Culture-Specific Neurodevelopmental Assessment of HIV-Affected Children

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GLOSSARY

ART	Antiretroviral Treatment
ARVs	Antiretroviral drugs
cART	Combination Antiretroviral Treatment
BPG	Brain Powered Games
CBAs	Computer-based assessment programs
CCRT	Computerized Cognitive Rehabilitation Therapy
CRS Site	Clinical Research
CTU	Clinical Trials Unit
DAIDS	Division of AIDS
DMC	Data Monitoring Center
EF	Executive Function
HIV	Human Immunodeficiency Virus
HEU	HIV-exposed uninfected
HUU	HIV-unexposed uninfected
IRB	Institutional Review Board
I o R	Investigator of Record
JHSOM	Johns Hopkins University School of Medicine
KABC-II	Kauffman Assessment Battery for Children 2nd edition
NIH	National Institutes of Health
MOP	Manual of Operations
MSU	Michigan State University
MSU-GEL	Michigan State University Games for Entertaining and Learning
MU-JHU	Makerere University–Johns Hopkins

PEPFAR	President's Emergency Plan for AIDS Relief
PROMISE	Promoting Maternal and Infant Survival Everywhere
PROMOTE	PROMise Ongoing Treatment Evaluation
PTID	Participant Identification
QA Assurance	Quality
QC	Quality Control
SMC	Safety Monitoring Committee
SOE	Schedule of Evaluation
SOP	Standard Operating Procedure
SSA	Sub-Saharan Africa
VL	Viral Load
WHO	World Health Organization

SCHEMA

Title: Culture-specific neurodevelopmental assessment of HIV-affected children

Purpose: This proposal will adapt and validate Brain Powered Games (BPG), a computerized cognitive rehabilitation therapy (CCRT) program as a neurocognitive assessment for Sub-Saharan African school-age children suffering from neurological insults such as neurotropic infections. We will add an additional game for executive function training, and then test whether BPG cognitive assessment data gathered in at-risk children playing with BPG can provide a more sensitive measure of the child's developing brain. We expect to demonstrate that a child's performance on a neurocognitive "stress test" involving game training with an app on a computer tablet, will better characterize integrity of brain/behavior function as compared to performance outcomes from traditional one-time cognitive testing sessions.

Design: This is a multi-site observational prospective study.

Study Population: A total of 240 HIV-exposed but uninfected (HEU) and 240 HIV un-exposed uninfected Malawian and Ugandan infants and their caregivers recruited in the Promoting Maternal and Infant Survival Everywhere Neurodevelopmental follow-up study (PROMISE ND) sites at Malawi College of Medicine-Johns Hopkins University (MCM-JHU), Blantyre, Malawi; and at Makerere University–Johns Hopkins University (MU-JHU), Kampala, Uganda respectively. In addition, 120 HIV infected (HIV+) children and their caregivers will be recruited from affiliated health clinics at both Malawi and Uganda sites.

Sample size: A total sample size of 600 children and their caregivers in two study sites (n=300 per site) will be included in this study

Study duration: Approximately 5 years.

Overall goal: This research will adapt and validate BPG as a measure of cognitive performance in school-age children as both a static (1 session of BPG) and dynamic assessment (12 training sessions of BPG)

Aims and objectives:

Aim1: To adapt and evaluate the concurrent and predictive validity of BPG as a static (baseline) and dynamic (during 12 training sessions) cognitive assessment at the Malawi and Uganda sites.

Objective 1.1 To evaluate whether BPG static (baseline) assessment corresponds to the gold standard static measures previously adapted to HEU, HUU, and HIV+ study cohorts at Uganda and Malawi country sites (KABC-II, TOVA, CogState).

Aim2: To compare the validity of BPG static and dynamic assessments.

Objective 2.1 To evaluate the correspondence of BGP-based static and dynamic assessments of the cohorts' prior early childhood longitudinal trajectories (KABC-II), considering the effect of proximal (e.g. HIV status) & distal (height, weight, HIV disease factors, demographic) risk factors causing developmental delay and cognitive problems.

Aim3: To test the sensitivity of dynamic assessment to learning loss over time by evaluating how much BPG performance gains diminish during a 6-month absence of training

Objective 3.1 To assess change over time in KABC-II, TOVA and CogState scores (learning loss) 6 months after the children complete 12 sessions of BPG training, overall and by cohort.

Study Outcomes:

Primary Outcome: **To establish the validity of BPG as a measure of neurodevelopment in at-risk children. (e.g. HIV affected)** To establish BPG as a neurocognitive "stress test" or medical "challenge" test, in order to evaluate brain/behavior functional integrity in HIV-affected children.

Exposure Variables of Interest:

- HIV status (HEU, HIV+, HUU)
- Other clinical risk factors for poor neurodevelopment (child's weight, height, HIV disease and immunological factors)

CULTURE SPECIFIC NEURODEVELOPMENT ASSESSMENT OF HIV-AFFECTED CHILDREN STUDY

1.0 INTRODUCTION

Most computer-based cognitive assessment programs for children that are validated for easy cross-cultural adaptability on tablets are proprietary, limiting their affordability on mobile networks, particularly for resource-constrained settings. Examples of such expensive programs are CANTAB, CogState, and Tests of Variables of Attention or TOVA. Exceptions to this (e.g., NIH Toolbox-Cognition) are not well validated or readily adaptable either because of the technical expertise needed to administer them, or because English is required. Or, because they were designed for children of western cultures with prior exposure to culture-bound testing item content and testing task constructs. The access problem is the same for the most prominent CCRTs (e.g., Pearson's COGMED and Brain Train Corporation's Mind Powered Games). Being non-proprietary, BPG uniquely combines assessment and affordability into a single CCRT game package. BPG development was partially funded by NIH (R34 MH084782; PI: Boivin).

We deliberately created BPG to be available to children living in remote and resource poor areas that lack CCRTs or commercial computer-based assessment programs (CBAs). During this project Co-I Brian Winn and his MSU programming team will adapt BPG to work as an Android or Macintosh application suitable for a mobile device (e.g. tablet or smart phone). This will allow BPG dissemination on a mobile network — use of mobile communication is nearly universal in Sub-Saharan Africa — with the capacity for real-time performance assessment. Images, interactive scenes, and music will be designed to be engaging for the African child and do not require English language. This removes major potential confounding factors in interpreting cognitive assessment data for these children. BPG will be pilot tested before full protocol implementation to ensure cultural acceptability and feasibility through an iterative process led by Michigan State University programmers involved with game design and production.

Using a computer cognitive games intervention as a "challenge" test for evaluating brain/behavior integrity of HIV-affected children is the *principal innovative feature* of this proposal. It is like a neurocognitive version of the "cardiovascular stress test" with the use of increasingly strenuous exercise on a treadmill as a diagnostic evaluation for heart disease. A similar rationale is used in "medical challenge tests", when for example, a patient breathes in histamine to allow pulmonary specialists to evaluate bronchial function; or when glucose is used during pregnancy to test for the risk of diabetes in gestational diabetes.

An additional advantage of our use of BPG as a "neurocognitive 'stress' or 'challenge' test", is that it can also be administered at a given time point (*static assessment)* to obtain data on cognitive performance (attention, memory, learning) based on the child's progress playing the games. This is a significant language-independent/culture-fair assessment bonus. When BPG is then administered over 12 training sessions, it becomes a computerized cognitive rehabilitation training (CCRT) intervention in treating neurocognitive deficits or disabilities. BPG is **NOT** a "black box" intervention, as the data on child's performance is monitored each training session and provides a learning-based dynamic evaluation. *This is a key feature of any stress or challenge test in medicine,* ***and the principal innovative aspect of this proposal.*** These dynamic changes provide deeper insight into the developing brain than the static assessments, either via BPG at one time point or using "gold standard" tools that can only be administered at fixed times. We also provide *neuroimaging evidence of the neurocognitive brain changes from CCRT*, in the seminal work by Duncan Astle using COGMED training along with magnetoencephalography (MEG) in UK normal children.

2.0 BACKGROUND AND LITERATURE REVIEW

In field tests with HIV+ rural Ugandan children, BPG as a CCRT intervention achieves significant neuropsychological change in computerized attention and cognitive performance outcomes.[1]Based on this success, we will rigorously test BPG with 3 cohorts of children (HIV, HEU, HUU) at study sites in Uganda and Malawi where both well-characterized P1104s and PROMISE ND children are available. These cohorts are very well-characterized from infancy to school-age. These cohorts will allow us to rigorously test the sensitivity of BPG assessments in capturing developmental delay and neurocognitive disabilities as they pertain to both proximal and distal risk factors in pediatric HIV (e.g., Figure 1: clinical risk factors and health history, ARV/HIV exposure & treatment history, SES and care giving quality, nutrition//growth). Our assessment sensitivity controls will be the current gold standard battery of tests (KABC-II, TOVA, CogState).

We will use a battery of neuropsychological tests previously validated with children enrolled in IMPAACT P1104s at 5 to 14yrs of age at 6 study sites in South Africa, Malawi, Zimbabwe, & Uganda in 10 local languages.[2-4]Our gold-standard cognitive (KABC-II), computer-based attention/impulsivity (TOVA), and memory and learning (CogState) tests are also validated in the context of pediatric HIV and CCRT.[5,6] See (Figure 1 center, & Section 4.10 descriptions of the KABC-II, TOVA, CogState).

Figure 1 depicts the evaluative model we used in our prior work (R34 MH084782; PI Boivin) using both BPG and a product by BrainTrain called *Captain's Log* computerized cognitive rehabilitation therapy (CCRT).[5,6]We also used this evaluative model with our Ugandan and Malawian IMPAACT PROMISE Neurodevelopmental (ND) R01 study HEU and HUU cohorts, and our P1104s HIV cohorts. In this proposal, we will administer our BPG CCRT game package (Fig. 1, far right) along with cognitive ability, sensory/motor, and psychiatric tests (Fig. 1, middle) to validate the static (baseline) and dynamic (pre- to post-CCRT spanning 12 weeks) neuropsychological profiles of our HIV, HEU, and HUU cohorts — as assessed by the BPG games performance data. We will adjust the relationship between BPG and our neuropsychological domains on the basis of HIV/ARV exposure neuropathogenic modifiers (Fig. 1, left) for the HIV+ children (**proximal effects**), and neurodevelopmental risk-factor covariates (far left; **distal effects**) assessed in both the PROMISE ND (HEU, HUU cohorts) and P1104s (HIV) studies.

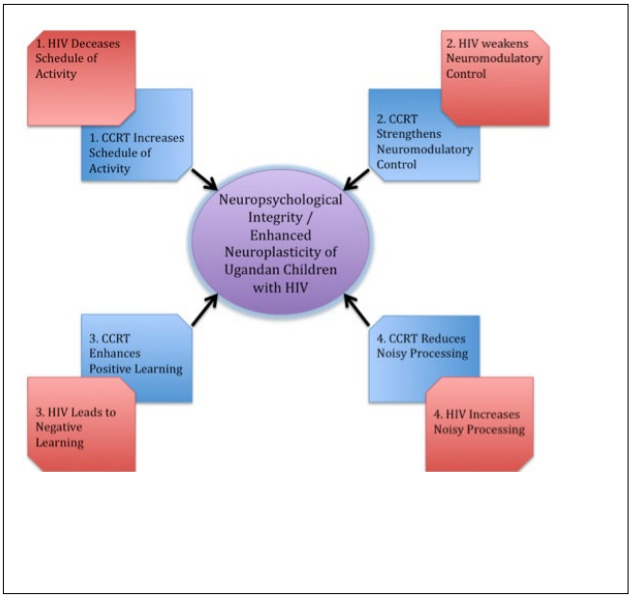


Figure 1. How CCRT remediates the root cause of functional decline in pediatric HIV. *As the first dual assessment CCRT to be validated,* we expect BPG will show analysis of CCRT neurocognitive assessments can be much improved.

2.9 For deeper insight into a child's ability to learn, BPG will be the first CCRT validated for dual assessment capability — both dynamic and static. Sternberg and Grigorenko argue that dynamic assessment is more sensitive to brain/behavior integrity than traditional static assessment.[7]Dynamic assessment uses a cognitive ability test to measure active learning ability *across numerous learning sessions*. Static assessment uses the same test to measure neuropsychological function in a single testing session. In dynamic assessment, children learn skills needed for a given type of test item during testing through teaching and feedback on performance. Dynamic assessment then notes improvements in cognitive performance in response to multiple learning sessions. By evaluating brain/behavior learning as part of testing, dynamic assessment evaluates a higher level of positive biocultural plasticity and brain integrity. Dynamic assessment does this by evaluating the child's ability to adapt and improve from feedback and learning.[8,9]The advantage of dynamic assessment is supported by cross-cultural

assessment work in Tanzania. This work showed conventional tests for working memory and analogous reasoning (e.g., Raven's Progressive Matrices) did not adequately assess the full range of cognitive skills children could demonstrate — whereas dynamic assessment did.[9]Figure 2 models how CCRT remediates (inner squares) the four principal causes of pediatric HIV-related neurocognitive disability in children (outer squares).[10]Our hypothesis is that CCRT-based dynamic assessment measures of brain/behavior integrity can characterize neuroplasticity in children in a cross-culturally consistent and valid manner. As explained by Boivin &Giordani, dynamic assessment may be our best way to evaluate brain/behavior integrity in the face of pediatric HIV disease in the CNS, ARV treatment, and remediation.[11,12]

Brain training and neuroimaging evidence support the need for dynamic assessment. Duncan E. Astle and colleagues published the first conclusive evidence that CCRT in children strengthens cortical connective pathways for working memory, as well as the attention processes targeted by CCRT.13 Using magnetoencephalography (MEG), they confirmed that the right hemispheric frontoparietal seed network is considerably strengthened in resting state after 24 sessions of COGMED CCRT for visual-spatial working memory (Figure 3A). Placebo (active) controls did not show strengthening (Figure 3B). The degree to which these neural connections were strengthened significantly correlated with improved COGMED performance from beginning until completion of 24 sessions of CCRT training (Figure 3C). When dynamic assessment detects improved neuropsychological performance over multiple CCRT sessions, we propose we are seeing a reflection of the integrity of neurocognitive function. On this basis we believe dynamic measures can provide more valid and sensitive assessments in children affected by HIV.

