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A Culturally Fair Test of Processing Speed: Construct validity, preliminary normative data, and effects of HIV infection in South African adults

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Abstract

Processing speed (PS) is a complex cognitive function that is often impaired in neurological disorders. Hence, some measure of PS is almost always part of a neuropsychological test battery. *NeuroScreen* is a computerized test battery that contains several PS subtests. Given that it is time- and cost-effective, and designed to be culturally fair and insensitive to the effects of language variation, literacy status, socioeconomic status, and education, it might be of great utility in South African neuropsychological practice given the country's low-resource and culturally-diverse clinical climate. Additionally, South Africa has the highest population prevalence of people living with HIV/AIDS, and a major cognitive domain affected by the HIV infection is PS. Hence, the current research aimed to assess the construct validity of the NeuroScreen PS subtests for use in South Africa, and to establish preliminary normative data for those PS tasks in healthy South African adults. It also aimed to assess the extent of PS impairment in a sample of HIV-infected South African adults. Study 1 confirmed, using a sample of healthy adults (N = 112) and a factor analytic statistical approach, that all NeuroScreen PS outcome variables load onto one overarching processing speed factor, and that performance on those variables converges with that on paper-and-pencil PS tests taken from a standard neuropsychological test battery. Multiple regression analyses indicated that age was a significant predictor of performance on all NeuroScreen PS outcome variables. Study 2 confirmed that HIV-infected adults (N = 102) performed significantly more poorly on NeuroScreen PS tests than the HIV-negative adults from Study 1. Taken together, these results suggest that NeuroScreen has cross-cultural utility in assessing PS in adults, and that it might be particularly useful in tracking the trajectory of PS decline in HIV-infected adults.

Keywords: construct validity; HIV; normative data; processing speed; South Africa; HIV-associated neurocognitive impairment.

A Culturally Fair Test of Processing Speed: Construct validity, preliminary normative data, and effects of HIV infection in South African adults

Processing speed (PS), defined as the swiftness with which one is able to complete mental tasks, is a complex cognitive function that is often impaired in neurological disorders (e.g., multiple sclerosis and HIV dementia; Dobryakova, Costa, Wylie, & DeLuca, 2016; Kore et al., 2015; Lu, Chan, & Lam, 2017). The faster one's PS, the more quickly information is made available to higher-level cognitive operations, and the more likely it is that one will perform better on tasks tapping into those operations (Albinet, Boucard, Bouquet, & Audiffren, 2012). Unsurprisingly, then, performance on tasks assessing PS is closely associated with performance on tasks assessing working memory (WM) and executive functioning (EF; Fellows, Byrd, & Morgello, 2014). Hence, some measure of PS is almost always part of a comprehensive neuropsychological test battery. Very few PS measures have been validated cross-culturally, however. The current study used South African samples to (a) investigate the construct validity of the processing speed tasks contained within the NeuroScreen computerized test battery (Robbins et al., 2014), (b) generate locally appropriate normative data for performance on those tasks, and (c) assess whether NeuroScreen PS performance is impaired in HIV-infected adults relative to their HIV-negative counterparts.

South Africa is a developing-economy country with a relatively high burden of psychiatric and neurological disease (Msemburi et al., 2016; Petersen et al., 2015). For instance, it houses the world's largest population of HIV-infected individuals (approximately 7 million people; Statistics South Africa, 2016; UNAIDS, 2016). Studies of South African and other HIV-infected samples confirm impaired performance within a number of cognitive domains, including motor function, attention, learning, WM, and EF (Heaton et al., 2015; Kabuba, Menon, Franklin, Heaton, & Hestad, 2017; Sacktor & Robertson, 2014; Witten, Thomas, Westgarth-Taylor, & Joska, 2015). However, a core component of the disorder, even in the era of combination antiretroviral therapy (cART), is reduced speed of information transfer and cognitive slowing (i.e., impaired PS; Fellows et al., 2014; Vance, Wadley, Crowe, Raper, & Ball, 2011).

South African neuropsychologists attempting to assess and describe these impairments, and to make treatment and rehabilitation recommendations, have a complicated task because the country's population is especially heterogeneous, with 11 official languages,

cultural diversity across geographic regions, and vast differences in individual socioeconomic power and educational attainment (Ferrett, Carey, et al., 2014; Statistics South Africa, 2016). There are also high levels of adult illiteracy in the country, with some estimates placing it as high as 35% (Posel, 2011). This latter factor is particularly important when considering how one might best assess PS in South Africa, given that performance on tests assessing that construct is strongly linked to reading and writing fluency (Roivainen, 2011). It is also important to note that, for many individuals born and/or residing in low- and middle-income countries such as South Africa, overall cognitive functioning is severely negatively affected by poverty, illness, malnourishment, and poor medical resources (Kieling et al., 2011; McCoy et al., 2016). Moreover, South African clinics, particularly those in rural areas, have a significant shortage of suitable facilities and professionals with appropriate training in cognitive test administration, scoring, and interpretation (Watts & Shuttleworth-Edwards, 2016; Yechoor et al., 2016).

This contextual description suggests South Africa requires a PS test that is time- and cost-effective, simple enough for lay professionals to administer, culturally fair, and insensitive to the effects of language variation, literacy status, socioeconomic status, and education. *NeuroScreen* is a computerized (tablet-based) screening tool that assesses PS, along with EF, WM, language, learning and memory, and other cognitive functions (Robbins et al., 2014). It does not require highly-trained medical professionals to administer and score as instructions, tasks, and results are displayed and stored digitally.

The research described here comprises two studies. Study 1 investigated the construct validity of the NeuroScreen PS tasks, and established preliminary normative data for those PS tasks, in a South African sample. Study 2 assessed whether PS, as assessed by the NeuroScreen tasks, was impaired in a sample of HIV-infected South African adults.

Study 1:
Construct Validity and Preliminary Normative Data

The first aim of this study was to investigate, using data from a group of healthy, cognitively intact South African adults, the construct validity of the NeuroScreen PS tasks. Specifically, I performed a series of exploratory factor analyses on the NeuroScreen PS outcome variables to ascertain whether the most significant amount of variance observed in participants' performance on each variable could be explained by a single underlying construct (viz., processing speed). I then investigated convergent validity by assessing the degree of shared variance between performance on the NeuroScreen PS subtests and on

standardized and frequently used pencil-and-paper tests of PS, WM, and EF. Thereafter, I investigated the divergent validity of the NeuroScreen outcome variables by assessing the degree of shared variance with standardized tests not relating to these three domains. My reasons for focusing on the WM and EF domains emerge from a relatively large literature indicating that (a) faster PS is associated with better performance on WM tasks, and with increasing the quantity and the quality of the information remembered (Kievit et al., 2016; Nettelbeck & Burns, 2010; Salthouse, 1996), and (b) PS accounts for a substantial amount of variance in performance on many EF tasks, such that reduced PS is positively correlated with impaired EF (see, e.g., Albinet et al., 2012; Bugaiska et al., 2007; Lee et al., 2012; Schretlen et al., 1999).

The second aim of this study was to construct a set of preliminary normative data, appropriate for use with South African adults, for the NeuroScreen PS tasks. The specific stratification factors in which I was interested were age, sex, and education. Numerous studies suggest that older adults perform more poorly than their younger counterparts on PS tasks (Burgmans et al., 2011; Hong et al., 2015; Manly et al., 2011). In one particularly notable study, Joy, Kaplan, and Fein (2004) showed that, after controlling for other demographic factors (e.g., sex, education), age accounted for nearly 50% of the variance in PS performance. Regarding sex differences, Camarata and Woodcock (2006) found that females displayed better PS performance than males, and Roivainen (2011) reported that women performed more accurately (i.e., made fewer errors) than men on PS tasks, but that men exhibited faster reaction times. Regarding education, there is no consistent conclusion regarding its influence on PS task performance. For example, one study found no evidence supporting a relationship between these two variables (Ritchie, Bates, Der, Starr, & Deary, 2013), whereas Tucker-Drob, Johnson, and Jones (2009) suggest that higher levels of education may help mediate the frequently documented PS decline.

Almost all of those studies were conducted in predominantly Western societies in the global north, and none have included South African samples. Hence, it is unknown to what extent non-organic / sociodemographic factors, such as age, sex, and educational attainment, affect PS task performance in non-Western contexts.

