveal/discuss participants' health information with third parties and that evidence of such violation will be associated with strict penalties including the loss of employment.
The first page of the risk-factor questionnaire, which contains identifying information, names and addresses, is removed after data entry and stored at INRB in a locked file dedicated to this

research study. The data files include only study numbers, which are linked through a security system, to a named file maintained for the purpose of informing individuals of information pertinent to their health. The name file is only accessible to the PI of the Kinshasa sub-contract (INRB), Professor Desire Tshala-Katumbay (R01 PI), and Professor Michael Boivin (R21 PI). The computer files are password-protected to ensure data security. All results will be reported in the aggregate. All data (including questionnaire, clinical, molecular) biomarkers are stored on a dedicated computer at INRB equipped with a back-up system. A tracking system will use unique ID numbers for all data files. These ID numbers will be used in the transfer of biomarker data and samples from the INRB to OHSU. Produced video/photo materials will be permanently kept by both the research team PI and the study participant. Flour cyanide and U-SCN surveillance date for the mother/child dyads, and neurodevelopmental and caregiver functionality mental health and HOME quality of caregiving data, all will be stored and managed in the MSU Biomedical Research Informatics Core (BRIC) secure server system (https://ctsi.msu.edu/bric) for access only by R21 PI Boivin and Co-Investigators Familiar-Lopez (MISC and caregiver mental health) and Sikorskii (biostatistician and clinical trial methodologist).

16. Withdrawal of Subjects. ☒ Not Applicable

If there are any anticipated circumstances where the researcher will withdraw subjects from the study regardless of the subject's wishes, describe the circumstances and the procedures when subjects are withdrawn from the study.

17. Monitoring Plan to Assess Data to Ensure Safety of Subjects.

A. Is there a monitoring plan to periodically assess the data to ensure the safety of subjects or to ensure negative outcomes do not occur? ☒ No ☐ Yes

Explain your answer. If you answered Yes, describe the monitoring plan.

The University of Kinshasa Neurology Department and the Oregon Health and Sciences University are presently maintaining a formal research collaboration, under the direction of Professor Desire Tshala- Katumbay. Professor Tshala-Katumbay is PI of the R01 randomized RCT for the wetting method prevention of konzo, within which the proposed R21 will be embedded. They are presently sponsoring the formation of a standing data safety and monitoring board based at the University of Kinshasa Medical School as part of ongoing NIH and CDC sponsored clinical trials research program. Clinical faculty members from the bioethics program at OHSU are supporting this effort in the formation of a DSMB for the R01 study. Also, the MSU Office of Clinical Research (OCR) within the Institute for Clinical and Translational Sciences is also committed to supporting the Thrive Early psychiatry global research initiative in the formation and support of any DSMB relevant to our efforts. For the MISC caregiver training clinical trials with HIV-affected households in Uganda, that provided regulatory guidelines and lists of key membership from our program in Epidemiology, Biostatistics, and Bioethics and Humanities for the DSMB for those clinical trials. In the meantime, the R21, R01, and Sub-Contractor (INRB) PIs will be responsible for monitoring any adverse events notably breach of confidentiality related to home-based MISC training, emotional duress for caregiver evaluation of mental health and caregiving functionality, and profound neurodisability for study children that becomes evident from this domain of outcomes assessment. Monitoring will be done on a continuous basis. Any adverse events will be reported to the Institutional Review Boards (IRB) of participating institutions to ensure that appropriate action is taken. This is an appropriate strategy because the proposed intervention for the present R21 proposed study is behavioral in nature and very low risk. Likewise, the outcomes assessments specific to this R21 are on-invasive lab (urine thiocyanate

levels) or behaviorally based and established to be low-risk from prior use in our preliminary assessment work in the DRC with konzo-affected households.

CLICK IRB: Upload any data safety monitoring plans to the Supporting Documents SmartForm pages.

B. If there is a data safety monitoring committee or board, describe the composition and frequency of meetings. ☒ Not Applicable

18. Results and Data Sharing.

A. Could this research generate any results that could be clinically relevant, including individual research results, or general, or aggregate research findings?

☒ No
☐ Yes, clinically relevant individual research results
☐ Yes, clinically relevant general or aggregate research findings

1. If yes, explain what clinically relevant research results will be generated, whether they will be disclosed to subjects or others (e.g. subject's primary care physician), and if so, under what conditions. Address individual research results and/or general or aggregate research findings, as appropriate. *This also needs to be explained in the consent document.*

B. For other research results, select all that apply: ☒ Not Applicable

☐ Overall study results will be shared directly with subjects
☐ Individual results or incidental findings of individual subjects will be shared with subjects or others
☐ Data will be submitted to a repository or database as part of data sharing agreement (e.g. genomic data sharing)

1. Explain your selection(s), including how the data or results will be shared and with who (e.g. subject's primary care physician, data repository).

19. Local Context and Multi-Site Study.

A. Describe the locations of where the study team will obtain information or biospecimens through intervention or interaction with the subject or obtain the subjects' private identifiable information.