By combining a neurocognitive games assessment with CCRT capability, BPG can provide a valid assessment at the static level (baseline). BPG can then be used for CCRT training (12 sessions), during which we will record performance data as dynamic assessments of performance gains.

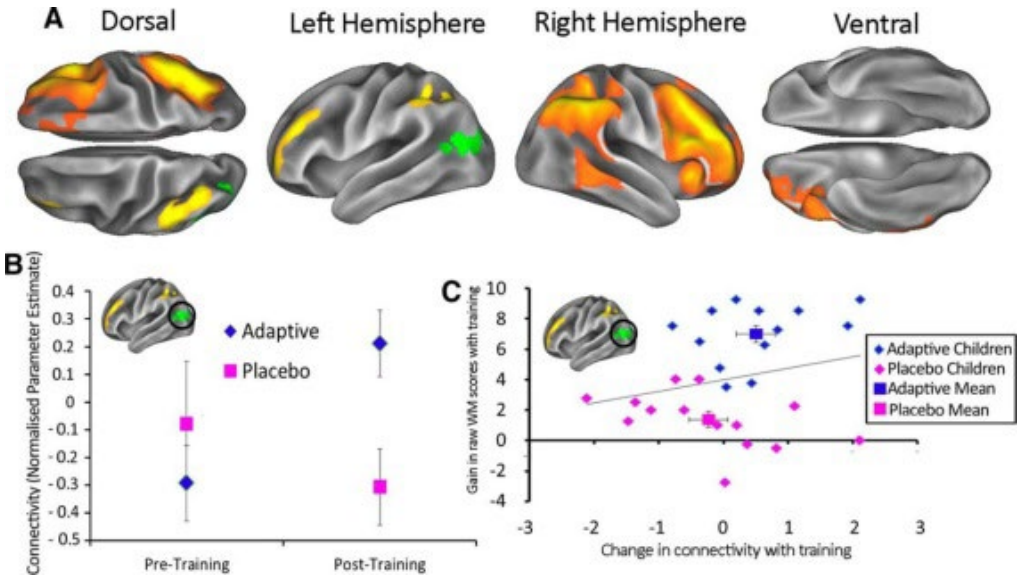


Figure 3. Using dynamic assessments in this proposal to test how BPG improves cognition in HIV+ school age children is supported by the recent results (presented above in 3A, 3B and 3C) of Duncan et al. (20), who show 24 sessions of CCRT training with COGMED strengthens cortical connectivity for working memory and attentional processes.

Our central hypothesis is that the performance gains (dynamic assessment) will explain the additional variation in the gold-standard measures at time points after static (baseline) assessment, and more effectively capture the effects of HIV/ARV exposure and treatment across our cohorts (HIV, HEU, HUU) in Uganda and Malawi.

Overall Impact**:** Once BPG is proven as a dynamic assessment tool, BPG mobile apps can be used in tablets and smart phones for "real-time" cognitive assessment monitoring (or surveillance) for HIV disease progression and treatment. BPG can also monitor other diseases causing brain/behavior problems in children.

BPG will be the first adapted and validated instrument for dual assessment capability, both static and dynamic. It will also be the first to include a static and dynamic intervention-based measured of executive function (EF) in

younger children. By combining computerized assessment with cognitive training, BPG will make possible the most innovative aspect of this proposal: a fundamental experiment to compare traditional static neuropsychological assessment with dynamic assessment in their ability to capture effects of HIV/ARV exposure, infection, and treatment in well-characterized cohorts. We choose to validate BPG for dynamic assessments because we expect this advance in cognitive assessment methodology will provide fundamental new insights into how HIV affects brain development in children, and so make an exciting advance in our field. We also expect BPG will prove useful in monitoring brain development in children burdened by other diseases with brain/behavior effects; e.g., malaria. To illustrate, an important innovation to BPG is the addition and field testing this past year of Spatial Navigation Training (SNT). This game is unique in that it stimulates not only the hippocampus, but also other mobility-related brain areas (similar to what happens in imaging studies when a person is asked to imagine walking).[14] In two recent publications, Co-I Giordani and colleagues showed that after 12 sessions of SNT, older adults demonstrated improvements in both executive functioning and more complex aspects of mobility.[15,16] Our proposal will provide for the use of this task for both static and dynamic assessment of children affected by HIV and other diseases that can compromise brain/behavior development.

3.0 PROBLEM STATEMENT AND JUSTIFICATION

Currently, most standardized neurodevelopment assessments are limited by their reliance on highly-trained evaluators administering tests in a controlled, clinic-based environment. These lengthily assessments frequently involve children following instructions in order to perform a specific task utilizing specially designed props, making them also dependent on language. To begin to address these challenges, we propose to adapt and evaluate the validity of a digital platform with rehabilitative capacities as an evaluation tool for children in LMIC. We hypothesize that given the available evidence, BPG can be effectively and efficiently calibrated to assess neurodevelopment at a lower financial and human resources costs than standardized tests currently available.

Given the success of ARV's more children are surviving HIV and/or are living as perinatally exposed but uninfected children. Recent studies suggest that HIV+, HEU and HUU children display different developmental trajectories over time. It is therefore that as a proof of concept we are including both HIV+ and HEU children in this study. Additionally, HUU children are included as community controls.

This proposal will validate Brain Powered Games (BPG), a computerized cognitive rehabilitation therapy (CCRT) as neurocognitive assessment for Sub-Saharan African school-age children suffering from neurological insults. BPG is especially intended to help children affected by HIV as it evaluates domains at risk for delayed development such as expressed language, cognitive processing speed and executive function [1,2] . BPG is the first game package to combine games for neurocognitive assessment and training in a way that is low-cost and designed for scalability on mobile networks, removing economic barriers that frequently hinder expanded use of these tools in low- and middle-income countries. BPG games does not depend on language and uses images and sounds that are engaging and more familiar to African children, thus removing cultural biases frequently associated with other standardized tests of neurodevelopment. Android and Mac apps of BPG for tablets and smartphones will take advantage of mobile communication networks to make BPG feasible to use anywhere in Sub-Saharan Africa.

With NIH funding we previously developed BPG (Brain Powered Games), a CCRT (Computerized Cognitive Rehabilitation Therapy) digital games package for HIV+ school children in the sub-Sahara. As a child plays, BPG gathers game data that can be used for neurocognitive assessment. In this new study, we will further evaluate the capability of BPG as a test for neurodevelopment. In a second phase, we will add an award-winning game developed at the MSU-GEL lab that will train executive function (EF), allowing us to dynamically assess this often-neglected neurocognitive domain in previously tested and well-characterized HIV+, HEU and HUU cohorts of children.

In Study Aim 1 we will adapt and evaluate concurrent and predictive validity of BPG. Here we will evaluate whether BPG as a static (baseline) assessment corresponds to a gold standard of static measures (KABC-II,

TOVA, CogState). Compared to these, we ***hypothesize*** that dynamic BPG assessments will be feasible and acceptable, providing for a more sensitive evaluation of brain/behavior function as affected by more proximal factors of HIV exposure, disease and treatment. We also ***hypothesize*** that dynamic assessments will be more sensitive to distal developmental risk factors (e.g., SES, nutrition/growth, maternal caregiving quality), measured in early childhood in study cohorts.

In **Study Aim 2,** we will compare the validity of BPG static and dynamic assessments. Here we will validate BPG static and dynamic assessments with a gold standard of neuropsychological tests previously used with school-age children at our two study sites (Kampala, Uganda and Blantyre, Malawi). Cohorts will be well characterized due to participating in our previous NIH-sponsored HIV clinical trials. We ***hypothesize*** that BGP-based static and dynamic assessments will be sensitive to cohorts' prior longitudinal trajectories as affected by proximal and distal risk factors that cause developmental delay and cognitive problems, as measured in our previous clinical trial studies with these cohorts. The executive function game will prove especially sensitive.

In **Study Aim 3,** we will test the sensitivity of dynamic assessment to learning loss after training ends. An advantage of dynamic assessment should be its sensitivity to learning loss over time as a measure of strength of positive neuroplasticity in brain/behavior functions. Here we will test sensitivity by evaluating all 3 cohorts with BPG and gold standard tests (KABC-II, TOVA, CogState) 6 months after the children complete their 12 sessions of BPG training. We ***hypothesize*** that BPG dynamic assessment of learning loss at 6-month follow-up post-CCRT will be especially sensitive to integrity of brain/behavior function in pediatric HIV.

Overall Impact: BPG will be the first CCRT validated for dual cognitive assessment, both static and dynamic. We expect BPG's dynamic assessment capability will provide fundamental new insights into how HIV disease and treatment effects. BPG can also be an accessible and inexpensive assessment tool in resource-constrained settings to enable community health workers to monitor brain development in children burdened by other diseases and injuries. It can do so as a mobile-based touch-screen tablet, lending itself to easy use by kids, and scalability of language-free cognitive testing; all made possible by a dual-purpose tablet program.

4.0 RESEARCH APPROACH

In this proposal we will build upon previous NIH funding by validating BPG's CCRT neurological assessment capability for HIV+ and HIV-exposed children. Study sites will be in Uganda and Malawi. We will more fully develop and validate BPG assessment capability, building on its CCRT capabilities for children affected by HIV and all manner of infections that can compromise brain/behavior function. We will validate BPG assessment capability with 3 cohorts of children — 1) HIV, those with HIV; 2) HEU, those perinatally exposed to HIV but uninfected; and 3) HUU, those unexposed and uninfected children — in an African urban (Kampala, Uganda) and peri-urban (Blantyre, Malawi) setting. These areas represent divergent sets of economic resources and diverse dialects. These children are well characterized with longitudinal assessments of growth, haematological, neurological, neurodevelopmental, and neuropsychological evaluations at 12, 24, 48, and 54-60 months of age. These assessments are from an NIH study of the effects of HIV and ARV exposure on clinical and neurodevelopmental outcomes (HEU and HUU, R01 HD073296; PIs: Fowler, Boivin). Our Ugandan and Malawian HIV cohorts recently completed a 3-year longitudinal neuropsychological assessment protocol IMPAACT P1104s (NIH/DAIDS UM1 AI068632: PI, Boivin) with HIV+, HEU, and HUU cohorts embedded within an ARV clinical trials study, monitoring children from HIV diagnosis (3 months to 3 years of age) to middle childhood.[17-20]

4.1 Preliminary studies

Our preliminary evaluation of BPG was part of a clinical trial evaluating the effectiveness of *Captain's Log* CCRT (a "for profit" commercial CCRT game package) with HIV+ Ugandan children.[6] We used the same configuration of Captain's Log as earlier.[5,21] Boivin and Giordani reviewed each of 35 possible training tasks

with their Ugandan Co-Is and selected 9 games considered to be culturally fair. The games included 3 tasks emphasizing visual-spatial working memory, vigilance attention, and nonverbal reasoning. Using *Captain's Log* internal performance evaluation, we evaluated the static vs dynamic CCRT-related performance measures in comparison to the gold standard neuropsychological assessment battery (KABC-II, TOVA, CogState). Our severe malaria CCRT RCT results for Boivin *et al* 2018 are "in press" in *Brain Research Bulletin*, available online (https://doi.org/10.1016/j.brainresbull.2018.03.002

Static vs Dynamic Performance Evaluation for *Captain's Log* CCRT with KABC-II MPI gains. In Boivin et al, 2018, *Captain's Log* performance data for severe malaria survivors were analyzed for N=104 children (both the full and limited CCRT intervention arms) who participated in the *Captain's Log* CCRT RCT. There was a very strong (R-squared over 0.9) linear relationship between performance measures averaged.

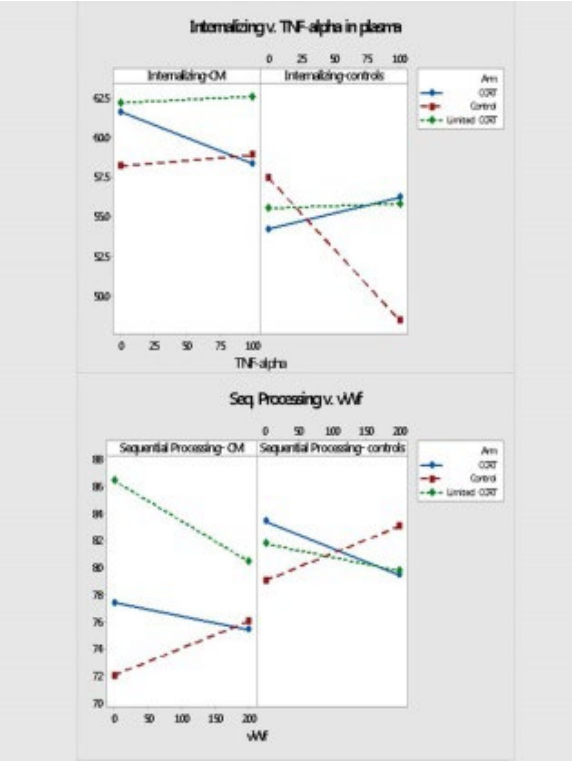
Table 1. Concurrent validity of dynamic performance measures for 12 training sessions (N=104).