Method

Design and setting. This exploratory study was nested within a larger research programme, one of whose aims was to describe the performance of HIV-infected and HIV-negative South African adults on the NeuroScreen battery (Robbins et al., 2017). The data collection sites were two government clinics located in low-income communities close to

Cape Town. The parent study obtained ethical approval from the University of Cape Town's Human Research Ethics Committee (Appendix A).

Participants. I analyzed data from 112 HIV-negative cognitively intact adults (56 men and 56 women, aged 18-64 years). All were resident in low-income communities, and all were Xhosa- and/or English-speaking, with relatively low levels of educational attainment. Most participants (approximately 75%) were unemployed.

Regarding recruitment, study staff approached individuals after they had tested negative for HIV during a routine clinic visit. A staff member outlined the research program and provided information regarding ethical considerations, including consent, confidentiality, right to withdraw without penalty, and compensation. If the approached individual expressed interest, the staff member determined his/her eligibility for the study (using, for instance, a review of medical records and/or a semi-structured clinical interview). If eligibility was confirmed, the study nurse began the formal consent and enrolment process.

Inclusion criteria required that each participant had recently tested negative for HIV, and was (a) willing to undergo a psychiatric and neuropsychological examination, (b) between the ages of 18 and 75 years, (c) English- or Xhosa-speaking, (d) cognitively capable of giving informed consent, (e) willing to allow the study nurse to access his/her medical records, and (f) medically and psychologically healthy (i.e., carried no serious and/or chronic illnesses known to negatively affect cognitive functioning).

Power analysis. An a priori power analysis suggested the sample size be set at N = 107 for a hierarchical regression analysis to achieve statistical power of .95, given parameters of a medium effect size (Cohen's f^2 = .15), the conventional threshold for statistical significance (α = .05), and three predictor variables (Faul, Erdfelder, Buchner, & Lang, 2009).

Materials. Participants were administered a sociodemographic questionnaire, the NeuroScreen battery, and a comprehensive paper-and-pencil neuropsychological test battery.

Sociodemographic questionnaire. This self-report study-specific instrument gathered information about participant age, sex, and educational attainment.

NeuroScreen. This 25-min battery was administered on a smartphone (a Samsung Galaxy Note using an Android operating system) with a 5.3-inch (diagonal) touchscreen. For all tasks, the participant entered input directly onto the screen (Robbins et al., 2014). I analyzed data from the four PS tasks whose outcome variables are listed in Table 1.

Table 1
NeuroScreen Processing Speed Subtests: Primary outcome variables

Subtest	Outcome Variable
Trails 1[a]	Completion time
Timed Number Input[a]	Completion time
Trials 1-5	Completion time (per trial)
Total Across Trials 1-5	Completion time (sum across trials)
Timed Visual Discrimination A	Number of correct responses
Timed Visual Discrimination B	Number of correct responses

Note. [a]Subtest recorded total number of errors as a secondary outcome variable. Those data are not analyzed here.

Trails 1. This task requires participants to use a finger to connect the numbers 1 through 8 on the device's touchscreen. The numbers are scattered across the screen in no particular order (although the order is consistent from one test administration to the next). The test discontinues automatically at 35 seconds. If the participant makes a sequencing error, a pop-up screen appears instructing him/her to continue from the last correct number.

Timed Number Input. This task requires the participant to enter a target number sequence (presented at the top of the screen) into a keypad (presented lower on the screen) as quickly as possible. The target sequence increases incrementally with each trial, from five to nine digits. Each trial is timed individually. Participants have 75 seconds to complete all five trials.

Timed Visual Discrimination A. This task presents the participant with a series of digit-symbol pairs running across the top of the screen. While the pairs remain on the screen, the participant is presented with a target symbol at the bottom of the screen, and must then identify with which digit the symbol is paired by tapping the appropriate number on the on-screen keypad. Once complete, another target symbol appears. The participant has 45 seconds to complete as many trials (up to a maximum of 61) as possible.

Timed Visual Discrimination B. This task presents the participant with an array of symbols in a row across the top of the screen. While the symbols remain on the screen, the participant is presented with two target symbols at the bottom of the screen, and is required to determine which one of those two targets is present in the array at the top of the screen. Once a decision is made, the participant taps on the appropriate target symbol, and another set of two target symbols appears. The participant has 45 seconds to complete as many trials (up to a maximum of 150) as possible.

Comprehensive neuropsychological test battery. This battery, which took 2-3 hours to complete, is comprised of standardized tests used frequently in neuropsychological

assessment. As a whole, it has proven useful in the assessment of HIV-associated cognitive impairment in South African samples (Joska, Westgarth-Taylor et al., 2011; Joska, Fincham, Stein, Paul, & Seedat, 2010). The PS tests contained in the battery were Trail Making Test Part A (TMT-A; Reitan, 1992; Reitan & Wolfson, 1985), Digit Symbol-Coding and Symbol Search (Wechsler, 1997), and Color Trails Test 1 (CTT1; Maj et al., 1993). The WM test was Digit Span-Backwards (Wechsler, 1997). The EF tests were CTT2 (Maj et al., 1993), the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1981), and category fluency tests (Benton & Hamsher, 1976). Other tests in the battery included the Finger Tapping Test (FTT; Reitan & Wolfson, 1985), Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001), Brief Visuospatial Memory Test-Revised (BVMT-R; Kaplan, Goodglass, & Weintraub, 1983), and Judgement of Line Orientation (JLO; Benton, Hamsher, Varney, & Spreen, 1983).

All test instructions and stimuli were translated from the original English into Xhosa. Translated tests were used only if Xhosa was the participant's preferred language.

Procedure. The study staff scheduled the assessment dates and times. Lay counsellors administered the NeuroScreen battery, and a trained research psychometrist administered the neuropsychological test battery. Both followed standardized administration, data recording, and scoring procedures. To avoid experimenter bias, the test administrators were blind to the HIV status of the participants.

All participants signed a consent form (see Appendix B) prior to testing. The assessment instruments were administered in the same order for each participant. To avoid possible fatigue effects, participants were given the option of taking a break at any point during testing. If testing was not completed on one day, another session was scheduled, and took place within the next 7 days. Upon completion of the study procedures, participants were reimbursed ZAR400 (at the time of study, approximately US$45).

Data management and statistical analyses. I used SPSS (version 24.0) to analyse the data, with α set at .05 for decisions concerning statistical significance.

Generating descriptive statistics. I produced a complete set of descriptive statistics that provided information regarding the characteristics of the study sample and the data distributions.

Factor analyses. I investigated the construct validity of the NeuroScreen PS subtests using four separate factor analyses. The first assessed whether the nine NeuroScreen PS outcome variables (i.e., completion time for Trails 1, and for each of Timed Number Input Trials 1-5; total completion time for Timed Number Input; and number of correct responses

for Timed Visual Discrimination A and for Timed Visual Discrimination B) loaded onto one overarching factor. The second assessed convergent validity by examining whether the set of NeuroScreen PS outcome variables and the set of outcome variables derived from the PS tests within the comprehensive neuropsychological test battery (i.e., TMT-A completion time, Digit Symbol-Coding raw score (number of items completed correctly), Symbol Search raw score (number of items completed correctly), and CTT1 completion time) loaded onto one overarching factor. The third also assessed convergent validity by examining whether the set of NeuroScreen PS outcome variables loaded onto the same factor as the set of outcome variables derived from WM and EF tests within the comprehensive neuropsychological test battery (i.e., Digit Span Backward raw score, CTT2 completion time, WCST Total Correct and Total Errors, animal category fluency raw score, and fruit-and-vegetable category fluency raw score). The fourth assessed divergent validity by examining whether the set of NeuroScreen PS outcome variables loaded onto different factors from the set of outcome variables derived from other tests within the comprehensive neuropsychological test battery (i.e., FTT average number of taps with the dominant hand and average number of taps with the nondominant hand, HVLT-R Total Learning, BVMT-R Total Learning, and JLO raw score).

Regression-based normative data. Using multiple regression analyses, I investigated the extent to which age, sex, and educational attainment contributed to performance on the NeuroScreen PS subtests. I used stepwise multiple regression, adding age in block 1 and sex and education together in block 2. The final regression equation for each subtest served as the basis for establishing preliminary South African normative data for NeuroScreen-measured PS.