This study will take place in Kahemba, a district with the highest known incidence of konzo in the world. The district of Kahemba has been continuously affected by konzo since 1990. Residents of Kahemba rely heavily on cassava farming and possess very limited livestock (goat, pigs, chicken) for subsistence. During the last decade, the population of Kahemba has experienced a severe economic crisis due to the return of Congolese refugees from Angola with the end of armed conflicts in Angola. Due to food production shortfalls coupled with increased demand, residents of Kahemba have been forced to take short-cuts in the proper processing of cassava, a phenomenon that has led to an increase in food cyanogenic exposure. These short-cuts typically involve "short-soaking" the cassava (soaking the peeled tubers in water for less than the 3 days necessary for adequate fermentation), and failing to adequately dry the soaked tubers in sunlight (at least a day) before pounding the tubers into flour for storage. Coincidently, an unprecedented rise in the number of konzo cases has been documented with prevalence up to 20% in certain villages. There is good field research clinical trial capacity so support our study in Kahemba because it is also presently the site of an NIEHS non-inferiority clinical trial. This R01 trial (2R01ES019841; PI: Tshala-Katumbay) is evaluating the comparative efficacy of peer- versus

professional-led wetting method training (WTM) of caregivers in an effective approach for detoxifying their cassava flour before consumption. This approach is the standard of care for our present R21 study because it has been repeatedly demonstrated to reduce cyanogenic levels in poorly processed cassava flour to safe levels, even if the flour is initially very toxic due to short-cuts that have been taken in the processing of the cassava

B. If the study will engage employees or agents of non-MSU organizations (e.g. performance sites), explain how the employees or agents will be engaged (e.g. will they perform research procedures, will they obtain informed consent from subjects). ☐ Not Applicable

Research staff in DRC will be managed on-site by our local partners (PRONANUT and INRB). This is highly experience staff who has participated in previous clinical trials (a parent R01 to this application). All research staff will have completed Human Subjects Research training and will be in direct supervision by Drs. Kashala-Abotnes and Tshala, who will report directly to Dr. Michael Boivin (PI).

C. If the study involves multiple performance sites, describe the methods for communicating with engaged sites related to the protection of human subjects (e.g. any potential unanticipated problems that may involve risks to subjects others). ☐ Not Applicable

Drs. Tshala and Kashala-Abotnes will oversee all study activities at each site and report directly to the PI (Dr. Michael Boivin) by email or call as needed. During the enrollment period, sites will communicate with the MSU PI and co-investigators on a weekly basis through a secure conferece call system to report on enrollment numbers and any issues encountered.

D. If there are any cultural or local contexts or requirements that may impact the protection of human subjects or present additional risks to subjects that have not otherwise been described, please describe. If research is conducted outside the state of Michigan, this could include additional state or international requirements or laws. ☐ Not Applicable

This study will be reviewed by the local IRB in DRC (housed at PRONANUT)

E. If translations to a language other than English will be provided to subjects, describe the translation process. ☐ Not Applicable

Consent and assent forms will be translated to the local language by local research staff and back translated for accuracy. Final versions will be reviewed by Dr. Itziar Familiar (co-I)

CLICK IRB: Upload translated documents to the appropriate SmartForm page(s).

20. Resources and Financial Compensation and Costs.

A. If someone will receive a payment for recruiting the subjects, explain the amount of payment, who pays it, who receives it, and why they are being paid. ☒ Not Applicable

B. If subjects will be compensated for participation in the study, provide details concerning payment, including the amount and schedule of payments including any terms and conditions. Payment should be proportionate to participation. ☐ Not Applicable

The Kinshasa-based PRONANUT and INRB study teams (sub-contractor) have carried out international research studies on cassava- based health problems and thus is known and trusted in DRC. Subjects will be recruited with the full knowledge, consent and support of tribal leaders

and with the knowledgeable assent of other trusted parties, including village leaders and resident missionaries or church leaders. These parties will be informed of the study purpose, namely to assess the interplay between the body's structure and function and its exposure to natural substances in cassava. They will also be told that the initial and continued participation of the village and individual villagers is entirely voluntary. Participation includes answering a series of simple questions and providing sample of cassava flour, blood and urine at enrolment and in subsequent annual visits. Those who decide they wish to participate will be compensated equivalent of ~ $ 10 monthly in local currency for the duration of the caregiver training interventions, either WTM or WTM/MISC).
Caregivers will be reimbursed for travel costs to the clinic visits up to $5 USD per visit

C. If subjects will incur additional financial costs as a result of their participation in this study, explain the additional costs. ☒ Not Applicable

D. Describe any resources not otherwise described elsewhere in the submission (e.g. internal funding) for the protection of human subjects. ☒ Not Applicable

CLICK IRB: Upload any funding materials not accessible in Kuali Coeus in the Supporting Documents SmartForm page.

E. If subject's biospecimens (even if identifiers are removed) may be used for commercial profit, describe whether the subject will or will not share in the commercial profit. *This also needs to be explained in the consent document.* ☒ Not Applicable

21. Information and/or Biospecimen(s) Management and Confidentiality.

A. Select the appropriate option:

☒ Identifying or coded information will not be stored with the information and/or biospecimen(s)
☐ Identifying or coded information will be stored with the information and/or biospecimen(s)

B. Please explain your selection. If you are storing identifying or coded information with the information and/or biospecimen(s), explain why identifiable or coded information and/or biospecimen(s) needs to be maintained and how long it will be necessary to maintain it.