Dynamic CCRT performance assessment measures across first 12 training sessions.	Correlation with baseline (Static Pre-) MPI, p-value	Correlation with post-training (Static Post-) MPI, p-value	Coefficient (standard error) predicting post-training MPI over and above baseline (Dynamic) MPI, p-value
Mean memory success performance	r=0.32, p<.01	r=0.37, p<.01	aBeta=0.34 (0.16), p=.04
Mean probability of success performance	r=0.32, p<.01	r=0.38, p<.01	aBeta=0.27 (0.12), p=.04
Mean accuracy of memory performance	r=0.34, p<.01	r=0.41, p<.01	aBeta=0.30 (0.12), p=.01
Mean accuracy of memory processing	r=0.39, p<.01	r=0.47, p<.01	aBeta=0.35 (0.12), p<.01
Mean accuracy of visual special learning	r=0.31, p<.01	r=0.39, p<.01	aBeta=0.34 (0.13), p=.01
Slope memory success performance	r=0.24, p=.01	r=0.32, p<.01	aBeta=0.78 (0.33), p=.02

Slope probability of success performance	r=0.28, p<.01	r=0.34, p<.01	aBeta=0.55 (0.26), p=0.04

For children at each session, with consistent linear growth across all successive training sessions (Fig.4). Dynamic measures derived based on the first 12 sessions (left side of Fig. 4 slope) had the same rate of gains over time as measures across the final 12 sessions (right side of Fig. 4 slope). Thus, dynamic measures over 12 sessions carry the same information as measures over all 24 sessions.

Table 1 shows correlations of CCRT performance gains with the KABC-II mental processing index (MPI) pre-training (Static Pre-) and post-training (Static Post-). Measures over first 12 sessions (4 weeks) had the same or stronger correlations with the KABC-II MPI, than measures based on 24 sessions (Dynamic), further confirming the adequacy of 12 sessions for dynamic measurement. To determine the value added by dynamic measures over existing static (Static Pre- or Post-) assessments, we used general linear models relating the KABC-II MPI post-training to the KABC-II MPI pre-training, and each dynamic performance measure (one at a time over each successive training session). While the KABC-II MPI at baseline was strongly associated with the KABC MPI post-training, the performance measures were significantly related to the KABC MPI post-training over and above baseline MPI (Dynamic column in Table 1), capturing variation in post-training KABC-II MPI not captured by the *Captain's Log* Static Pre- or Post- measures.



Justification for 12 Rather than 24 BPG Training Sessions for Dynamic Performance Outcomes. As noted above, BPG training for the dynamic phase of assessment will consist of 12 sessions, not the usual 24 sessions recommended for therapeutic CCRT intervention.[22,23] Although 24 CCRT sessions is considered the "standard of care" in cognitive rehabilitation,[22-24] our preliminary findings indicate the cognitive gains from CCRT are stable after just 12 sessions. To illustrate, Figure 5 (above right) depicts the relationship between CCRT benefit (vertical axis) and severity of illness (horizontal axis) as measured by CSF neuroinflammatory (TNF-alpha) and endothelial activation (von Willibrand Factor: vWF) during acute illness. The full CCRT (blue), limited CCRT (green) and control (red) arms are represented for the cerebral malaria (left side) and non-malaria (right side) cohorts. More severely affected children show poorer positive neuroplasticity in terms of CCRT learning benefit. We expect the same result for our HIV-affected cohorts, further showing the sensitivity of CCRT assessment measures.

Table 2. Results of CCTP Repeated Measures Analyses Severe Malaria Study

	Significance Level (p =)		
CCTP Score	Group	Time	GroupXTime
Memory	0.93	0.0001	0.40
Concentration	0.92	0.0001	0.58
Auditory Processing	0.41	0.0001	0.78
Visual Processing	0.74	0.0001	0.68
Problem Solving	0.99	0.0001	0.96
Self-Discipline	0.78	0.0001	0.70

Since the focus is on assessment as part of neurocognitive rehabilitation (CCRT), we propose that using computer games to provide for dynamic measures across 12 sessions is much more feasible, from the standpoint of disseminating BPG as an assessment and rehabilitative tool. Also, our initial pilot study with CCRT and Ugandan children with HIV had a significant gold standard test benefit across just 12 training sessions.[5]

4.2 Overview of Planned Research

Team and Study Environment. Principal investigator Michael J. Boivin has pioneered neuropsychological assessment in Sub-Saharan Africa since 1989 with the support of 2 Fulbright awards (DR Congo1990; Uganda 2003). Boivin and Co-I Bruno Giordani pioneered the use of computerized assessment and rehabilitation in Africa,[1,5,6,21,25-28] sharing much of that work in their co-edited book on the *Neuropsychology of Children in Africa* (2013), the first of its kind.[12] This book includes six chapters dedicated to the assessment of pediatric HIV, four of which Boivin and Giordani co-authored.[21,29-31] Co-I Brian Winn is director of the MSU-GEL graduate program and lab and originator of BPG. He has accompanied Boivin to Blantyre, Malawi and Kayunga, Uganda to field test BPG on laptops and tablets in clinic and village settings.[1] Winn will oversee enhancement of BPG's internal evaluation capacity, and adapting BPG to tablets on a mobile network for real-time static and dynamic assessment in the clinic and field for HIV, HEU, and HUU cohorts of children in Blantyre and Kampala. Prof. Mary Glenn Fowler specialized in maternal and child medical care and treatment of HIV in Africa as a program officer with the CDC and NIH, and is now at Johns Hopkins University (JHU). She is PI of the NIH/NIAID PROMISE clinical trials and HIV prevention clinical trials program at 14 sites throughout Africa. Together with Boivin, Fowler also serves as PI for the PROMISE ND R01 at the proposed Uganda and Malawi sites. Co-I Taha Taha is an epidemiology professor at JHU who oversees the Malawi College of Medicine/JHU HIV clinical trials research program. Prof. Alla Sikorskii is principal statistician on the Fowler and Boivin PROMISE ND R01 study, and on Boivin's Severe Malaria CCRT and Pediatric HIV CCRT Uganda NIH-sponsored studies. She has co-authored 12 pediatric HIV-related papers with Boivin's study team and his biostatistician for PROMISE ND. Dr. Itziar Familiar (global mental health) has oversight for Boivin's NICHD-sponsored studies and is an expert in maternal mental health as it impacts on child care in households affected by HIV. She has published on the effects of caregiver mental health and caregiving quality in our prior pediatric neurodevelopmental HIV work pertaining to the distal[32-35] and proximal[36] assessments in this study.

4.3 Research Sites

The Culture-specific neurodevelopmental assessment of HIV-affected children study will be carried out at the MU-JHU Research Collaboration clinic located at the Mulago National Referral Hospital in Kampala, Uganda. The second clinical research site is the Johns Hopkins-College of Medicine Research Project in Blantyre, Malawi which also has extensive research infra-structure. The clinical aspects of the protocol will be conducted at these two research sites along with BPG training and assessments.

The Uganda and Blantyre Malawi sites participated in the Promoting Maternal and Infant Survival Everywhere Neurodevelopment follow-up study (PROMISE ND Study) from which the Culture-specific neurodevelopmental assessment of HEU and HUU children participants will be recruited (Drs. Fowler and Taha were PROMISE Co-chairs). The NIH-sponsored PROMISE 1077-BF study (NCT01061151 clinicaltrials.gov registry) from which children for the PROMISE ND study were co-enrolled, was the first Africa-based multi-site randomized clinical trial comparing the safety and efficacy of use of maternal triple ARVs to antenatal maternal ZDV alone; and postnatal maternal triple ARVs to infant NVP throughout breastfeeding. For the PROMISE ND study, a prospective cohort of HIV-exposed uninfected (HEU) children was co-enrolled from the IMPAACT/PROMISE-BF randomized clinical trial. Age-and-gender-matched controls were enrolled from child-well clinics between 09/2013-10/2014 at two sites: Blantyre, Malawi and Kampala, Uganda.

Figure 5: Flow of the PROMISE Trial and PROMISE ND Study from which we will recruit the Culture-specific neurodevelopment assessment of HIV-affected children study (HEU and HUU participants)

PROMISE Trial

N=3490

--14sites S. and E. Africa, India,

--Enrolled HIV+ pregnant women

--Antenatal Maternal ART versus

Mat ZDV/sd NVP

--Breastfeeding: Maternal ART

Versus infant NVP during BF

--March2011-Sept2106

PROMISE ND

N=738

--Enrolling PROMISE ND sites: Uganda, Malawi

--5-year cohort follow up PROMISE

Mothers and their HEU children

--Age and gender-matched HUU children

--Evaluated neurodevelopmental outcomes in children at 12, 14, 48 and 60 months of age

--Enrolled2013-2014.

Culture-specific neurodevelopment assessment of HIV-affected children

N=600

--HEU and HUU children at 2 PROMISE ND sites: Malawi and Uganda

--Establish validity of static and dynamic measures of neurodevelopment using Brain Powered games thru' 12-sessions

-- 6monthspost-trainingfollowup

-- Additional training for underperforming children

5.0 NEURODEVELOPMENTAL ASSESSMENT PROTOCOL DESIGN

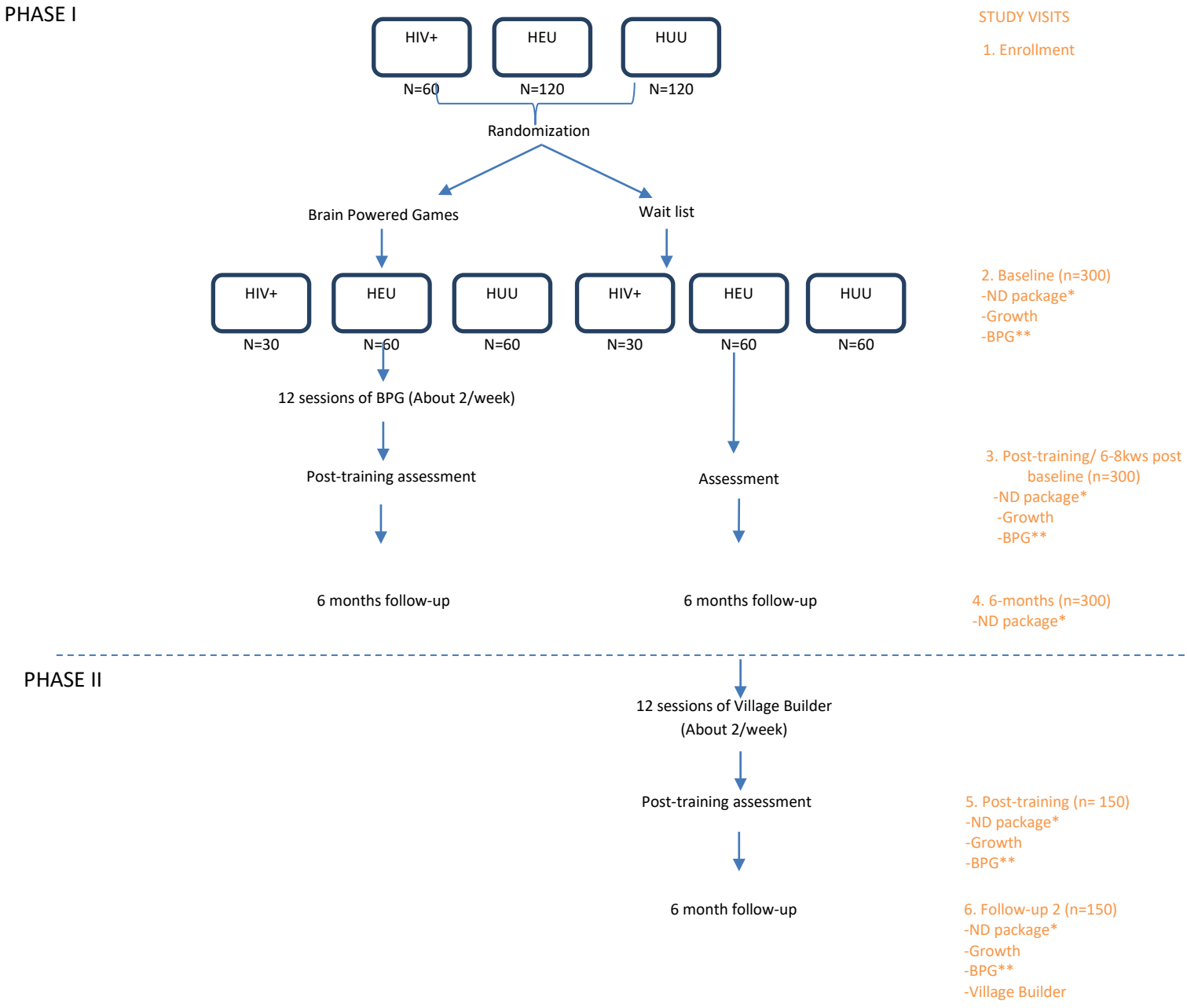
5.1 Overview of Study Design:

Static and Dynamic Assessment Process for Each Study Child. Figure 6 provides an overview of study visits and assessments. Following enrollment and physical and medical exams, each child will return to the clinic with their principal caregiver for a half-day of gold standard neuropsychological assessments (KABC-II, TOVA, CogState). At this time the caregiver will complete the Achenbach CBCL questionnaire for school-age children, the Caldwell HOME scale, the SES material possessions evaluation, and the Hopkins Symptom Checklist-25 (caregiver psychological well-being). We will explain assessments and provide instructions in the local language. Study assessments will proceed in two phases. In Phase I, children will be randomized to start BPG trainings (50% of sample) or to a wait-list condition. Within a week after baseline assessment, the full sample of children will be contacted by a field research assistant and facilitate a first BPG session. This first session will be completed by the full sample because it will be considered as an internal performance evaluation session with BPG and will be completed on a tablet, supervised by the field research assistant. This will be done as part of the 50-60 minutes training session on the 5 BPG games (about 10 minutes per game), and will constitute the BPG static assessment. Thereafter, the field research assistant will return with children allocated to the BPG trainings (50% of sample) at a convenient time and supervise BPG training several times per week until 12 training sessions are completed. The 12th session internal evaluation performance measures for the 5 core games and one added EF game will provide the endpoint for BPG dynamic assessment (gain in BPG performance from session 1 to session 12). Because BPG training will occur on a tablet connected to the internet through the mobile network, performance data can be uploaded for analysis via the MSU GEL lab principal server, as done in the Kayunga Uganda CCRT study with BPG [1].