Results

Sample characteristics. As noted earlier, there were equal numbers of men and women in the sample. Most participants were aged between 30 and 40 years and had at least some high school education, and all but two had Xhosa as their home language (the exceptions spoke Zulu and Sesotho). Analyses detected no significant between-sex differences in terms of age and education (see Table 2).

Table 2
Sample Characteristics (N = 112)

	Group				
Variable	Women (*n* = 56)	Men (*n* = 56)	*t*	*p*	ESE
Age (years)					
M (*SD*)	36.57 (11.89)	34.30 (11.76)	1.02	.312	0.19
Range	19-64	18-54			
Education (years)					
M (*SD*)	10.41 (1.47)	10.70 (1.4)	-1.05	.295	0.20
Range	7-13	8-13			

Note. Means are presented, with standard deviations in parentheses. ESE = effect size estimate (in this case, Cohen's *d*).

Factor analyses.

Data screening. A screening of the data for univariate outliers identified three values (each due to an administration error) in the third factor analysis. I recoded these values as missing data. Hence, the minimum amount of data for exploratory factor analysis was satisfied, with a final sample size (using listwise deletion) of $N = 112$ ($N = 109$ in the instance of the third factor analysis; MacCallum, Widaman, Zhang, & Hong, 1999).

I performed no rotations on the data as there were sufficient numbers of primary loadings. Moreover, because all four factor analyses contained nonpositive eigenvalues and several of the subtest outcome variables were highly correlated, I cannot report the anti-correlation matrix, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy, or Bartlett's test of sphericity. Communalities were all above .30, confirming that each outcome variable shared some common variance with others.

Construct validity. The first factor analysis indicated that each of the nine outcome variables correlated at least .30 with at least one other outcome variable, suggesting reasonable factorability, and that all of the NeuroScreen variables subtests loaded heavily onto one factor (see Table 3). In that table, Factor 1 represents a combined contribution of 56.16% to the observed variance in scores, whereas the analogous statistic for Factor 2 is 11.35%. Hence, it appears there is one underlying factor to which all variables in the analysis are related, and that that factor might be labeled Processing Speed.

Table 3
Factor Analysis I: Factor loadings for NeuroScreen processing speed subtests (N =112)

Outcome Variable	Factor 1	Factor 2	Communalities
Trails 1	.58	.59	.68
Timed Number Input			
Trial 1	.62		.53
Trial 2	.61		.49
Trial 3	.81		.74
Trial 4	.80		.77
Trial 5	.79	-.43	.81
Total Across Trials 1-5	.97		.95
Timed Visual Discrimination A	-.72		.52
Timed Visual Discrimination B	-.75		.60

Note. Factor loadings < .40 have been suppressed.

Convergent validity. The second factor analysis indicated that each of the 13 outcome variables correlated at least .30 with at least one other outcome variable, suggesting reasonable factorability, and that the NeuroScreen PS subtests and the PS subtests of the comprehensive battery loaded onto one overarching factor (see Table 4). In that table, Factor 1 represents a combined contribution of 53.44% to the observed variance in scores, whereas the analogous statistic for Factor 2 is 9.90%. Hence, it appears there is one underlying factor to which all variables in the analysis are related, and that that factor might be labeled Processing Speed, particularly given that the subtests from the comprehensive battery are purported to all measure that construct. This, then, is evidence of convergent validity.

The third factor analysis indicated that each of the 15 outcome variables correlated at least .30 with at least one other outcome variable, suggesting reasonable factorability. The analysis further indicated that the NeuroScreen PS subtests, and the WM and EF subtests of the comprehensive battery, loaded onto three main factors (see Table 5). In that table, Factor 1 (which might be labeled Processing Speed) represents a combined contribution of 39.21% to the observed variance in scores, whereas the contribution for Factor 2 (Executive Function - Problem Solving) is 12.42%, and for Factor 3 (Executive Function – Generativity) is 9.43%. No outcome variable loaded sufficiently uniquely on Factor 4, which contributed 6.96% to the observed variance in scores. Hence, this analysis provides further evidence of convergent validity.

Table 4
Factor Analysis II: Factor loadings for NeuroScreen and comprehensive battery PS subtests (N = 112)

Outcome Variable	Factor 1	Factor 2	Communalities
Trails 1	.58		.35
Timed Number Input			
Trial 1	.57		.38
Trial 2	.61		.39
Trial 3	.77		.68
Trial 4	.75	.44	.76
Trial 5	.74	.46	.75
Total Across Trials 1-5	.92		.95
Timed Visual Discrimination A	-.75		.56
Timed Visual Discrimination B	-.79		.64
TMT-A	.74	-.45	.74
Digit Symbol-Coding	-.81		.69
Symbol Search	-.77		.65
CTT1	.63	-.53	.69

Note. Factor loadings < .40 have been suppressed. TMT-A = Trail Making Test Part A; CTT1 = Color Trails Test 1.

Table 5
Factor Analysis III: Factor loadings for NeuroScreen and comprehensive battery PS, WM, and EF subtests (N = 109)

Outcome Variable	Factor 1	Factor 2	Factor 3	Factor 4	Communalities
Trails 1	.58			.52	.61
Timed Number Input					
Trial 1	.58				.46
Trial 2	.61				.47
Trial 3	.76				.71
Trial 4	.76				.77
Trial 5	.73			-.44	.83
Total Across Trials 1-5	.94				.94
Timed Visual Discrimination A	-.70				.60
Timed Visual Discrimination B	-.78				.66
Digit Span Backward	-.47				.32
CTT2	.70				.61
WCST					
Total Correct		.90			.97
Total Errors	.41	-.88			.96
Category Fluency					
Animals Total			.75		.69
Fruit and Vegetables Total			.68		.62

Note. Factor loadings < .40 have been suppressed. TMT-A = Trail Making Test Part A; CTT2 = Color Trails Test 2; WCST = Wisconsin Card Sorting Test.

Divergent validity. The fourth factor analysis indicated that each of the 14 outcome variables correlated at least .30 with at least one other outcome variable, suggesting reasonable factorability. The analysis further indicated that the NeuroScreen PS subtests and the non-PS, non-WM, and non-EF subtests of the comprehensive battery loaded onto three main factors (see Table 6). In that table, Factor 1 (Processing Speed) represents a combined contribution of 40.74% to the observed variance in scores (of interest here is that the BVMT-R outcome variable forms part of this factor), whereas the contribution for Factor 2 (Spatial Coordination) is 12.49%, and for Factor 3 is 8.16% (Memory). No outcome variable loaded sufficiently uniquely on Factor 4, which contributed 7.43% to the observed variance in scores. Overall, the comprehensive battery subtest outcome variables (with the exception of the BVMT-R) did not load onto the same overarching factor as the NeuroScreen PS subtests, and so this analysis provides evidence of divergent validity.

Table 6
Factor Analysis IV: Factor loadings for NeuroScreen and comprehensive battery non-PS, non-WM, and non-EF subtests (N = 112)

Outcome Variable	Factor 1	Factor 2	Factor 3	Factor 4	Communalities
Trails 1	.57			-.58	.67
Timed Number Input					
Trial 1	.64				.53
Trial 2	.59				.60
Trial 3	.77				.74
Trial 4	.78				.78
Trial 5	.76				.78
Total Across Trials 1-5	.95				.95
Timed Visual Discrimination A	-.71				.52
Timed Visual Discrimination B	-.79				.67
FTT					
Dominant Hand		-.74			.76
Nondominant Hand		-.80			.77
HVLT-R Total Learning			.69		.72
BVMT-R Total Learning	-.66		.48		.68
JLO raw score		.51			.46

Note. Factor loadings < .40 have been suppressed. FTT = Finger Tapping Test; HVLT-R = Hopkins Verbal Learning Test-Revised; BVMT-R = Brief Visuospatial Memory Test-Revised; JLO = Judgement of Line Orientation.