C. Describe the procedures and safeguards you will use to secure the information and/or biospecimen(s), including during transport of information and/or biospecimen(s).

Procuring cassava flour samples and urine samples from villagers in Bandundu are routine activities for the INRB sub-contractor and the teams from the Congo Ministry of Health. They are experienced in collecting, processing, storing and shipping samples. Pre-printed labels with unique identification numbers are placed on each sample tube. Cassava flour and urine samples and their analysis are performed in the village setting, with results evident to both subject and investigator. The significance of the reagent-induced color change (density varying directly with SCN concentration) will be explained to the villager as part of the intervention. The SCN content and color of the urine sample will be entered into the questionnaire and the sample discarded. In the R01 study, additional urine, dry blood spots (DBS), and blood (serum/plasma) samples are being individually labeled for laboratory analysis of the different biomarkers (8.12-isop, pep1, pep2, and homocitrulline). Therefore, a good procedure is already in place in terms of securing the custody chain for handling specimens of this sort for our R21. Again, this information will be gathered before, at 6- and at 12-months following MISC training in coordination with the R01

study, and be made available for the proposed R21 study for co-enrolled caregivers and the very young study children in their households. In the present R21 study, urine samples are individually labeled with their unique ID numbers, flash-frozen or in a dry-ice refrigerated container as needed and transported to INRB Kinshasa. A transmittal slip (multiple copies) accompanies each sample, and a copy is retained in the study office chain-of-custody (COC) procedures ensure security of transportation from the origin (Bandundu villages) to destination (INRB, Kinshasa). The local study coordinator fills out a three-part check-in sheet using the sample tracking codes. The study number in combination with the sample number is identified as the key field, and all the information specific to the sample is referenced by the codes. The check-in sheet must be complete in order to track biological samples. After the check-in sheet is completed, the first copy is used to enter the information into the Sample Tracking Database and then filed with the laboratory liaison. The second copy is given to the Kinshasa project leader. The sample custodian compares each sample with its corresponding
COC, then signs and dates the COC showing receipt at the warehouse. A three-part check-out sheet is used to enter data into the Sample Tracking Database and track sample location. Comparable COC procedures will be used for the secure mailing of samples from the DRC to the USA, for delivery to MSU (R21) and OHSU (R01). Unique sample ID numbers will be used by the OHSU study coordinators to register the samples upon arrival, with crosschecking of each sample on a listing provided by the Kinshasa dispatcher.
Data are being entered into the secure database immediately after each batch of samples has been analyzed.

22. Drug and/or Device Storage, Handling, and Administration. ☒ Not Applicable

Describe the procedure and plan for storage, handling, and administration of the drug and/or device so that they will be used only on enrolled subjects and be used only by authorized study personnel.

23. Future Research.

If the research involves the collection of identifiable private information or identifiable biospecimens, select the appropriate option: ☐ Not Applicable

☒ The subject's information or biospecimens, even if identifiers are removed, could be used for future research studies or distributed to another investigator for future research studies
☐ The subject's information or biospecimens, even if identifiers are removed, will NOT be used or distributed for future research studies

Please be sure to carefully consider the appropriate option, as this needs to be explained in the informed consent and can limit what is done or used for future research.

24. MSU Additional Information. ☒ Not Applicable

Identify if your study involves any of the following: (check all that apply)

☐ Use of human stem cells
☐ Research with biospecimens will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen). *If so, this needs to be explained in the consent document.*

Other Click IRB Document Uploads As Appropriate
(Applicable to Expedited or Full Board Studies)

- *Upload list of external study team members (non-MSU individuals) to the Study Team Members SmartForm page, Question 2.*
- *Upload other institution(s) approval letter(s), if submitted to other IRB(s) or ethics committees, to the Supporting Documents SmartForm page.*
- *Upload FDA communications, package inserts, FDA form 1572, or other information related to drugs or devices to the appropriate Drug or Device SmartForm pages.*
- *Upload the HRP-540 - Template - ICH-GCP - For Investigator to the MSU Additional Study Information SmartForm page.*
- *Upload HRP-541 - Template - Involvement of Prisoners in a Research Project to the MSU Additional Study Information SmartForm page.*
- *Upload the investigator brochure to the Supporting Documents SmartForm page*
- *Upload the MRI Screening Form – Women to the Supporting Documents SmartForm page.*
- *Upload the translation of instrument(s) provided to non-English speaking subjects to the Supporting Documents SmartForm page.*
- *Upload the curriculum vitae(s) when research is more than minimum risk to the Supporting Documents SmartForm page.*
- *Upload case report forms to the Supporting Documents SmartForm page.*
- *Upload the Non-MSU Employee Conflict of Interest Disclosure Form to the Supporting Documents SmartForm page.*
- *Upload any other pertinent documents related to the proposed research study to the Supporting Documents SmartForm page*