Post Testing and 6-month BPG Dynamic Assessment Follow-up. Within 2-4 weeks after completing BPG training and dynamic assessment, the full sample of children and their caregivers will return to the clinic for a full gold standard neuropsychological evaluation as the caregiver once again completes the CBCL. The final step in Phase I of our study process will be when the field research assistant returns with the child one final time after 6 months to administer 1 session of the BPG games to the full sample (corresponding to an internal performance evaluation for one final time). Within 2-4 weeks of this final BPG assessment, all children and their caregivers will return to the clinic for a gold standard neuropsychological evaluation. Our rationale for choosing when to have the final assessment is based on past work: after 6 months without training, the benefits of training may begin to diminish in terms of a slower rate of change in comparison to the rate of change during the training period. This BPG performance change from post training to 6-mo follow-up will provide an additional dynamic outcome for validity analyses.

In Phase 2 of the study we will assess the static and dynamic properties of an executive behavior-focused cognitive rehabilitation game package called Village Builder. In this Phase, children allocated to the wait-list condition will complete 12 sessions of training with Village Builder in a mobile device and facilitated by a research assistant. Within 2-4 weeks of the final Village Builder session, children will attend the clinic for a gold standard neuropsychological evaluation using the same battery of tests as in Phase 1. The last visit of Phase 2 will be 6 months (+/- 4 weeks) after completion of the training, where a final session of Village Builder will be administered (static evaluation) along with the battery of neuropsychological tests. Caregivers will also complete the CBCL, SES and HOME assessments in the same study visits as their children.

Figure 6. Study visits and assessments (numbers for 1 site shown)



5.2 Study goals, aims and objectives

5.2.1 Study Goal
The overall goal of this research is to adapt and validate BPG as a measure to assess cognitive changes as a child plays with BPG once (static assessment) and over the course of 12 training sessions (dynamic assessments of cognitive change over time).

5.2.2 Aims and objectives:
Aim 1: To adapt and evaluate concurrent and predictive validity of BPG static (baseline) and dynamic (during 12 training sessions) cognitive assessments at the Malawi and Uganda sites.

Objective 1.1 To evaluate whether BPG static (baseline) assessment corresponds to the gold standard static measures previously adapted to HEU, HUU, and HIV+ study cohorts at Uganda and Malawi country sites (KABC-II, TOVA, CogState).

Aim 2: To compare the validity of BPG static and dynamic assessments.

Objective 2.1 To evaluate the correspondence of BGP-based static and dynamic assessments the cohorts' prior early childhood longitudinal trajectories (KABC-II), considering the effect of proximal (e.g. HIV status) & distal (height, weight, HIV disease factors, demographic) risk factors causing developmental delay and cognitive problems.

Aim 3: To test the sensitivity of dynamic assessment to learning loss over time by evaluating how much BPG performance gains diminish during a 6-month absence of training

Objective 3.1 To assess change over time in KABC-II, TOVA and CogState scores (learning loss) 6 months after the children complete 12 sessions of BPG training, overall and by cohort.

5.3 Study Outcomes and Exposure Variables of Interest
Primary Outcome: Correlation between coefficients of gold-standard measures (KABC-II, TOVA, CogState) and BPG scores. We will evaluate the concurrent validity by computing correlation coefficients of the BPG and "gold standard" measures at intake, 1 and 7 months after intake.

Exposure Variables of Interest:

BPG package

BPG executive function reasoning/planning game (to be developed)

HIV status (infected, exposed, unexposed)

Nutritional and growth history (PROMISE NeuroDev R01 HEU and HUU cohorts)

ARV exposure and clinical response to treatment history (HIV cohort)

5.4 Recruitment
Six hundred African children will be recruited into this study at Clinical Research Sites in Kampala, Uganda and Blantyre, Malawi (n=300/site). These will include 120 HIV infected children from affiliated clinics serving children living with HIV; 240 HEU children from PROMISE study, and 240 HUU children from PROMISE ND study of

similar age group. We will enroll roughly equal numbers of boys and girls, but will not be powered to detect statistically significant differences between them.

Enrollment for the HEU and HUU Cohort

All HIV-exposed but uninfected (HEU) children from the Promoting Maternal and Infant Survival Everywhere Neurodevelopment follow-up (PROMISE ND R01 study) in Blantyre, Malawi (N=188) and Kampala, Uganda (N=208) study sites will be eligible for enrollment for our study since during Year 1 they will be 5 years and older (mean age at both sites 6.6 years, range 5.4-7.7 years). Our target enrollment for this proposal of 120 HEU children from each site (total HEU sample of n=240) during the study's first 2 years that can be easily obtained as it represents 60% of the HEU PROMISE ND cohort at both sites. Our HUU cohort will also consist of 120 HUU children at each study site (total HUU sample of n=240) and will also be recruited from the PROMISE ND cohort study, comprised of 178 HUU children in Malawi and 195 in Uganda. Our target enrollment of HUU children of 120 at each of these two sites is feasible given that it represents 64% of the PROMISE ND cohort and children will be within the required age range (mean age at both sites 6.2 years, range 4.9-7.4 years). In total, 240 HEU and 240 HUU children will be enrolled for the present study.

The great advantage to enrolling the HEU and HUU cohorts in the present study is that they have been assessed with the Mullen Scales of Early Learning (MSEL) at 12, 24, and 48 months of age and are being evaluated with the KABC-II at 48 and 54 to 60 months of age. Thus, we can rigorously establish their neurodevelopmental trajectory with the MSEL across 3 longitudinal time points and relate that trajectory to BPG static and dynamic outcomes respectively in terms of correspondence validity. We can do this while both controlling for and evaluating independently the BPG neurocognitive outcomes as affected by health history, hematology/CBC, neurological exam, and physical growth measures — more distal factors that are typically strongly related to neurocognitive function, and which should be adjusted for (see Figure 1; Section 2.8).

In the unlikely scenario that recruitment target numbers are not met and/or PROMISE ND participants cannot be traced, we will recruit from study roasters affiliated with MUJHU and Blantyre sites.

Enrollment for the HIV-Positive Cohort

For the children to be enrolled in the HIV cohort at each site, several hundred children across both sites living with HIV attend routine appointment at Kampala MUJHU and Blantyre JHU sites. We will approach the parents/caregivers to get permission to screen their children for eligibility. After obtaining informed consent, we will administer a baseline assessment including detailed medical histories and as much data as possible on age of HIV diagnosis and ARV initiation and treatment history, previous hospital admissions, diagnosis of opportunistic infections and ART initiation, regimens, side effects, and adherence. We will also obtain detailed standardized medical, hematological, immunological, and neurological information from these children. The children will then undergo the same gold standard (KABC-II, TOVA, CogState) and BPG assessment and training procedures as all other participating HEU and HUU children.

In case the sample size for the HIV cohort is not reached within affiliated health clinics, we will recruit from children that graduated from the P1104s study in both Uganda and Malawi. The P1104s study was an observational multicenter longitudinal study aiming to compare neuropsychological outcomes between the perinatally HIV+, HEU and HU children in sub-Saharan Africa. Children and their caregivers were recruited from the IMPAACT P1060 study. Dr. Boivin served as protocol chair for the P1104s study. Potentially recruiting from these cohorts of HIV children is advantageous given their full neurodevelopmental characterization and medical data available.

5.5 Eligibility criteria

5.5.1 Inclusion criteria

We will enroll HEU and HUU children from 5 years to 14 years of age from the PROMISE ND study into the present study. The HIV+ children needed for the target enrollment at each of the two sites will be new recruitments carried out in the MUJHU Kampala or JHU Malawi clinical care treatment programs serving children living with HIV. These HIV+ children will be age-matched and gender balanced to the PROMISE ND HEU and HUU cohorts enrolled in the present study. When evaluating BPG neuropsychological outcomes for the HEU and HUU cohorts, we will control for number of prior neuropsychological assessments, since these children will have had three prior assessments with the KABC-II test, and will be more experienced in that regard than the testing-naïve clinic HIV+ children. The PROMISE ND HEU HUU cohorts in the present study will all be equally experienced in terms of prior neuropsychological testing.

5.5.2 Exclusion Criteria

At pre-BPG 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. This will be screened withP1104s medical history questionnaires. Serious CNS neurodisabilities would prevent such children from completing the BPG intervention, and possibly significant portions of the neuropsychological test battery serving as the evaluative gold standard for static and dynamic assessment outcomes.

5.6 Study Procedures

Study staff will inform PROMISE clinic staff about the Culture-specific neurodevelopment assessment of HIV-affected children Study. After all regulatory approvals are in place and staff trainings have been done, the Culture-specific neurodevelopment assessment of HIV-affected children study staff will receive referrals and recruit interested PROMISE participants into the Culture-specific neurodevelopment assessment of HIV-affected children study. They will then screen and enroll interested PROMISE children at the Kampala and Blantyre PROMISE sites.

To recruit the HIV-infected cohort from the Pediatric HIV Care Center, the Malawi site will first approach the Blantyre District Health Officer for endorsement of the study. Community Educators will then visit health centers to map out their pediatric ART clinic hours, their case load of children living with HIV on ART, general staffing structure and competing research efforts at the clinic that could affect recruitment for the BPG validation study. The Community and Study Clinic departments will follow the proper channels to request permission to give waiting room talks to the children and their caregivers during the pediatric ART clinics and will provide small tokens (pens, etc.) as a reminder about the study to the parents and children approached.

Staff will be positioned at the clinic to meet with patients interested in learning more about the study. When study staff are not present, local health center staff will be asked to call the JHP study clinic anytime a potential participant expresses interest. Recruitment and enrollment will take place at the main study clinic located at the Queen Elizabeth Central Hospital. We will begin by targeting the health centers closer to Blantyre, as persons from these areas have better retention and they are easier to trace in case of a missed visit. We anticipate no challenges in achieving the target 60 HIV-infected children using this approach.

To recruit the HIV-infected cohort (n=60), the Uganda site will approach HIV-infected children from the Pediatric HIV Care Center and Young Generation Alive psychosocial support group, which are affiliated with MUJHU clinical trials unit. Hundreds of children are medically served at the HIV Care Center, most living with HIV. We anticipate no challenges in achieving the target 60 HIV-infected children. Staff will invite to the clinic to

meet with patients interested in learning more about the study. Recruitment and enrollment will take place at the main study clinic located at the MUJHU clinic in Kampala.

To accommodate school-age children's schedules, the site proposes to conduct most study visits during afternoons, weekends and schools' holidays/breaks. To maximize retention, we will ask caregivers whether they prefer to bring the child to the clinic for testing visits or if there is a safe space near their home or school where they are comfortable conducting the tablet-based trainings with BPG and/or Village Builder for about one hour. We anticipate mothers will be interested in conducting training sessions closer to home, especially given the schedule of Brain Powered Games (BPG) expected to be 2-3 training sessions per week for a total of 12 sessions; however, some might have significant concerns about disclosure of HIV status or study participation if sessions are conducted outside of the study clinic, which is why we will offer different options for training site. We will offer to conduct partner information sessions so that husbands and children's fathers learn of the child's study participation in a transparent, open manner, rather than inadvertent disclosure, which can then lead to premature discontinuation from the study.
Written consent will be obtained from interested participants after explanation of the study and opportunity given to them to ask questions of the study staff. Only after obtaining written informed consent will any study procedures be undertaken for the Culture-specific neurodevelopment assessment of HIV-affected children study visits as described below. For participants who do not meet the eligibility criteria, screening will be once in eligibility is determined.

Consented enrolled Culture-specific neurodevelopment assessment of HIV-affected children study participants will have enrollment and follow-up evaluations related to BPG assessments of neurodevelopment over a 7-months period as outlined below and detailed in the Schedule of Evaluation (SoE)s—see Appendices 1-2.

5.6.1 Randomization procedure
Systematic randomization will be used to assign children within each HIV exposure cohort into BPG training or wait-list conditions. Lists of all children within each cohort will be generated and a simple random sampling will be used to assign children into treatment groups. The first child will be assigned to BPG and the next to wait list. For the HEU and HUU cohorts, separately, two sets of random numbers ranging from 001 to 120 will be generated, and the first 60 random numbers drawn from each set will be assigned to start BPG. The second 60 numbers from HEU and 60 from HUU drawn will be assigned to the wait list condition.

A third set of random numbers ranging from 01 to 60 will be generated for the HIV+ group, the first 30 numbers drawn will be assigned to the BPG group. The second 30 numbers drawn from the HIV+ cohort will be assigned to the wait list condition.

5.6.2 Overview of Anthropometric and Clinical Procedures
Collection of medical, concomitant medications, anthropometric assessments (weight, height, BMI) and clinical assessment for physical signs of malnutrition will be performed per the SOEs. The questionnaires will be brief enough not to add undue respondent burden.

5.6.3 Overview of Planned Neurodevelopment assessments .
The KABC-II (comprehensive cognitive testing), TOVA (attention, impulsivity), CogState (working memory and learning cognitive screening) have all been validated in the Ugandan context [11] and as such they are all represent "gold standard" assessments for Uganda in their respective neurocognitive domains; particularly in the absence of any normative data for any such tests for Uganda.

In fact, in the context of pediatric HIV in Africa, the KABC is the best validated comprehensive cognitive performance task available.

These tests (KABC-II, TOVA, CogState, and CBCL) are described in detail below. We used these tests previously to evaluate the neuropsychological gains from CCRT training in Ugandan children with HIV, [1,5,6] the effects of HIV Clade I subtype on neuropsychological outcomes [38], and neuropsychological effects of HIV on treatment-naïve Ugandan children with high CD4 counts.[39] These tests have also been used to evaluate cognitive gains from CCRT intervention for Ugandan children surviving cerebral malaria.[21,25,26]and they have been validated in the P1104s study.[2-4]

Kaufman Assessment Battery for Children (second edition). Used in both the PROMISE NeuroDev study with the HEU and HUU cohorts, and in P1104s with HIV+ children, the KABC-II will be the principal test for cognitive ability.[40] It is validated in sub-Saharan Africa[41-44] and has been adapted for pediatric HIV research.[1,6,39,45-48] Using the Luria model for neuropsychological assessment within KABC-II, the primary outcome variables are the global scores of Sequential Processing (memory), Simultaneous Processing (visual-spatial processing and problem solving), Learning (immediate and delayed memory), Planning (executive reasoning), Delayed Recall, Nonverbal Index (NVI) subtests not dependent on understanding instructions in English, and Mental Processing Index (MPI), a composite of all the cognitive performance areas.