Regression-based normative data. Four separate multiple regression analyses (one each on data from on Trails 1, Timed Number Input Total, Timed Visual Discrimination A, and Timed Visual Discrimination B) allowed generation of preliminary normative data. (I included only total completion time across the five Timed Number Input trials because the

analysis aimed to establish normative data for performance of the subtest as a whole, and the total score could not have been achieved without completion of each individual trial). The analyses indicated that age was a significant predictor of performance on all of these NeuroScreen PS outcome variables (see Table 7). Additionally, education was a significant predictor of performance on Timed Number Input and on Timed Visual Discrimination B, and sex was a significant predictor of performance on Timed Number Input. Table 8 presents the consequent regression equations that can serve to produce preliminary normative data.

Table 7
Stepwise Regression Analysis: NeuroScreen processing speed subtests (N = 112)

Subtest / Outcome variable	Significant predictor(s)	R^2	*F*	*df*	*p*	*β*
Trails 1: Completion time		.15	19.73	1,110	< .001***	
	Age				< .001***	0.39
Timed Number Input: Total completion time		.45	29.67	1,108	< .001***	
	Age				< .001***	0.62
	Sex				.031**	0.16
	Education				.042**	-0.15
Timed Visual Discrimination A: Number of correct answers		.30	47.60	1,110	< .001***	
	Age				< .001***	-0.55
Timed Visual Discrimination B: Number of correct answers		.43	41.20	1,109	< .001***	
	Age				< .001***	-0.58
	Education				.009**	0.20

Note. The first row for each outcome variable presents the final model statistics.
*p <. 05. **p < .01. ***p < .001.

Table 8

Regression-based Normative Data: NeuroScreen processing speed subtests (N = 112)

Subtest / Outcome variable	Regression equation
Trails 1: Completion time	$Y = 2.85 + (0.31*\text{Age})$
Timed Number Input: Total completion time	$Y = 25.80 + (0.74*\text{Age}) + (4.43*\text{Sex}) + (-1.49*\text{Education})$
Timed Visual Discrimination A: Number of correct answers	$Y = 19.73 + (-0.21*\text{Age})$
Timed Visual Discrimination B: Number of correct answers	$Y = 30.92 + (-0.45*\text{Age}) + (1.26*\text{Education})$

Study 2:
Performance of HIV-Infected South African Adults on NeuroScreen Processing Speed Tasks

Slowed processing speed is a key cognitive characteristic of a number of neurological conditions (Lu et al., 2017; Sachs-Ericsson & Blazer, 2015). Of particular relevance to the South African clinical context is that HIV-infected individuals often display slowed PS, and that the latter is a marker of the trajectory of cognitive decline in HIV-associated cognitive impairment (Carey et al., 2004; Kore et al., 2015). A meta-analysis of 41 studies, published between 1987 and 2000 (i.e., studies that spanned the pre-cART and cART eras), examining the neuropsychological sequelae of HIV infection indicated that PS was one of three domains associated with the greatest decline in overall cognitive ability as the disease progressed (Reger, Welsh, Razani, Martin, & Boone, 2002; see also Woods, Moore, Weber, & Grant, 2009). Recently, Fellows and colleagues (2014) identified slowed PS as a primary deficit in HIV-infected individuals, and suggested that this impairment may, to a degree, underlie the memory and executive function deficits that are typically present in cART-era HIV-associated cognitive deficits.

Furthermore, these PS impairments are evident during both early and late stages of the disease (Woods et al., 2009). This fact is important for clinicians to consider because this PS dysfunction is associated with impaired performance on activities of daily living (ADLs), such as financial and medication management, shopping, and cooking (Casaletto, Weber, Iudicello, & Woods, 2017; Ettenhofer et al., 2009; Vance et al., 2011).

Given that 12.5% of the South African population (approximately 7 million people) is HIV-positive, and that, of that number, approximately 60% (almost 4 million people) experience some form of cognitive impairment (Joska, Hoare, Stein, & Flisher, 2011), it is important to assess the extent to which PS is impaired in South African HIV-infected individuals. This is the first study to investigate whether NeuroScreen is sensitive to such PS impairment in that population.

Methods

Design and setting. This cross-sectional quasi-experimental study compared the NeuroScreen PS performance of HIV-infected and HIV-negative South African adults. The setting was identical to that of Study 1.

Participants. I analyzed data from 112 HIV-negative adults (the Study 1 sample) and from 102 HIV-infected adults (19 men and 83 women, aged 18-56 years). The latter were also sampled from low-income communities, and were also Xhosa- and/or English-speaking,

with relatively low levels of educational attainment. Most (approximately 60%) were unemployed.

The HIV-infected participants were all part of a cohort recruited into a randomised controlled trial, *Masivukeni*, that evaluated the efficacy of a multimedia-based adherence intervention for adults initiating antiretroviral therapy. These participants were recruited from the two same two clinics described in Study 1. The study nurses at each clinic approached individuals after they had completed their 12-month Masivukeni assessment. In a manner similar to that described for the Study 1 participants, she provided information about the research program and ethical considerations, and determined whether interested individuals were eligible for study participation.

Inclusion criteria for the HIV-infected sample was identical to that of the HIV-negative sample, with the exception that the former were required to have tested positive for HIV, and were required to confirm, via self-report, that they were not using any illicit substances.

Materials and procedure. These were identical to those for Study 1, with the exception of HIV-infected participants signing a different consent form (see Appendix C).

Data management and statistical analyses. As in Study 1, I used SPSS (version 24.0) to analyse the data, with α set at .05 for decisions concerning statistical significance.

Generating descriptive statistics. I produced a complete set of descriptive statistics that (a) provided information regarding the characteristics of the study sample, (b) assessed whether all of the assumptions of inferential statistical testing were upheld, and (c) identified any significant outliers in the distributions or missing data.

Between-group comparisons. Because Study 1 established that all of the NeuroScreen PS subtests loaded onto a single factor (Processing Speed), I used those factor loadings (see Table 3) to create a composite PS score for the purposes of this study. First, I converted each participant's score on each outcome variable to a standardized (*z*) score, using the equation $\frac{observed\ score - group\ mean}{group\ SD}$. Each participant's *z* score on each outcome variable was multiplied by the factor loading for each variable, and then summed. (The reason for multiplying by the factor loading is because each item contributed differently to the Processing Speed construct.) I divided this aggregate score by nine (the total number of NeuroScreen outcome variables) to derive an average PS composite score for all participants.

Using the *z*-based outcome variables, independent-samples *t*-tests compared HIV-negative and HIV-infected performance on each subtest and on the overall PS construct.

Regression equation-based comparisons. I used the regression equations created in Study 1 (see Table 8) and chi-square tests of independence to investigate whether, for each NeuroScreen PS outcome variable, the proportion of HIV-infected participants who performed more poorly than normative predictions significantly exceeded the proportion of HIV-negative participants who did not meet normative standards. Specifically, I entered the relevant sociodemographic information for each participant into the regression equation calculated for each outcome variable, established the proportion of participants in each group who performed more poorly than normative standard, and then used chi-square tests to assess whether cell sizes were significantly different for the HIV-negative and HIV-infected samples.

Results

Sample characteristics. Analyses detected no significant between-group differences in terms of age, education, and home language (see Table 9). Most participants in both groups were aged between 30 and 40 years and had a high school education. Regarding sex distribution, analyses detected a significant between-group difference, with a far larger proportion of women in the HIV-infected group. However, I did not use sex as a covariate in subsequent analyses because Study 1 suggested that, barring Timed Number Input Total, the variable did not significantly affect NeuroScreen PS performance. Regarding home language, most participants in both groups spoke Xhosa; however, in the HIV-negative group, one participant spoke Sesotho and one Zulu, whereas in the HIV-infected group, two participants spoke Zulu, one spoke Afrikaans, and three marked ‘other’ as home language.

Between-group comparisons. Table 10 presents the relevant descriptive statistics and *t*-test results for the *z*-score comparisons. For Trails 1 and the Timed Number Input subtests, a positive *z*-score indicates poorer performance, as the outcome variable for those subtests was completion time. In contrast, for the Timed Visual Discrimination A and B subtests, a positive *z*-score indicates better performance, as the outcome variable for those subtests was number of correct responses. As the Table shows, participants in the HIV-infected group performed significantly more poorly on most of the individual outcome variables, and on the PS composite variable. All of these significant differences were associated with small-to-moderate effect sizes. Of note, however, is that the only significant difference that survived the Bonferroni correction was that for the composite variable.

Table 9
Sample Characteristics (N = 214)

Variable	Group: HIV-negative (*n* = 112)	Group: HIV-infected (*n* = 102)	t / χ^2	*t*	ESE
Age (years)			1.93	.055	0.26
M (*SD*)	35.44 (11.83)	32.80 (7.46)			
Range	18-64	18-56			
Education (years)			1.31	.192	0.17
M (*SD*)	10.55 (1.44)	10.25 (1.99)			
Range	7-13	2-13			
Sex			23.08	< .001***	.33
Female	56 (50%)	83 (81.4%)			
Male	56 (50%)	19 (18.6%)			
Home language				.089	.13
Xhosa	110 (98.2%)	95 (93.1%)			
Other	2 (1.8%)	7 (6.9%)			

Note. For the variables *Sex* and *Home Language*, counts are presented with percentages in parentheses. ESE = effect size estimate (in this case, Cohen's *d* for *t*-tests, Cramer's *V* for chi-squared tests of contingency and Fisher's exact tests).
****p* < .001.

Table 10
Independent-sample t-tests: Performance on NeuroScreen PS subtests (N =214)

Variable	Group: HIV-negative (*n* = 112)	Group: HIV-infected (*n* = 102)	*T*	*P*	ESE
Trails 1[a]	-0.16 (.74)	0.18 (1.21)	-2.45	.015*	0.34
Timed Number Input					
Trial 1	-.18 (0.71)	.19 (1.22)	-2.76	.006**	0.37
Trial 2	-.08 (1.00)	.09 (1.00)	-1.26	.211	0.17
Trial 3	-.14 (0.90)	.15 (1.09)	-2.14	.033*	0.29
Trial 4	-.14 (0.82)	.16 (1.15)	-2.20	.029*	0.30
Trial 5	-.14 (0.91)	.16 (1.07)	-2.24	.026*	0.30
Total	-.18 (0.86)	.20 (1.10)	-2.87	.005**	0.38
Timed Visual Discrimination A	.12 (1.08)	-.13 (0.88)	1.87	.062	0.25
Timed Visual Discrimination B	.12 (1.06)	-.13 (0.92)	1.86	.064	0.25
PS Composite	-.09 (0.45)	.10 (0.49)		.002**[§]	0.40

Note. Means are presented, with standard deviations in parentheses. ESE = effect size estimate (in this case, Cohen's *d*). [a]Analyses based on *n* = 101 for the HIV-infected group; data were missing for one participant (a 39-year-old man) in that group.
p* < .05. ***p* < .01. *[§]*p* < .005 (Bonferroni-corrected *p*-value).

Regression equation-based comparisons. Table 11 shows that, on all NeuroScreen outcome variables, a significantly greater proportion of the HIV-infected group displayed impaired PS compared to the HIV-negative group when judged against the regression-based

normative data. These significant differences were associated with small-to-moderate effect sizes.

Table 11
Chi-Square Tests of Independence: Proportion of participants in each group who performed more poorly than normative standard (N = 214)

	Group				
Variable	HIV-negative (*n* = 112)	HIV-infected (*n* = 102)	χ^2	*p*	ESE
Trails 1	34.82	58.82	12.31	< .001***	.24
Timed Number Input (total)	46.43	72.55	14.97	< .001***	.26
Timed Visual Discrimination A	51.79	65.69	4.23	.040*	.14
Timed Visual Discrimination B	48.21	65.69	6.61	.010*	.18

Note. Values represent the percentage of participants who performed more poorly than predicted given the regression-based normative data. ESE = effect size estimate (in this case, phi).
*$p < .05$. **$p < .01$. ***$p < .001$.

General Discussion

The present paper described two studies. Study 1 confirmed, using exploratory factor analyses on data from a group of healthy, cognitively intact South African adults (*N* = 112), the construct validity of a suite of processing speed subtests contained within the NeuroScreen computerized test battery (viz., Trails 1, Timed Number Input, and Timed Visual Discrimination A and B). Subsequently, multiple regression analyses run on the same set of data allowed creation of locally relevant and appropriately stratified preliminary normative data for the NeuroScreen PS subtests. Applying those findings to the South African clinical context, Study 2 showed that (a) HIV-infected participants (*N* = 102) performed significantly more poorly on NeuroScreen PS subtests than matched healthy controls (*N* = 112), and (b) a significantly greater proportion of HIV-infected participants than healthy controls displayed PS impairment when judged against the regression-based normative data.

To accomplish the first aim of Study 1, I used a series of four exploratory factor analyses to assess the construct validity of the NeuroScreen PS subtests. Assumption-testing revealed a nonpositive definite matrix, which did not allow for analysis of the anti-image matrix, or for calculation of the KMO and Bartlett test statistics. A primary explanation for the nonpositive matrix is due to high multi-collinearity in the data (Brown, 2006). This level of multi-collinearity is ideal for the purposes of this study, as the aim here was to establish if

the NeuroScreen PS subtests are related to the same underlying construct (processing speed). As a result, high multi-collinearity among the data is promising. For this reason, I proceeded with the factor analyses as planned.

The first of these analyses indicated that all of the NeuroScreen PS outcome variables loaded onto one overarching factor, thus allowing the inference that all of NeuroScreen PS subtests measure the same cognitive construct. The second and third factor analyses demonstrated convergent validity by showing, respectively, that (a) NeuroScreen PS outcome variables loaded onto the same factor as outcome variables derived from standardized paper-and-pencil tests of PS (viz., Trail Making Test A, Wechsler Digit Symbol-Coding and Symbol Search, and Color Trails Test 1), and (b) NeuroScreen PS outcome variables partially loaded onto the same factor as standardized paper-and-pencil tests of working memory and executive function (viz., Wechsler Digit Span Backwards, and Color Trails Test 2). The fourth factor analysis demonstrated divergent validity by showing that NeuroScreen PS outcome variables loaded onto a different factor as outcome variables derived from standardized paper-and-pencil tests of constructs other than PS, WM, and EF (viz., Finger Tapping Test, Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Judgement of Line Orientation). Overall, then, the factor analyses suggest that the suite of NeuroScreen PS subtests are valid measures of the processing speed construct.

There are three notable individual results among this pattern of factor analytic data. First, the current study replicated previous findings suggesting that the PS and executive functioning constructs are related but separable (e.g., Albinet et al., 2012; Burgmans et al., 2011; Kievit et al., 2016; Lee et al., 2012) by showing that outcome variables derived from the Wisconsin Card Sorting Test and from category fluency tests partially loaded onto the Processing Speed factor, but primarily accounted for, respectively, the emergence of an Executive Function-Problem Solving factor and an Executive Function-Generativity factor.

The separability of these two factors from the primary Processing Speed factor might be accounted for by the fact that time pressure is a significant contributor to PS performance (Olfiesh, 2000; Salthouse, 2000). Hence, any paper-and-pencil executive functioning task containing a timed component is more likely to load onto the same factor as the NeuroScreen PS subtests. So, for instance, because the primary outcome of Color Trails Test 2 is completion time it should, and did, load more heavily onto the same factor as outcomes from the NeuroScreen PS subtests. In contrast, neither of the WCST outcome variables (Total Correct and Total Errors) has any timed component (Heaton et al., 1981), and hence they loaded predominantly onto another factor (Executive Functioning-Problem Solving).

Furthermore, although category fluency tasks are traditionally considered to measure a distinct domain of executive functioning (viz., generativity; Benton & Hamsher, 1976; Brandt et al., 2009; Friedman et al., 2006; Troster et al., 1998), a recent study suggests that these tasks probably fit better within the cognitive domain of language (Whiteside et al., 2016). Nonetheless, performance on these tasks should not, and did not, load onto the same factor as outcomes from the NeuroScreen PS subtests.

The second notable individual result among the overall factor analytic findings is that the Digit Span Backwards outcome variable loaded strongly, and uniquely, onto the Processing Speed factor. This result replicates previous studies showing that working memory has strong associations with processing speed, where WM capacity is largely determined by PS efficiency (Kail & Salthouse, 1994; Myerson, Emery, White, & Hale, 2003; Nettelbeck & Burns, 2010).