Test of Variables of Attention (TOVA). TOVA is a computerized visual continuous performance test used in to screen, diagnose and monitor children and adults at risk for ADHD.[49] TOVA consists of the rapid (tachistoscopic) presentation of a large geometric square on the computer screen with a smaller dark box either in the upper position (signal) or lower position (non-signal). The child is asked to press a switch held in the preferred hand as fast as possible in response to the signal (measuring vigilance attention), but to withhold responding to the non-signal (measuring impulsivity). Following spoken instructions in the local language and practice trials, TOVA takes ~11 minutes for children 5 to 5.5 years old, and 22 minutes to administer for children 5.5 years and older. TOVA had been adapted for pediatric HIV research in Uganda.[1,5,6,38,39] TOVA's primary outcome variables are response time variability (a sensitive indication of inattention), response time, percent commission errors (impulsivity), percent omission errors (inattention), an attention deficit hyperactivity disorder (ADHD) index score (missed signals in proportion to incorrect responses to non-signal), and a D prime signal detection measure of overall test performance (correct signal "hits" in proportion to correct non-responses to non-signal).

CogState.[50,51] We used this computerized neurocognitive assessment in our prior CCRT studies.[26,52]CogState presents a 30-min session that includes playing cards in a game-like manner to assess memory, attention, discrimination learning, and executive function that is non-language dependent. CogState tests include Card Detection (simple reaction time), Identification (choice reaction time), One-Back Working Memory, and One-Card Learning. CogState also includes the Groton Maze Task, which can measure visual-motor tracking (Maze Chase) and executive functioning/planning (Maze Learning). CogState is available on tablets, but its assessment data must be uploaded via the internet, and assessment results downloaded from CogState's central server. CogState has strong correspondence validity with KABC-II and TOVA. These three are the trilogy of our gold standard.[28]

Achenbach Child Behavior Checklist (CBCL). This is NOT part of the neuropsychological gold standard, but is an important parent-based screening tool for emotional and behavioral problems observed in the child. The CBCL is important to assess when a child's social environment is enriched by adult oversight in game assessment and training, reflecting a collateral training benefit.[21] the CBCL has been translated and adapted in our severe malaria research in Kampala[53] and Blantyre[54,55] and structure validated for use with HIV-affected children[35]for the PROMISE ND study and pediatric HIV research in Uganda,[56,57] and in CCRT intervention studies in Uganda.[5,6,26]Our principal outcomes are Internalizing, Externalizing, and Total symptoms.

Quality of Home Environment and Caregiving. We will use the middle childhood version of the Caldwell Home Observation for the Measurement of the Environment (HOME) validated for use as an important distal measure predictive of our gold standard assessments.[58,59] The HOME assesses the stimulation and learning opportunities offered by the child's home environment. Along with HOME, we will also use a socioeconomic evaluation scale of physical quality of the home environment (SES score) also used with Ugandan children and sensitive to long-

term (distal) neurocognitive outcomes such as the KABC-II.[60]

Hopkins Symptom Checklist -25 items. The HSCL is a 25-item self-response questionnaire that will be used to evauate depression and anxiety symptoms in caregivers .This questionnaire has shown adequate performance in Ugandan populations [34, 36]. Questions are scored in a severity scale from 1 to 4, with higher scores indicating more symptoms of distress.

5.6.4 Overview of CD4+ T-cell counts, immune activation, and viral load assessments (HIV cohort only)

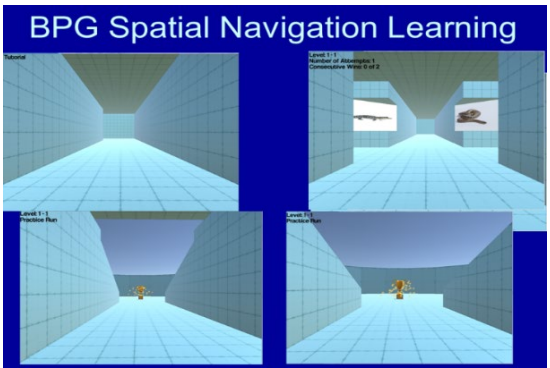
As part of their standard of care (HIV cohort only), CD4, CD8, viral load and other immunology measures will be available from a blood draw taken within a week from the time of neuropsychological assessment as a more proximal predictor of disease effects on assessment performance. CD4 and CD8 T-cell activation level testing will be performed on EDTA anti-coagulated whole blood using a fresh-lyse/no-wash flow cytometry procedure. Blood will be incubated with monoclonal antibodies including CD3, CD8, CD4, CD38, and HLA DR, then processed and acquired on a multi-laser bench top flow cytometer. For each run of patient samples, a separate sample of stabilized blood product (CD-Chex, Streck Labs) is processed. CD4 T cell and CD8 T cell activation levels will be defined as % CD38 and HLA-DR co-expression.[61]

5.6.5 Overview of Brain Powered Games

The BPG subtests were designed/selected based on what has been validated from the attention/working memory/visual-spatial categorization and analysis subtests validated in previous CCRT clinical trials work from BrainTrain Captain's Log [1]. However, Captain's Log was proprietary and not available for transition to scale for LMICs in Africa. Furthermore, it is no long available or supported, and its successor has not been tested in Uganda. BPG is designed to address the very same cognitive skills as Captain's Log Uganda was, but is scalable, accessible and affordable for the African context. Additionally, BPG has been previously proven to improve neurocognition among Ugandan children with HIV[18].

Each BPG game includes a visual tutorial, several adjustable settings on the administrative side (Admin), and records game play data for research purposes. As part of a current preliminary study using BPG with aging Ugandan adults with HIV, we have now adapted BPG as a mobile app for the touch screens of tablets and smart phones, as part of a preliminary study of BPG dynamic assessment in aging adult HIV patients in Uganda. Our preliminary findings thus far have documented that the neuropsychological gain scores from pre- to post-training with BPG are sensitive to the clinical and health parameters of our patients at enrollment, including ARV adherence, viral load, adverse health events, and CD4 nadir. We will also use gain scores pre- to post-training for our gold standard of neuropsychological tests as our principal performance outcomes in the present study, as noted in Table 3 (far right column) for each of the BPG training games below.

Butterfly. Here a butterfly flies across the screen and the child touches it when the butterfly stops moving. When the child touches the butterfly, the child earns 10 points, the butterfly moves somewhere else on the screen, and the process is repeated. The game continues until the child scores a set number of points. Butterfly serves as a training exercise, letting a child become familiar with the game interface on the tablet.



iSpy. This is a memory game. iSpy shows the child a scene with several objects. After a few seconds in which the child is supposed to memorize the objects, iSpy removes the scene. A few seconds later the scene reappears — but now with a new object. The child must recall which objects were in the previous scene

and touch the new one before iSpy again takes the scene away. The game progresses with one more object every time the scene reappears, and the child is challenged to recall which objects have been seen before. iSpy has another mode in which objects are removed from the scene and the child has to remember where the missing object used to be.

Stampede. Another memory game, Stampede shows the child an animal to remember. A group of animals, including the one the child has been shown, runs across the screen. The child must touch the featured animal before it moves all the way across the screen. The number of animals that appear is based on the current round and the admin settings. As the game progresses, the child is given an increasing number of animals to remember and touch before they run across the screen.

Whacky Animal. Whacky Animal is a memory game inspired by whack-a-mole. Similar to Stampede, the child is shown an animal to remember at the beginning of the round. A random animal then pops up from the sides of the screen and the click must touch the animal before it ducks behind the edge.

Figure 5. The BPG Spatial Navigation Learning game was just added to the package and field tested with HIV patients at the MUJHU Kampala study site in July/August 2016. In this game the child "moves" about in a virtual maze with pictures of common African animals at intersections. Performance gains (correct turns, time to complete maze to obtain prizes) are

Spatial Navigation Training (SNT; Figure 5). This is BPG's newest game, piloted in Uganda for the first time in June, 2016 with adults and also with children with HIV. SNT involves a relatively new approach to cognitive training that uses a procedure (spatial navigation) that is localized to the hippocampus, the area most involved with visual-spatial memory and learning.[62] Spatial navigation is getting increased emphasis in computer gaming because spatial navigation training generalizes to other aspects of verbal and visual learning and memory performance. In this game the child "moves" about in a virtual maze with pictures of common African animals at intersections (Figure 5). SNT stimulates not only the hippocampus, but also other mobility-related brain areas (similar to what happens in imaging studies when a person is asked to imagine walking).[14] In two recent publications, Co-I Giordani and colleagues showed that after 12 sessions of SNT, older adults demonstrated improvements in both executive functioning and more complex aspects of mobility.[15,16] SPN is presently being used by Giordani and Boivin in a pilot study with aging HIV adult patients in Uganda.

Village Builder (VB). Professor Winn and his MSU-GEL team will develop a game emphasizing social cooperation (prosocial) and emphasizing reasoning and planning skills. This executive function game will use the same African village motif and animals in the existing BPG package. However, it will differ in that children will use their avatars in a cooperative manner to add dwellings to the village and domesticated animals (livestock such as goats, cattle, pigs, chickens) to the surrounding village compounds so as to increase the available resources in a positive manner.

Unlike the existing games in Africa BPG that emphasize vigilance attention, monitoring and working memory, and visual spatial learning and navigation (mazes task), this new Village Builder game will emphasize executive function and reasoning in children. It will be intuitive, culture-fair, non-violent, and designed to be engaging for the computer novice and casual gamer. Boivin has served as a consultant on NIH application to develop a touch screen Android Tablet assessment game package for assessment of executive functioning in preschool-age children, called "EF Touch". This app has undergone pilot testing with Kenyan children 4 to 6 years of age.[63] Using a model of EF development based on self-control interventions, pro-social values, and validated in early and middle childhood in terms of social and academic outcomes,[64] Boivin, Giordani, and Wynn will work together to incorporate the best validated response features of EF Touch (Animal Go/No-Go, Silly Sounds Stroop, Pick the Picture)[63] into the new Village Builder EF game. The eventual goal is to compare the dynamic versus static BPG cognitive assessment features when they emphasize attention, memory, and learning tasks and when they emphasize planning and reasoning tasks in school-age children. Both types of BPG games (attention/memory/learning versus planning/reasoning) will also be compared to the gold standard of tests presently validated for the study sites (KABC/TOVA/CogState) in terms of their comparative sensitive to more proximal (HIV exposure and treatment) and distal (nutrition and quality of caregiving and home environment)

risk factors.

By comparing Village Builder executive function (EF) game to the existing Africa BPG package, we can better understand what value it adds in terms of a static and dynamic assessment of brain/behavior function in younger school-age African children. At present, no such CCRT intervention or assessment program exists that has been validated for African children, despite the great importance of EF in frontal lobe brain development at this stage of middle childhood. EF and frontal lobe development are vitally important precursors for future neurocognitive adaptation and function in children affected by HIV (e.g., self-management, impulsivity, planning, treatment adherence, psychosocial adjustment and prosocial behavior) as they age into adolescence and eventually into early adulthood.

5.6.6 Summary of Procedures by Study visit

The following procedures will be conducted at the screening and enrollment visit of all enrollees

Table 1: Enrollment and Intake Visit(s) for all enrollees	
Component	Procedures
Administrative and Regulatory	• Assess eligibility • Obtain written informed consent/ assent • Assign a Participant Identification (PTID) Number • Provide reimbursement for study visit
Clinical	• Obtain medical history • Conduct a brief physical examination (main organ systems and
Neurodevelopment Assessments	KABC-II TOVA
Caregiver-reported assessments	CBCL HOME
Brain Powered Games	1st session for treatment condition (e.g. training) and only 1 session for wait list group (e.g. assessment)

*Depending on staff availability and scheduling, enrollment and baseline visits will be done on the same day

Table 2: BPG training visits for 50% of sample	
Component	Procedures
Administrative and	• Schedule next visit
Brain Powered Games package	• Complete 10 sessions (About 2 per week for 6 weeks) of approximately 30-45 min

Table 3: Follow-up Visits for all enrollees	
Component	Procedures
Administrative and	• Provide reimbursement for study visit

Clinical	• Obtain medical history • Conduct a brief physical examination (main organ systems and
Neurodevelopment Assessments	KABC-II TOVA
Caregiver-reported assessments	CBCL HOME
Brain Powered Games	12th session for BPG training group and 1 session for wait list group 1 session at 6-months follow-up for entire sample

Table 4: 12 session trainings of Village Builder (wait-list) and	
Component	Procedures
Administrative and	• Provide reimbursement for study visit
Clinical	• Obtain medical history • Conduct a brief physical examination (main organ systems and
Neurodevelopment Assessments	KABC-II TOVA
Caregiver-reported assessments	CBCL HOME
Village Builder	• Complete 12 sessions (About 2 per week for 6 weeks) of approximately 30-45 min

Table 5: Follow-up visits for wait-list group	
Component	Procedures
Administrative and	• Provide reimbursement for study visit
Clinical	• Obtain medical history • Conduct a brief physical examination (main organ systems and
Neurodevelopment Assessments	KABC-II TOVA
Caregiver-reported assessments	CBCL HOME

Village Builder	• 1 session at 6-months follow-up

5.6.7 Retention Strategies to Ensure Follow-up

We will leverage the long-established retention strategies at the research site to retain participants in this study. Participants will be closely tracked by a dedicated experienced team of dedicated staff to minimize missed visits and loss to follow-up at both the Uganda and Malawi sites. This will be done primarily calling participants by mobile phone and reminding/re-scheduling visits as appropriate. Our staff also works with home locators to conduct a home visit as needed. This approach has proven highly successful at the two sites with 2-year retention rates>95%at prior trials in the Uganda and Malawi sites.