The third notable individual result among the overall factor analytic findings is that the BVMT-R Total Learning outcome variable loaded onto the Processing Speed factor. Although at first glance this might appear a counterintuitive finding, there is a literature suggesting that PS is a predictor of performance on visual memory tasks that feature brief exposure to test stimuli (Brown, Brockmole, Gow, & Deary, 2012; Tam & Schmitter-Edgecombe, 2013).

To accomplish the second aim of Study 1, I used a series of multiple regression analyses to determine whether, and which, sociodemographic variables affected NeuroScreen PS performance. The set of predictor variables entered into the regression models (viz., age, sex, and level of educational attainment) were those identified by previous research as bearing some relationship to performance on commonly used, standardized paper-and-pencil PS tests (Lezak, Howieson, & Loring, 2004; Roivainen, 2011; van Hooren et al., 2007). Consistent with previous research (e.g., Hong et al., 2015; Manly et al., 2011; Sheppard et al., 2015), the models indicated that age was the strongest sociodemographic predictor (i.e., it significantly influenced performance on all NeuroScreen PS subtests, such that increasing age was associated with poorer performance). Sex and education were weaker predictors (i.e., they significantly influenced performance on only Timed Number Input and Timed Visual Discrimination B, and even in those cases the amount of variance they accounted for was less than that accounted for by age). This result is also consistent with previous research showing that women sometimes perform marginally better than men on PS tests, and that higher levels of education are sometimes associated with better PS performance (Camarata & Woodcock, 2006; Joy et al., 2004; Tucker-Drob et al., 2009; but see Lowe & Reynolds, 1999; Ritchie et

al., 2013; and Roivainen, 2011, for contrasting results). Using equations developed from the regression models, I then created appropriately stratified preliminary normative data, suitable for the local population, for each of the NeuroScreen PS subtests.

Establishing the construct validity of the NeuroScreen subtests, and creating normative data for them, is important and valuable because of the potential utility of such computerized screening tools in resource- and expertise-limited clinical settings such as those found commonly in African countries (Boivin et al., 2010; Robertson, Liner, & Heaton, 2009; Watts & Shuttleworth-Edwards, 2016). For instance, NeuroScreen does not require highly-trained professionals to administer and score as instructions, tasks, and results are displayed and stored digitally. Additionally, the digital, touchscreen component of the battery makes it insensitive to literacy status; this is a particularly important consideration when tests that are heavily influenced by reading and writing fluency need to be administered to populations with high levels of illiteracy (Hahn et al., 2004; Posel, 2011; Roivainen, 2011).

Study 2, then, presented a direct application of the suite of NeuroScreen PS subtests to the South African clinical context. Because South Africa has the highest burden of HIV diagnoses in the world (Statistics South Africa, 2016; UNAIDS, 2016), clinical psychologists and neuropsychologists in this country are often faced with the task of assessing HIV-infected individuals, with particular focus on detecting areas of cognitive impairment and on plotting the trajectory of cognitive decline. Impaired processing speed is a key component of the manifestation of the disease, and serves as a marker of overall cognitive decline in HIV-associated cognitive impairment (Fellows et al., 2014; Kore et al., 2015).

The Study 2 analyses suggested that HIV-infected participants performed significantly more poorly than demographically matched HIV-negative participants on the suite of NeuroScreen PS subtests, and that, relative to the preliminary normative data created in Study 1, a significantly greater proportion of HIV-infected participants than HIV-negative participants displayed PS impairment. Overall, then, these results are consistent with those from previous studies, conducted in both Clade B- and Clade C-preponderant regions, suggesting that PS is an important domain of cognitive deficit in HIV-infected participants (see, e.g., Gupta et al., 2007; Joska et al., 2012; Vance et al., 2011; Woods et al., 2009).

Adding a brief, culturally fair, valid, and deficit-sensitive PS measure to the armamentarium of neuropsychological practitioners is valuable not only for cognitive diagnostic purposes, but also for assisting patients and their families in preparing for everyday challenges associated with the development of HIV-associated cognitive impairment (Cody, Fazeli, & Vance, 2015). HIV-infected individuals with slowed PS also

exhibit poor performance on ADLs, such as completing financial tasks, medication management, shopping, driving, cooking, and cleaning (Casaletto et al., 2017). This is especially true for older persons with HIV, a population that is growing rapidly because (a) the increasingly widespread and effective dissemination of cART has increased the life expectancy of those living with the disease, and (b) the additive effects of age- and HIV-related impaired PS are profound (Fazeli et al., 2015; Morgan et al., 2012; Saylor & Sacktor, 2016).

Fortunately, cognitive retraining programs that aim to help ameliorate PS impairments might aid in boosting ADL performance (see, e.g., Cody et al., 2015; Kaur, Dodson, Steadman, & Vance, 2015; Vance, Fazeli, Ross, Wadley, & Ball, 2012). These behavioural interventions are often computerized, and require the participant to complete a number of timed tasks that gradually increase in difficulty, with the specific goal of translating the associated improvements in PS into enhanced everyday functioning (Ball, Edwards, & Ross, 2007).

Limitations and Directions for Future Research

Conclusions and inferences that might be drawn from the present research must be tempered by acknowledgement of the following limitations. First, in both studies the sample age range was somewhat restricted, excluding children and adolescents and without significant numbers of older adults. Particularly because of the strong effects of age on PS performance, regression-based normative predictions would be improved by sampling across a wider age range. Moreover, it remains to be established whether the NeuroScreen PS subtests can track PS decline successfully throughout older adulthood in HIV-infected adults, or whether basement effects would start to impede effective assessment.

Second, in Study 2 the HIV-infected group was not matched on sex, with women comprising the major proportion (81.4%) of the sample. This statistic is not representative of base rates in South Africa, where women comprise 60.29% of the population of HIV-infected individuals (UNAIDS, 2016). Of note too, however, is that even though being female was associated with improved performance on the only task for which sex had proven a significant predictor in Study 1 (Timed Number Input Total), on average HIV-infected participants still performed significantly more poorly than HIV-negative participants. Hence, it appears the discrepancy in sex distribution across groups did not bias the results. Future studies should, however, aim to eliminate or control for between-group sex differences.

Third, although the study protocol did require potential participants to report on their patterns of illicit substance use, I did not medically screen for this usage. Past and current

substance use is a frequent co-morbid condition in HIV infection that contributes to impaired neuropsychological performance (Devlin et al., 2012). Hence, if there was significant substance use among the current HIV-infected participants, the data presented might overestimate the extent of PS performance deficits. Future studies should, therefore, use reliable medical screening methods (e.g., urine toxicology screening) to either include current or prior substance use as an exclusion criterion, or measure such use accurately so that it might be used a covariate in statistical analyses.

A final suggestion for future research is that more studies adopt a longitudinal approach, in order to track the degree of PS (and other cognitive) impairment across time in HIV-infected samples (see, e.g., Baldewicz et al., 2004). Although Neuroscreen might be an ideal tool for use in such longitudinal studies given that it is easily re-administrable and that it stores all results digitally, there are no studies examining whether, as is the case with other measures of PS (e.g., TMT-A), the suite of Neuroscreen PS subtests might be susceptible to practice or carryover effects (Buck, Atkinson, & Ryan, 2008; Calamia, Markon, & Tranel, 2012).

Summary and Conclusion

This is the first study to examine the construct validity of the NeuroScreen PS subtests, to establish locally relevant and appropriately stratified preliminary normative data for those tasks, and to provide HIV-related diagnostic data for those tasks. Considering the significance of PS decline in the trajectory of HIV, and the prevalence of the disease in South Africa, the potential utility and benefits of NeuroScreen are far-reaching. The battery is also highly suited for use in low-resource clinical contexts, as it is time- and cost-effective, simple enough for lay professionals to administer, culturally fair, and insensitive to the effects of language variation and literacy status.