6.0 DATA MANAGEMENT

Standard operating procedures will be developed for all data management activities to ensure consistency and quality of data. All questionnaires and other study implementation materials will be pre- tested and the necessary revisions made prior to implementation. Date for paper-based neurodevelopment assessments and questionnaires will originally be encoded from hard copies into the Research Electronic Data Capture (REDCap) system with double data entry and error checklist verification for quality control. REDCap is a web-based database creation, management and entry tool. REDCap's easy design environment allows quick creation of web-based databases and data capture forms with special features like ad-hoc reporting and scheduling. It is widely used in the academic research community: REDCap Consortium is a collaborative, international network of more than 1700 institutional partners in over 95 countries. REDCap was developed by staff at Vanderbilt University in 2004 in order to help researchers manage data for small/medium sized projects in a systematic manner (metadata defined, secure, audit trails, etc). The system is continually updated and enhanced by the Project REDCap team at Vanderbilt. This installation of REDCap will be provided by Michigan State University Biomedical Research Informatics Core (BRIC). REDCap is maintained by the IT staff at BRIC. Access to REDCap database will be password protected to ensure confidentiality. Performance-based measures data from Brain Powered Games (BPG) will be off-loaded from the training tablets directly to Michigan State University Games for Entertainment and Learning (GEL) Lab's server and from there to BRIC for data merge and management.

Data for all portions of the study will originally be encoded from hard copies into the REDCap database system by the data managers at the Uganda and Malawi project offices. Double data entry and error checklist verification for quality control will be performed for all electronic files at the same office. Hardcopies will be archived at the Uganda and Malawi offices in safe and secure locations in locked cabinets at all times. All database systems at our Malawi and Uganda project offices will be password protected and Personal Identifier Information (PID) matched to participant Study ID numbers will be kept and encrypted in a separate electronic file and kept secured separately in a different study file cabinet on site.

Monthly email communications with Michigan State University will include updated enrollment and admissions data to monitor study progress. At MSU, the Data Management group for the MSU Biomedical Research Informatics Center (BRIC) will assist in the set-up and securing of all of our study data using their internet-based RIX information management system. The capabilities of this center are described in the MSU Resources section. Password protected database files will be sent by e-mail to Michael Boivin, Itziar Familiar-Lopez and Alla Sikorskii at Michigan State University.

We will be able to download our project datasets and data definition dictionary from the RIX system to make data available to other research groups. We will require a collaborative agreement from such groups before making

such datasets available, as approved through the Intellectual Property Office at Michigan State University. See http://newsroom.msu.edu/site/indexer/3004/content.htm for an overview of this office and http://oip.msu.edu/documents/CDA2001_002.pdf for an example of such an agreement. In addition, we will ask to have final approval of all publications from other research groups who include our study data. MSU also has a Clinical Translational Science Institute (CSTI) described in our resources section of this application that provides support for DSMP surveillance in a clinical trials study.

No interim analyses of data are planned, and the study will not be stopped based on any statistical rules. To ensure reliability of data entry, a random sample will be reviewed by the investigators, and the results compared with the information recorded on the data base program. An acceptable error rate is less than 0.3%, i.e., three per 1000 entries. During data collection, quality assurance reports will be prepared on a quarterly basis and reviewed by the investigators. The reports will inform the investigators about missing, invalid, and inconsistent data on selected key variables. Co-I Dr. Sikorskii will oversee preparation of the reports.

7.0 STATISTICAL CONSIDERATIONS

7.1Power and Sample Size Calculations

7.1.1 General Statistical Approach

This study will utilize an observational longitudinal design. The analyses will account for repeated measurements within a child using generalized estimating equations, and marginalization to the unique participant level. Because this design is observational, potential confounders will be adjusted or in the analyses, and will be minimized by matching on parity, age, and site. This study is comprised of three groups: 1) HIV infected, 2) HEU, and 3) HUU children.

7.1.2 Statistical Approach by Specific Aim

Statistical analysis for Aims 1& 2. So as not to have to rely on American norms for standardizing our gold standard measures, we will use a statistical technique for standardization described from our cerebral malaria longitudinal studies with these tests.[65] Professor Sikorskii will evaluate the concurrent validity by computing correlation coefficients of the BPG and "gold standard" measures at intake (see Table 3) at 1 and 7 months. Correlations will be classified as: very strong (r≥0.8), strong (r range 0.6-0.79), moderate (r range, 0.4–0.59), weak (r range, 0.20–0.39), and very weak (range: 0-0.19). We will summarize the sensitivity of the BPG-based vs gold standard measures to the proximal (HIV infection) and distal factors (SES, home environment, growth) using : 1) relative validity coefficient; 2) standardized effect size;[66-69] 3) standardized response mean (SRM) and Guyatt's SRM.[66,67,69,70]Larger values of these summary statistics correspond to greater sensitivity or ability to discriminate known groups. Interpretations similar to Cohen's effect sizes[68] will be considered (e.g. SRM: ≥1.0: excellent; 0.80-0.99: good; 0.50-0.79: moderate; and < 0.5: weak). *We will evaluate the predictive validity of the BPG-derived measures in the LME model with the repeated gold standard measures at 1 and 7 months (6-month follow-up).* Covariates will include the BPG static measure at intake (baseline) and 1 month (post-training BPG; time-varying covariate), time (1 and 7 months), other covariates (proximal and distal factors, Figure 1), and number of prior neuropsychological testing sessions.

Statistical analysis for Aim 3. Two sets of the LME models will be fit: one with 3 repeated "gold standard" measures, and one with 3 BPG-derived measures. To model potential non-linear patterns over time, we will enter time as a class variable with levels of intake, 1, and 7 months. Based on past experience, we expect gains in outcomes between intake and 1 month due to training, and a slower rate of change in the subsequent 6-month period with no training. Summary statistics for change over time for the gold standard vs BPG-derived measures will be compared as described under statistical analysis for Aim 1.

Sample sizes for Aims 1, 2, and 3. Sample size considerations are based on having sufficient power to discriminate known groups based on the proximal factor of HIV status/exposure, a key factor for Aim 1. The preliminary data from PROMISE ND study indicate that the differences in the composite neurodevelopmental score (the Mullen Scale of Early Learning) between HEU and HUU cohorts corresponded to the effect size of Cohen's d=0.26 (difference between the means of 0.26 of the standard deviation). To detect this difference between HUU and HEU cohorts, n=240 per cohort is needed for power ≥ 0.80 in two-tailed tests at 0.05 level of significance. Based on the preliminary data, the effect size *d* for comparisons of the HIV vs HUU or HEU is at least 0.31. This can be detected with power ≥ 0.80 with n=120 in the HIV group. Therefore, the proposed total sample size for both sites combined is n=240 HUU; n=240 HEU; and n=120 for HIV+ children.

8.0 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in compliance with country-specific regulatory requirements for each of the participating sites and strictly follow GCP/HSP requirements. Written informed consent will be obtained in the local language of the mother after explanation of the purpose of the study, the procedures to be followed and the risks and benefits of participation; and answering the women's questions. A copy of the consent forms will be given to the subject unless he declines to take them. Every attempt will be made by study staff to ensure privacy and preserve confidentiality of study participants. All clinical study staff involved in the study is trained on GCP/HSP and their certificates will be reviewed on an annual basis

to ensure training compliance. All study records will be kept in a secured area with limited access. All computer entry and networking programs will be performed with coded numbers only. All laboratory specimen reports, and other records that are transferred or transmitted off-site will be identified by a coded number to maintain subject confidentiality.

8.1 Human Subjects Protection

The Culture-specific neurodevelopment assessment of HIV-affected children study will enroll HEU and HUU children and their caregivers from the PROMISE ND study at the Blantyre Malawi and MU-JHU Uganda Kampala Clinical Research Sites (CRSs); and HIV infected children of similar age and from the IMPAACT P1104s study and health clinics from which the CRSs enroll. This study's protocol will follow the Human Subjects requirements as summarized below. The proposed principal investigators as well as all key co-investigators are all highly qualified researchers and are incompliance with the Office for Human Research Protection (OHRP) requirement concerning protection of human research participants (HSP/GCP). All personnel working on this study have training on the protection of human research participants to ensure compliance and maintain confidentiality of study participants and their data.

8.2 Potential Risks

Distress for research participants: Although neuropsychological assessments bear no potential harm on participants, they can be long and tedious for some children. We will be particularly attentive to the child's needs, providing frequent breaks and refreshments as needed so the child is not unduly stressed. Training of our testing staff includes sensitization to each child's needs and the potential for stress and frustration reactions derived from testing. In case any participant becomes distressed at any point during the assessments, testing staff will suspend the test and assess the need for referral to psychological support available at each participating site in Uganda and Malawi. However, sections of the neuropsychological assessments involve game-like tasks that can be entertaining to the participant. Furthermore, sections of the testing (Cogstate and Brain Powered Games) are carried out on an appealing electronic console (i.e. tablet) popular among children, potentially entertaining the participant.

8.3 Adequacy of Human Subjects Protection against Risks

Recruitment and Informed consent: The subject population for this proposal will consist of 600 children roughly equally divided between males and females. These are Ugandan and Malawian children 5-14 years of age at study initiation who live in Uganda or Malawi. The caregiver may or may not be the biological parent of the study children but will be an adult who has a primary role in the child's growth and protection. Study staff already known to our previous R01 cohort participants (un-exposed - HUU, un-infected and exposed-uninfected children - HEU) will make the initial contact through clinic visits and telephone calls. HIV infected children from HIV care clinics at both sites and PROMISE ND studies (HEU, HUU) in Uganda and Malawi will be invited to participate using the same mechanism. Informed and signed consent will be obtained from all caregivers who will provide consent for their child to participate, while child assent will be obtained for children 7 years and older according to local regulations. Information will be provided and consent forms given in either English or one of the local languages (Luganda, Chichewa) they comprehend with the consent being administered in the language of their choice. The consent form will be read aloud and explained to the caregivers, who will then sign the consent or provide a thumb-print. A copy of the consent will be given to the caregivers. An assessment of understanding will be conducted for all participants after consent reading by an independent person to ensure that the potential participants understand what they are consenting for.

All centers participating in this study will have active institutional review board (IRB) approved protocols and maintain IRB and all other necessary approvals for this study throughout its conduct.

8.4 Potential Risks Protection against Breach of Confidentiality of Study Data

All participants enrolled into the study will be assigned a unique PTID. The PTID number will be used for identification purposes on all laboratory specimens, evaluation forms, and reports retained in the research records and generated in the protocol database. A list linking the subjects' names with PTID numbers will be stored at the clinical site under double lock and key in a secure area accessible only to limited staff on the study. All study records will be stored in secure areas with locks.

8.5 Consideration of Potential Benefits of Proposed Research

Children living in poverty and/or affected by HIV/AIDS are at risk, either directly or indirectly, of compromised care giving, economic impoverishment, and poorer overall quality of home environment throughout the sensitive period of childhood development. This could compound cognitive and psychosocial deficits that can affect a child's ability to fully benefit from schooling and could limit the child in other aspects of life. These children may have difficulty with learning and maintaining concentration, which will in turn affect their school performance, subsequent educational opportunities, and future economic prospects. Intervening to prevent cognitive deficits from the direct or indirect effects of poverty and stressful environmental conditions on the child and family requires understanding the impact of these on caregiving quality and overall quality of home environment and developmental milieu.

Our study will provide evidence for the usefulness of an innovative neurodevelopmental assessment for school-age children that could be of great importance to families in poverty-stricken countries such as Uganda and Malawi. In these countries, more than a third of all inhabitants live under the poverty line, with about four million children under the age of five being the primary victims of this deplorable economic situation. Given the scope of the humanitarian need of such children globally, our research could be of great benefit in terms of providing evidence in support of strategic and sustainable neurodevelopment assessments during childhood for children living in poverty and affected by HIV/AIDS.

8.6 Staff Training on Protection of Human Subjects

All research staff will be trained on GCP and HSP. Research health visitors will work with participants to establish other contact persons who may be contacted in case the health visitor is unable to reach the study

participant. The two CRS regulatory staff will ensure compliance with all GCP/HSP requirements.

8.7 Ensuring Participant Confidentiality

All efforts will be made not to release personally identifying information to non-study staff except to monitors, the IRBs and the sponsor as necessary. Clinically obtained evaluations will be identified by PTIDS. Any data sent to collaborating institutions will be only transmitted using unique PTIDs on the case report forms. The site investigator will make study records and pertinent records available for inspection by the local IRB, site monitors, the NIH, the OHRP, or the sponsor for confirmation of study data. This study is protected by a Certificate of Confidentiality provided by the NIH.

8.8 Safety Monitoring Plan

Site investigators (Investigators of Record or IoRs /designees) are responsible for continuous close safety monitoring of study participants, and for alerting the Protocol Team if unexpected concerns arise.

Both MU-JHU in Uganda and JHP in Malawi presently sponsor a Health Ethics Committee made up of a multidisciplinary team including representatives from the community and faculty members (medicine, law, economics, nursing, and administration). The Committee is responsible for the approval of all research projects carried out in the in these institutions, and of projects with external investigators collaborating with them. The Committee will be responsible for reviewing the project protocol and the consent forms, ensuring protection of human subjects' rights. The Committee will ensure fulfillment of the ethical principles of the research project and be available to research subjects in case of any doubt or concern with the project. The MSU Office of Clinical and Translational Research is also committed to supporting us in the formation and support of our DSMB.

8.9 Adverse Event Reporting

Cognitive/motor developmental and cognitive testing of children has clear potential benefits and no definable risk. All standards of care for study children in the event of illness will be observed according to Ugandan and Malawian Ministry of Health recommended hospital protocols for such illnesses.

Adverse event management plan: Our project field trainers in the Uganda and Malawi study sites will have clinical officers available who will be able to assess medical need during their assessment visits at the office. They will also be equipped to administer care and medication for most opportunistic infections and first aid care for any accidental injuries that subjects are likely to encounter. The Uganda staff will also notify Dr. Wambuzi (Co-I) by mobile phone for medical concerns and consultation while the Malawi staff will do so with Dr. Dadabhai (Co-I). Both Drs. Wambuzi and Dadabhai are experienced clinical biomedical scientists who can coordinate our clinical care support for the study children. If medical follow-up is needed, our medical staff will make the appropriate referrals.

Study participants will be provided instructions for contacting the study site to report any untoward occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation at the study clinic. With appropriate permission of the participant, whenever possible, records from non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs. Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity. The reports will also include experiences of social harm.

8.10 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the Culture-specific neurodevelopment assessment of HIV-affected children study could

become known to others and that social harms may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities if their participation in the Culture-specific neurodevelopment assessment of HIV-affected children study were to be inadvertently disclosed. Social harms that are judged by the site IoR /designee to be serious or unexpected will be reported promptly to the SMC and responsible site ECs/IRBs according to their individual requirements. In the event that a participant reports social harm, every effort is made

By study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling as defined in the site SOPs. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

8.11 Regulatory Requirements

Site IoRs /designees will submit AE information and other relevant safety information in accordance with local regulatory agencies' including IRB/ethical committees, other local authorities and sponsor requirements.

9.0 PLANNED TIME LINES

The Culture-specific neurodevelopment assessment of HIV-affected children Study is planned to run for 5 years including obtaining IRB approvals, data analysis, BPG development and deployment and report writing. Data cleaning will be ongoing and data analyses will also occur duringyear5 with presentation of findings at international and local meetings and to the local stake holders (e.g. MOH). These timelines are detailed be low regarding the various activities over5 years.

Timeline of the Project	**Year 1**				**Year 2**				**Year 3**				**Year 4**				**Year 5**			
Quarters:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
IRB approval	X	X																		
Update manuals; hire/train	X	X	X	X																
Enhance BPG software	X	X	X	X																
Enroll subjects; deliver					X	X	X	X	X	X	X									
Deliver BPG training, conduct						X	X	X	X	X	X	X	X	X						
Mobile network deployment													X	X	X	X	X			
Data management										X	X	X	X	X	X	X	X			
Data analysis													X	X	X	X	X	X	X	
Annual/final reports				X				X				X				X				X
Dissemination of results																			X	X

10.0 PUBLIC HEALTH IMPACT

BPG (Brain Powered Games) is designed as a scalable open-access cognitive rehabilitation intervention for HIV-positive school-age children living in Sub-Sahara Africa; used to train a child's fine motor skills, monitoring/attention, visual/auditory working memory, and spatial navigation ability. We will develop an additional game for executive function training, and then test whether BPG games cognitive assessment data gathered as at-risk children play with BPG, can provide a more sensitive measure of a child's developing brain. The Village Builder EF game will be prosocial, non-violent, non-threatening, and will draw from the African village context in a positive and familiar manner. We will pilot the same features with comparable children at the study sites and use their evaluative comments and observed engagement with the new game so further refine and finalize the Village Builder game features, as was the case with the development of African BPG with both

children in Blantyre, Malawi and in Kayunga, Uganda.[1,71]

Both the existing Africa BPG package and the new Village Builder EF games will be used to demonstrate that a child's performance on a neurocognitive "stress test"; involving game training with an app on a computer tablet, will better characterize integrity of brain/behavior function as compared to performance outcomes from traditional one-time cognitive testing sessions.

11.0 REFERENCES

1. Giordani B, Novak B, Sikorskii A, et al. Designing and evaluating Brain Powered Games for cognitive training and rehabilitation in at-risk African children. *Global Mental Health.* 2015;2(e6):1-14.
2. Bangirana P, Allebeck P, Boivin MJ, et al. Cognition, behaviour and academic skills after cognitive rehabilitation in Ugandan children surviving severe malaria: a randomised trial. *BMC Neurol.* 2011;11:96.
3. Bangirana P, Boivin MJ, Giordani B. Computerized Cognitive Rehabilitation Therapy (CCRT) for African Children: Evidence for Neuropsychological Benefit and Future Directions. In: Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience.* Vol 1. New York: Springer Science+Business Media; 2013:277-298.
4. Bangirana P, Giordani B, John CC, Page C, Opoka RO, Boivin MJ. Immediate neuropsychological and behavioral benefits of computerized cognitive rehabilitation in Ugandan pediatric cerebral malaria survivors. *J Dev Behav Pediatr.* 2009;30(4):310-318.
5. Bangirana P, Idro R, John CC, Boivin MJ. Rehabilitation for cognitive impairments after cerebral malaria in African children: strategies and limitations. *Trop Med Int Health.* 2006;11(9):1341-1349.
6. Boivin MJ, Bangirana P, Byarugaba J, et al. Cognitive impairment after cerebral malaria in children: a prospective study. *Pediatrics.* 2007;119(2):e360-366.
7. John CC, Bangirana P, Byarugaba J, et al. Cerebral malaria in children is associated with long-term cognitive impairment. *Pediatrics.* 2008;122(1):e92-99.
8. Boivin MJ, Barlow-Mosha L, Chernoff MC, et al. Neuropsychological performance in African children with HIV enrolled in a multisite antiretroviral clinical trial. *AIDS.* 2018;32(2):189-204.
9. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *J Int AIDS Soc.* 2013;16:18603.
10. Mellins CA, Elkington KS, Leu CS, et al. Prevalence and change in psychiatric disorders among perinatally HIV-infected and HIV-exposed youth. *AIDS Care.* 2013;24(8):953-962.
11. Chernoff MC, Laughton B, Ratswana M, et al. Validity of Neuropsychological Testing in Young African Children Affected by HIV. *J Pediatr Infect Dis.* 2018;13(3):185-201.
12. Ruisenor-Escudero H, Familiar I, Nyakato M, et al. Building capacity in neurodevelopment assessment of children in sub-Saharan Africa: A quality assurance model to implement standardized neurodevelopment testing. *Child Neuropsychol.* 2018:1-16.
13. Barlow-Mosha L, Angelidou K, Lindsey J, et al. Nevirapine- Versus Lopinavir/Ritonavir-Based Antiretroviral Therapy in HIV-Infected Infants and Young Children: Long-term Follow-up of the IMPAACT P1060 Randomized Trial. *Clin Infect Dis.* 2016;63(8):1113-1121.
14. Lindsey JC, Hughes MD, Violari A, et al. Predictors of virologic and clinical response to nevirapine versus lopinavir/ritonavir-based antiretroviral therapy in young children with and without prior nevirapine exposure for the prevention of mother-to-child HIV transmission. *Pediatr Infect Dis J.* 2014;33(8):846-854.

15. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med.* 2010;363(16):1510-1520.
16. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244.
17. Boivin MJ, Busman RA, Parikh SM, et al. A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV. *Neuropsychology.* 2010;24(5):667-673.
18. Boivin MJ, Nakasujja N, Sikorskii A, Opoka RO, Giordani B. A Randomized Controlled Trial to Evaluate if Computerized Cognitive Rehabilitation Improves Neurocognition in Ugandan Children with HIV. *AIDS Res Hum Retroviruses.* 2016;32(8):743-755.
19. Sternberg RJ, Grigorenko EL. *Dynamic Testing: The nature and measurement of learning potential.* New York, NY: Cambridge University Press; 2002.
20. Sternberg RJ. Culture and Intelligence. *American Psychologist.* 2004;59(5):325-338.
21. Sternberg RJ, Grigorenko EL, Ngorosho D, Tantufuye E, Mbise A, Nokes CJ. Assessing intellectual potential in rural Tanzanian school children. *Intelligence.* 2002;30(2):141-162.
22. Mahncke HW, Bronstone A, Merzenich MM. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. In: Moller AR, ed. *Progress in Brain Research.* Vol 157. Amsterdam: Elsevier B.V.; 2006:81-109.
23. Boivin MJ, Giordani B. Neuropsychological assessment of African children: evidence for a universal basis to cognitive ability. In: Chiao JY, ed. *Cultural Neuroscience: Cultural Influences on Brain Function.* Vol 178. New York, NY: Elsevier Publications; 2009:113-135.
24. Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience.* New York, NY: Springer; 2013. Fletcher-Janzen E, ed. Specialty Topics in Pediatric Neuropsychology; No. 1.
25. Astle DE, Barnes JJ, Baker K, Colclough GL, Woolrich MW. Cognitive training enhances intrinsic brain connectivity in childhood. *J Neurosci.* 2015;35(16):6277-6283.
26. Korthauer LE, Nowak NT, Moffat SD, et al. Correlates of virtual navigation performance in older adults. *Neurobiol Aging.* 2016;39:118-127.
27. Marusic U, Giordani B, Moffat SD, et al. Computerized cognitive training during physical inactivity improves executive functioning in older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* 2016:1-21.
28. Marusic U, Kavcic V, Giordani B, Gerzevic M, Meeusen R, Pisot R. Computerized spatial navigation training during 14 days of bed rest in healthy older adult men: Effect on gait performance. *Psychol Aging.* 2015;30(2):334-340.
29. Willoughby MT, Piper B, Kwayumba D, McCune M. Measuring executive function skills in young children in Kenya. *Child Neuropsychol.* 2018:1-20.
30. Bangirana P, Sikorskii A, Giordani B, Nakasujja N, Boivin MJ. Validation of the CogState battery for rapid neurocognitive assessment in Ugandan school age children. *Child Adolesc Psychiatry Ment Health.* 2015;9:38.
31. Busman RA, Oka E, Giordani B, Boivin MJ. Examining the psychosocial adjustment and school performance of Ugandan children with HIV/AIDS. In: Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience*. New York, NY: Springer Media & Business; 2013:117-138.

32. Busman RA, Page C, Oka E, Giordani B, Boivin MJ. Factors contributing to the psychosocial adjustment of Ugandan preschool children with HIV/AIDS. In: Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk & Resilience*. New York, NY: Springer Media & Business Publishing; 2013:95-115.
33. Lorencz EE, Boivin MJ. Screening for neurodisability in low-resource settings using the Ten Questions Questionnaire. In: Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk and Resielence*. New York: Springer; 2013.
34. Bass JK, Nakasujja N, Familiar-Lopez I, et al. Association of caregiver quality of care with neurocognitive outcomes in HIV-affected children aged 2-5 years in Uganda. *AIDS Care.* 2016;28 Suppl 1:76-83.
35. Familiar I, Murray S, Ruisenor-Escudero H, et al. Socio-demographic correlates of depression and anxiety among female caregivers living with HIV in rural Uganda. *AIDS Care.* 2016:1-5.
36. Familiar I, Nakasujja N, Bass J, et al. Caregivers' depressive symptoms and parent-report of child executive function among young children in Uganda. *Learn Individ Differ.* 2016;46:17-24.
37. Familiar I, Ruisenor-Escudero H, Giordani B, et al. Use of the Behavior Rating Inventory of Executive Function and Child Behavior Checklist in Ugandan children with HIV or a history of severe malaria. *J Dev Behav Pediatr.* 2015;36(4):277-284.
38. Ruiseñor-Escudero H, Familiar I, Nakasujja N, et al. Immunological correlates of behavioral problems in school-aged children living with HIV in Kayunga, Uganda. *Global Mental Health.* 2015;2(e9):1-9.
39. Boivin MJ, Nakasujja N, Sikorskii A, et al. Neuropsychological benefits of computerized cognitive rehabilitation training in Ugandan children surviving severe malaria: A randomized controlled trial. *Brain Res Bull.* 2018.
40. Klingberg T, Fernell E, Olesen PJ, et al. Computerized training of working memory in children with ADHD--a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry.* 2005;44(2):177-186.
41. Rabiner DL, Murray DW, Skinner AT, Malone PS. A Randomized Trial of Two Promising Computer-Based Interventions for Students with Attention Difficulties. *Journal of Abnormal Child Psychology.* 2010;38:131–142. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19697119.
42. Klingberg T, Forssberg H, Westerberg H. Training of working memory in children with ADHD. *J Clin Exp Neuropsychol.* 2002;24(6):781-791.
43. Moffat SD. Aging and spatial navigation: what do we know and where do we go? *Neuropsychol Rev.* 2009;19(4):478-489.
44. Gagne JR, Nwadinobi OK. Self-control interventions that benefit executive functioning and academic outcomes in early and middle childhood. *Early Education and Development.* 2018;https://doi.org/10.1080/10409289.2018.1496721.
45. Boivin MJ, Ruel TD, Boal HE, et al. HIV-subtype A is associated with poorer neuropsychological performance compared with subtype D in antiretroviral therapy-naive Ugandan children. *AIDS.* 2010;24(8):1163-1170.
46. Ruel TD, Boivin MJ, Boal HE, et al. Neurocognitive and motor deficits in HIV-infected Ugandan children with high CD4 cell counts. *Clin Infect Dis.* 2012;54(7):1001-1009.