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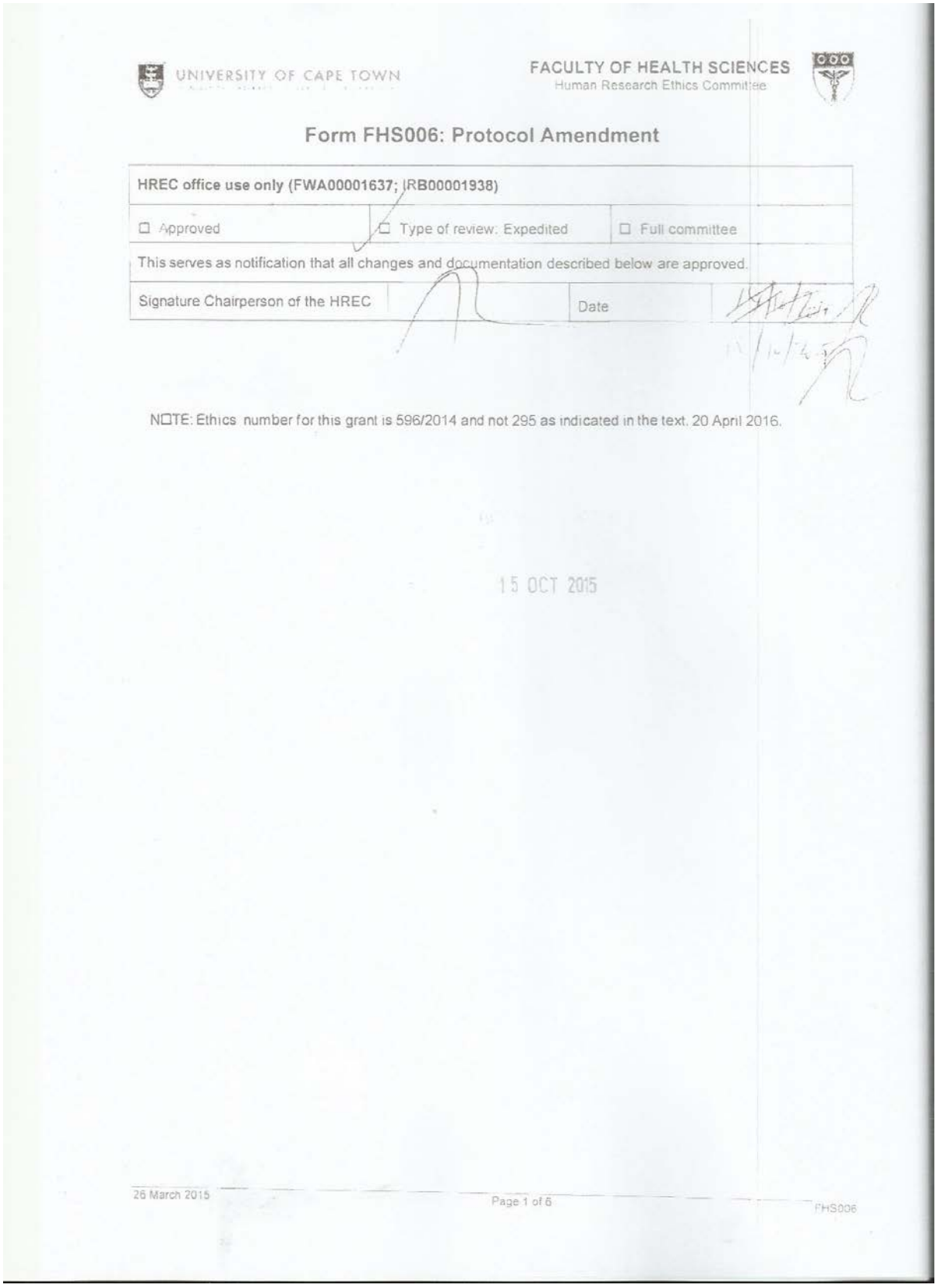
Appendix A
Certificate of Ethical Approval



UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)		
☐ Approved	☐ Type of review: Expedited	☐ Full committee
This serves as notification that all changes and documentation described below are approved.		
Signature Chairperson of the HREC	Date	

NOTE: Ethics number for this grant is 596/2014 and not 295 as indicated in the text. 20 April 2016.

15 OCT 2015

26 March 2015 Page 1 of 6 FHS006

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Note: All major amendments should include a **PI Synopsis** justifying the changes for the amendment (please see notice dated 23 April 2012)

Comments to PI from the HREC
We are requesting to make an amendment to our protocol 296/2014, "A Mobile App for LMIC Lay Health Workers to Screen for Neurocognitive Impairment." We would like to add a matched sample of 100 healthy, HIV-uninfected adults. This will not change or alter or study aims. Adding the control group will enhance the precision of the sensitivity and specificity estimates that will be generated for the app's ability to detect neurocognitive impairment for Aim 2 of the study. Further, we believe that adding the control group will make our findings more generalisable We would also like to add five more, standard, brief, neuropsychological tests to the full neuropsychological test battery being administered in the study. We would like to add the Montreal Cognitive Assessment (MoCA), the CLOX test, Judgment of Line Orientation, the Paced Auditory Serial Addition Test, and Action Fluency – all well-established and commonly used neuropsychological tests. All of these tests are brief, and we estimate that the addition of them will increase the study visit no more than 20-30 minutes. We also believe that the compensation remains fair given the increased burden. In our experience, the current test battery takes, on average, just under 2.5 hours to complete. Adding 20-30 minutes would still keep the study visit within the 3-hour maximum as stated in the consent form. Only the control group would receive these extra tests, as we will achieve our target sample size of 100 HIV-infected adults within the next 2-3 weeks. Adding the control group and additional tests will change or recruitment strategy, inclusion criteria, consent form, and assessment instruments. We have updated the following sections (all changes have been bolded): Lay Summary Description of Subject Population Recruitment Procedures Inclusion/Exclusion Criteria #2 Consent Procedures Assessment Instruments We have also included a new Consent Form specifically for the control participants. We have included a version with tracked changes and a version with accepted changes Please do not hesitate to contact me if you have any additional questions or need additional information. Sincerely, John Joska.

Principal Investigator to complete the following:

1. Protocol information

Appendix B
HIV-negative Consent Form

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE MAIN RESEARCH PROJECT: ***Masivukeni: A Multimedia ART Adherence Intervention for Resource-Limited Settings***

TITLE OF SUB-STUDY: A Mobile App for LMIC Lay Health Workers to Screen for Neurocognitive Impairment

PRINCIPAL INVESTIGATOR: Dr. John A. Joska

ADDRESS: Department of Psychiatry and Mental Health, J-block, Groote Schuur Hospital, Anzio Road, Observatory, 7925. Telephone: 021-404 2164/021-4042151

You have entered the Masivukeni study and have just completed your last study visit for it. We would like to invite you to take part in another linked study. Please take some time to read over the information about this new study. You do not have to enter this new study – it is your choice whether you want to or not. Your participation is **entirely voluntary.** If you say no, this will not affect you negatively in any way. It will not affect your participation in the Masivukeni study or services you are receiving at this clinic. You are also free to withdraw from the study at any point, even if you do agree to take part.

If you have any questions or are confused about anything, please ask the study staff or doctor any questions about any part of this new study that you do not fully understand. It is very important that you feel fully satisfied in your understanding of what participating in this study requires.

This study has been approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town and the Institutional Review Board of the New York State Psychiatric Institute in the United States. This study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- People living with HIV often experience memory, thinking, attention, and concentration problems, as well as problems with coordination (known as cognitive problems). These problems can interfere with daily life and put individuals at risk for developing more severe cognitive problems.
- Knowing if people are experiencing cognitive problems is challenging, and a new tool that can be used by community health workers has been developed to help screen for cognitive problems among people living with HIV.

- This study will be conducted at your local clinic to evaluate how accurately the new tool can detect cognitive problems, how well lay counsellors can use the new tool, and if results from the tool are related to treatment outcomes. The study will include up to 100 HIV-positive people who have completed the Masivukeni study.
- In this study, you will be asked to take short screening test on a tablet device that will be administered by one of the study counsellors. It will take approximately 20-minutes and assesses how quickly you can think, remember and do certain things. After that, you will be asked to complete a brief assessment of your mental health and a neuropsychological test battery that will take 2-3 hours. The neuropsychological battery will also ask you to remember things, drawing lines with your finger, and do other game-like activities that will assess your cognitive abilities. You will be able to complete this on the same day as you complete your last Masivukeni visit, or within 7 days of the visit.
- The study will not offer special treatment or medication. You will be financially compensated for participating in this study.

What will your responsibilities be?