47. Kaufman AS, Kaufman NL. *Manual for the Kaufman Assessment Battery for Children, Second Edition.* Circle Pines, MN: American Guidance Service Publishing/Pearson Products Inc.; 2004.
48. Bangirana P, Musisi S, Allebeck P, et al. A preliminary investigation of the construct validity of the KABC-II in Ugandan children with prior cerebral insult. *African Health Sciences.* 2009;9(3):186-192.
49. Giordani B, Boivin MJ, Opel B, Dia Nseyila D, Diawaku N, Lauer RE. Use of the K-ABC with children in Zaire, Africa: An evaluation of the sequential-simultaneous processing distinction within an intercultural context. *International Journal of Disability, Development and Education.* 1996;43(1):5-24.
50. Jansen P, Greenop K. Factor analysis of the Kaufman Assessment Battery for Children assessed at 5 and 10 years. *South African Journal of Psychology.* 2008;38(2):355-365.
51. Ochieng CO. Meta-Analysis of the Validation Studies of the Kaufman Assessment Battery for Children. *International Journal of Testing.* 2003;3(1):77-93.
52. Boivin MJ, Bangirana P, Tomac R, et al. Neuropsychological benefits of computerized cognitive rehabilitation training in Ugandan children surviving cerebral malaria and children with HIV. *BMC Proceedings.* 2008;2(Suppl 1):P7.
53. Brahmbhatt H, Boivin M, Ssempijja V, et al. Impact of HIV and Atiretroviral Therapy on Neurocognitive Outcomes Among School-Aged Children. *J Acquir Immune Defic Syndr.* 2017;75(1):1-8.
54. Wyhe KSv, Water Tvd, Boivin MJ, Cotton MF, Thomas KGF. Cross-cultural assessment of HIV-Associated Neurocognitive Impairment using the Kaufman Assessment Battery for Children: A systematic review. *Journal of the International AIDS Society.* 2017;in press.
55. Ajayi OR, Matthews G, Taylor M, et al. Factors associated with the health and cognition of 6-year-old to 8-year-old children in KwaZulu-Natal, South Africa. *Trop Med Int Health.* 2017;22(5):631-637.
56. *The T.O.V.A. (Version 6.X) (Computer Program)* [computer program]. Los Alamitos, CA1993.
57. Falleti MG, Maruff P, Collie A, Darby DG. Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. *J Clin Exp Neuropsychol.* 2006;28(7):1095-1112.
58. Maruff P, Thomas E, Cysique L, et al. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. *Arch Clin Neuropsychol.* 2009;24(2):165-178.
59. Boivin MJ, Busman RA, Parikh SM, et al. A pilot study of the neuropsychological benefits of computerized cognitive rehabilitation in Ugandan children with HIV. *Neuropsychology.* 2010;in press.
60. Bangirana P, Nakasujja N, Giordani B, Opoka RO, John CC, Boivin MJ. Reliability of the Luganda version of the Child Behaviour Checklist in measuring behavioural problems after cerebral malaria. *Child Adolesc Psychiatry Ment Health.* 2009;3:38.
61. Boivin MJ, Gladstone MJ, Vokhiwa M, et al. Developmental outcomes in Malawian children with retinopathy-positive cerebral malaria. *Trop Med Int Health.* 2010;16(3):263-271.
62. Boivin MJ, Vokhiwa M, Sikorskii A, Magen JG, Beare NA. Cerebral Malaria Retinopathy Predictors of Persisting Neurocognitive Outcomes in Malawian Children. *Pediatr Infect Dis J.* 2014.

63. Boivin MJ, Bangirana P, Nakasujja N, et al. A year-long caregiver training program improves cognition in preschool Ugandan children with human immunodeficiency virus. *J Pediatr.* 2013;163:1409-1416.

64. Boivin MJ, Bangirana P, Nakasujja N, et al. A year-long caregiver training program to improve neurocognition in preschool Ugandan HIV-exposed children. *J Dev Behav Pediatr.* 2013;34(4):269-278.

65. Caldwell BM, Bradley RH. *Home Observation for Measurement of the Environment.* Little Rock, AR: University of Arkansas Press; 1979.

66. Bradley RH, Caldwell BM, Corwyn RF. The Child Care HOME Inventories: Assessing the quality of family child care homes. *Early Childhood Research Quarterly.* 2003;18(3):294-309.

67. Bangirana P, John CC, Idro R, et al. Socioeconomic predictors of cognition in Ugandan children: Implications for community based interventions. *PLoS ONE.* 2009;4(11):e7898. doi:7810.1371/journal.pone.0007898.

68. Barry SM, Johnson MA, Janossy G. Increased proportions of activated and proliferating memory CD8+ T lymphocytes in both blood and lung are associated with blood HIV viral load. *Journal of acquired immune deficiency syndromes (1999).* 2003;34(4):351-357.

69. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med.* 2012;366(25):2380-2389.

70. Bergemann TL, Bangirana P, Boivin MJ, Connett JE, Giordani BJ, John CC. Statistical approaches to assess the effects of disease on neurocognitive function over time. *J Biomet Biostat.* 2012(S7:016):1-8.

71. Kosinski M, Bjorner J, Ware J, Batenhorst A, Cady R. The responsiveness of headache impact scales scored using 'classical' and 'modern' psychometric methods: A re-analysis of three clinical trials. *Qual Life Res.* 2003;12:903-912.

72. Beaton D, Hogg-Jonson S, Bombardier C. Evaluating changes in health status: Reliability and responsiveness of five generic health status measures in workers with musculoskeletal disorders. *Journal of Clinical Epidemiology.* 1997;50(1):79-83.

73. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* Hillsdale, NJ: Erlbaum; 1988.

74. Liang M, Fossel A, Larson M. Comparison of five health status instruments for orthopedic evaluation. *Medical Care.* 1990;28:632-642.

75. Guyatt GH, Walter S, Norman G. Measuring change over time: Assessing the usefulness of evaluative instruments. *J Chronic Dis.* 1987;40:171-178.

13.0 APPENDICES

13.1 Sample Consent Form

Michigan State University Research Participant Information and Consent Form

Study Title: Culture-Specific Neurodevelopmental Assessment of HIV-Affected Children Researcher and Title: Dr. Michael Boivin, Professor

Department and Institution: Departments of Psychiatry and Neurology, Michigan State University

Contact Information: 909 Fee Rd West Fee A327, +1 517-884-0281, boivn@msu.edu

Sponsor: National Institutes of Health, USA

BRIEF SUMMARY

You are being asked to participate in a research study. Researchers are required to provide a consent form to inform you about the research study, to convey that participation is voluntary, to explain risks and benefits of participation including why you might or might not want to participate, and to empower you to make an informed decision. You should feel free to discuss and ask the researchers any questions you may have.

You are being asked to participate in a research study to evaluate how your child is growing and developing now that he/she is 5 years and older. Your participation in this study will take about 6 months. You will be asked to bring your child to our office for testing, answer questions about how your child learns, talks and behaves, and have someone from the study come to your home to teach your child how to play a video game.

The most likely risks of participating in this study are that you or your child are asked questions that can be embarrassing or uncomfortable. If at any point this happens, neither you or your child need to answer. There is very little risk of the release of information from your responses or study records because they will be kept safe and not shared with anyone else. Findings from this study will not identify you or your children.

The potential benefits to you for taking part in this study are that we will know how your child is growing and learning. These tests will help us closely monitor your child's development, and you will be notified immediately in case we have any concerns or anything you need to know.

PURPOSE OF RESEARCH

The purpose of this research study is to evaluate how your child is growing and developing now that he/she is 5 years and older. We will do this by using special tests with toys, having him play with a video game, and questions made to you that measure how your child learns, talks, and behaves. We will see how well your child is developing.

WHAT YOU WILL BE ASKED TO DO

If you agree for your child to be part of this study, we will ask you to do the following:

-While your child is in a comfortable room, we will ask him/her to answer questions and perform tasks like games, to measure his/her memory, attention, body movements, learning and language. These activities will take place at our office so that they are done at a peaceful and comfortable place. Interviews and assessments will probably take two and a half to two hours. In case your child gets tired or irritable before the end of the assessment, we shall give your child time to rest and something to eat and drink.

-While your child is undergoing tests, you will also be asked questions to learn about your family and how your child behaves.

-We will also ask you child to learn how to play with a video game in a tablet several times. A researcher from our study will visit your home 12 times to teach your child how to play with the games. These visits will last about an hour.

-You may be contacted again at the end of the study to have your child play a few extra sessions of the same games.

You can refuse to answer any of the questions we ask, at any time.

We may ask you to allow us to take a blood sample from your child. The blood will be drawn by putting a needle into a vein in his/her arm. One small tube of blood will be taken. This will take about 10-15 minutes at the most. Blood samples will occur at study visits in the clinic, for a total of 4 blood samples taken as part of the study.

POTENTIAL BENEFITS

According to evidence from our previous studies, we believe that testing the child's abilities like memory, language and movement will predict how well the child is developing. This might relate to their performance at home as they grow and get older, learning at school and their general behaviors but this has not been confirmed yet. These tests will help us closely monitor your child's development, and you will be notified immediately in case we have any concerns or anything you need to know.

POTENTIAL RISKS

Asking questions about child development and these assessments have been done many times before with other children in Uganda, and are not dangerous or harmful to your child in any way. However, in a study like this, the child can be asked questions that can be embarrassing. If at any point your child is embarrassed or uncomfortable, there is no reason for your child to answer. There is very little risk of the release of information from your responses or study records because they will be kept safe and not shared with anyone else. Findings from this study will not identify you or your children.

The needle stick may hurt. There is a small risk of bruising and fainting, and a rare risk of infection.

PRIVACY AND CONFIDENTIALITY

Records for this study will be kept private and stored for the regulatory minimum of 3 years after the project closes. All files will be kept in locked cabinets at Makerere University- Johns Hopkins Research Collaboration (MUJHU- Zayed complex at Mulago). Your child's records for the study may be reviewed by MUJHU and the Human Research Protection Program at Michigan State University, who have authorized this study. No study information will be recorded in the child's medical or hospital record. Any study data that is to be transmitted via the Internet will not have any information that will allow you or your child to be identified. In any publications or presentations, we will not include any information that will make it possible to identify you or your child as

research subjects. Your confidentiality will be protected to the maximum extent allowable by law.To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health (NIH). With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

YOUR RIGHTS TO PARTICIPATE, SAY NO, OR WITHDRAW

You have the right to say no to participate in the research. You can stop at any time after it has already started. There will be no consequences if you stop and you will not be criticized. You will not lose any benefits that you normally receive.

COSTS AND COMPENSATION FOR BEING IN THE STUDY

You will not spend any money in this study. You will be reimbursed for your transport every time you attend the office for a study visit.

FUTURE RESEARCH

Thequestionnaires collected as part of the research, even if information that identifies you is removed, will not be used or distributed for future research studies.

CONTACT INFORMATION

If you have concerns or questions about this study, such as scientific issues, how to do any part of it, or to report an injury, please contact the researcher (Dr. Michael Boivin, 909 Fee Rd, Room 327, boivin@msu.edu, phone number +1 517-884-0281).

If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact, anonymously if you wish, the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517-432-4503, or e-mail irb@msu.edu or regular mail at 4000 Collins Rd, Suite 136, Lansing, MI 48910.

DOCUMENTATION OF INFORMED CONSENT.

Your signature below means that you voluntarily agree to participate in this research study.

_____ _____

Signature Date

_____ _____

Signature of Assenting Child (13-17; if appropriate) Date

You will be given a copy of this form to keep.

13.2 Sample Assent Form

Michigan State University
Participant Written Assent form (7-12 years old)

Study Title: Culture-Specific Neuro-developmental Assessment of HIV-Affected Children

Researcher and Title: Dr. Michael Boivin, Professor

Hello. My name is *[assessor's name]*. I'm a *researcher.* Right now, I'm trying to learn about how you learn new things in a research study and I want to ask if you will be part of it.

What is a research study?

A research study is when people like me collect a lot of information about a certain thing to find out more about it.

This letter tells you about my study so you can decide if you want to be in it. Before you decide, you can talk about it with your parents or anyone else you like. If you have any questions about the research, just ask me.

Why are we doing this study?

We are doing this study to find out how children like you learn and user their memory to play games. By being in the study, you will help me understand how you learn to play, and talk, and do things with your hands

What will happen if you are in this study?

If you agree to be in the study and your mother/father say it's ok, we will ask you to:

play with toys I will give you and do things with your hands like clapping. This can be fun because it will be like playing

play a video game in a tablet

After we first meet, we will spend some time together asking you questions and doing problems and games to help us understand how you think and solve problems. I will be with you in the clinic or at your home all the time

and this will take between two and two and a half hours. If you feel tired, we can stop and have a snack. We will have these meetings several times during the study.

In four study visits, we may ask you to give a small sample of your blood. A person specially trained to draw blood from kids will put a needle into a vein in your arm and draw the blood into a small tube. It will take about 10-15 minutes at the most.

If you don't want to be in the study, what can you do?

Your *mom* says it's okay for you to be in my study. But if you don't want to be in the study, you don't have to be. What you decide won't make any difference. I won't be upset, and no one else will be upset, if you don't want to be in the study. If you want to be in the study now but change your mind later, that's okay. You can stop at any time. If there is anything you don't understand you should tell me so I can explain it to you.

Will good things happen from being in this study?

Being in this study won't really change anything for you. But we hope that what we find out from this research will help kids in the future to learn

Are there things you might not like about being in the study?

You might get bored or tired and decide that you don't want to finish the study activities. If this happens, just tell us you want to stop.

Who will know that you are in the study?

You, your parents, and the researchers are the only ones who will know the details of your being in the study. When I tell other people about my study, I will not use your name, and no one will be able to tell who I'm talking about.

Will you get paid for being in the study?

No, you will not be paid for being in this study

Do you have to be in the study?

No, you don't! Research is something you do only if you want to. Nothing bad will happen if you don't want to be in the study. Just tell us. Whether you decide to participate or not, either way will have no effect on your grades at school. And remember, you can always change your mind later if you don't want to be in the study any more.

Do you have any questions?

You can ask me questions about the study. You can talk to me, or your parents, or someone else if you like.

Do you have any questions for me now?

Would you like to be in my study and *start playing games?*

ASSENT OF CHILD (7-12 years old)

If you decide to participate, and your parents agree, we will give you a copy of this form to keep. That way you can look at it later if you want to.

If you would like to be in this research study, please sign your name on the line below.

_____	_____
Child's Name/Signature (*printed or written by child*)*	Date
_____	_____
Signature of Investigator/Person Obtaining Assent	Date

****

**If verbal assent only is being obtained:*

Investigator or Person Conducting Assent Discussion: Initial here if child cannot sign, to document that child received this information and gave assent verbally: _____