- If you agree to take part in this study, you will sign this form.
- You will be administered a short series of neuropsychological tests on a smartphone, which consist of remembering some words, tapping buttons on a smartphone, repeating number sequences, and using your finger or a stylus to connect dots on the smartphone screen.
- Then, the study counsellor will administer the screening tool on the tablet to you, which consists of remembering some words, tapping buttons, repeating number sequences, and using your finger to connect dots on the tablet screen.
- You will also be asked to answer some questions about your experience using computers and mobile deceives, and what it was like to use the tablet device.
- Then, you will be asked to complete the longer assessment that will take 2-3 hours. You can complete it today or come back within 7 days to complete it.
- The longer assessment will ask you questions about how you've been feeling in the past month, and ask you to remember things, draw, tap your finger, put pegs in holes, repeat number sequences, and solve problems.
- Your name will not be attached to any of the forms and results: they will only be identified with a study identification number.
- As part of this research project, the researchers will collect your unique Masivukeni research ID number and get the following information from your Masivukeni research record: your demographic information (age, gender, race, ethnicity, years of education, handedness), information about your ARVs, medical information, such as your most recent CD4 count and viral load. No personal and identifiable information of yours will be collected or stored.

Will you benefit from taking part in this research?

- You will not personally benefit from participating in this new study. Participation could possibly help researchers and scientists understand if the new screening tool works accurately, and this could lead to improved health for people like you.

Are there any risks involved in your taking part in this research?

- During the testing, you may experience emotional upset, embarrassment, or discomfort. If you request it and if you agree, the tests and interview will be stopped and rescheduled. Referral to appropriate counselling or support services can be made if you wish.
- There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

If you do not agree to take part, what alternatives do you have?

- Participation in the study is voluntary. You may withdraw from the study at any time. There are no alternatives to participation. You are free not to participate or to withdraw at any time during the study. Your treatment will not be affected in any way, nor will your participation in the Masivukeni study. You may continue to attend your clinic. It would be helpful for the study team to let us know why you have decided not to take part, but you are free to not give a reason.

Can you be dismissed from the study for any reason?

- Once you begin study participation, study staff may ask you to leave the study before you complete it. This is rare. There are several reasons this could happen such as becoming so medically or mentally sick you cannot attend study visit. If this happens, the study staff will refer you to appropriate health services. If you get better and wish to continue in the study, you may contact the study staff.

What if you decide you no longer want to participate in the study?

- Your participation is completely voluntary. You may withdraw from the study at any time. If you do, you will not lose any benefits to which you are otherwise entitled. Withdrawal will not affect the services provided to you by the clinic.

Who will have access to your medical records?

- The information collected about you will be treated as confidential and protected. If we write about this work, we will not identify you personally. Only the research study team will have full access to the information.

Is the information you provide confidential?

- All research study staff are instructed to keep all of your study information secret. They are not allowed to discuss it with the clinic staff. They are only allowed to

discuss it with the research study staff. All study information will be identified by unique ID numbers and will be kept in locked file drawers. These records will only be available to research study staff. Institutional personnel may access it as part of routine audits. A list matching participant names with ID numbers will be kept in a separate locked file drawer. This information will only be available to research study staff. Study results will be reported only as a group. This way, no individual participant can be identified.

Will you be paid to take part in this study and are there any costs involved?

- You will be reimbursed for your transport costs and time to complete the study procedures. You will receive R400 when you complete all of the study questions and evaluations.
- The maximum compensation is R400.

What if you get injured as a direct result of participating in this study?

- Free essential medical treatment is available to you only if you are injured because of your participation in this study. You will not receive any money as compensation for injury.

In case of an emergency or if you feel you need to contact one of the study doctors, you can do so by phoning

Ms Michelle Henry or Dr Hetta Gouse or Dr John Joska at tel no 021-4042164

- You can also contact the Human Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

Information and Consent Summary

Ensure that each participant clearly understands each of the following points:

- You are being asked to partake in a research study linked to the Masivukeni study because you already in the Masivukeni study and have just completed it.
- As a participant in the study, **at one study visit** in the clinic, you will:
  - Allow the study counsellor to administer a screening tool on a tablet device and a brief questionnaire about your experience using the tablet.
  - Allow the study psychometrist to administer a comprehensive neuropsychological battery to you.
- Everything you share during the visits is confidential. Only those people involved in this research study will see your answers to the questions. The clinic staff will not have access to your answers.
- Your participation in this study is completely voluntary.
- Your participation or decision not to participate in the study WILL NOT affect your care at this clinic.
- You can withdraw from the study at any time without negative consequences and you can continue receiving care at this clinic.

DECLARATION BY PARTICIPANT

PARTICIPATION IN RESEARCH STUDY

By signing below, I _____ agree to take part in a research study entitled: "*A Mobile App for LMIC Lay Health Workers to Screen for Neurocognitive Impairment"*

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan as agreed.

Signed at (*place*) _____ on (*date*) _____ 20____.

_____

Signature/Fingerprint of participant

DECLARATION BY INVESTIGATOR/STUDY COORDINATOR

I *(name)* _____declare that:

- I explained the information in this document to _____
- I encouraged him/her to ask questions and took adequate time to answer them.

- I am satisfied that he/she adequately understands all aspects of the research, as discussed above.

Signed at (*place*) _____ on (*date*) _____ 20____.

_____

Signature of investigator/study coordinator

Appendix C
HIV-infected Consent Form

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE MAIN RESEARCH PROJECT: ***Masivukeni: A Multimedia ART Adherence Intervention for Resource-Limited Settings***

TITLE OF SUB-STUDY: A Mobile App for LMIC Lay Health Workers to Screen for Neurocognitive

Impairment

PRINCIPAL INVESTIGATOR: Dr. John A. Joska

ADDRESS: Department of Psychiatry and Mental Health, J-block, Groote Schuur Hospital, Anzio Road, Observatory, 7925. Telephone: 021-404 2164/021-4042151

You have entered the Masivukeni study and have just completed your last study visit for it. We would like to invite you to take part in another linked study. Please take some time to read over the information about this new study. You do not have to enter this new study – it is your choice whether you want to or not. Your participation is **entirely voluntary.** If you say no, this will not affect you negatively in any way. It will not affect your participation in the Masivukeni study or services you are receiving at this clinic. You are also free to withdraw from the study at any point, even if you do agree to take part.

If you have any questions or are confused about anything, please ask the study staff or doctor any questions about any part of this new study that you do not fully understand. It is very important that you feel fully satisfied in your understanding of what participating in this study requires.

This study has been approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town and the Institutional Review Board of the New York State Psychiatric Institute in the United States. This study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- People living with HIV often experience memory, thinking, attention, and concentration problems, as well as problems with coordination (known as cognitive problems). These problems can interfere with daily life and put individuals at risk for developing more severe cognitive problems.
- Knowing if people are experiencing cognitive problems is challenging, and a new tool that can be used by community health workers has been developed to help screen for cognitive problems among people living with HIV.
- This study will be conducted at your local clinic to evaluate how accurately the new tool can detect cognitive problems, how well lay counsellors can use the new tool, and if results from the tool are related to treatment outcomes. The study will include up to 100 HIV-positive people who have completed the Masivukeni study.
- In this study, you will be asked to take short screening test on a tablet device that will be administered by one of the study counsellors. It will take approximately 20-minutes and assesses how quickly you can think, remember and do certain things. After that, you will be asked to complete a brief assessment of your mental health and a neuropsychological test battery that will take 2-3 hours. The neuropsychological battery will also ask you to remember things, drawing lines with your finger, and do other game-like activities that will assess your cognitive abilities. You will be able to complete this on the same day as you complete your last Masivukeni visit, or within 7 days of the visit.
- The study will not offer special treatment or medication. You will be financially compensated for participating in this study.

What will your responsibilities be?

- If you agree to take part in this study, you will sign this form.
- You will be administered a short series of neuropsychological tests on a smartphone, which consist of remembering some words, tapping buttons on a smartphone, repeating number sequences, and using your finger or a stylus to connect dots on the smartphone screen.
- Then, the study counsellor will administer the screening tool on the tablet to you, which consists of remembering some words, tapping buttons, repeating number sequences, and using your finger to connect dots on the tablet screen.
- You will also be asked to answer some questions about your experience using computers and mobile deceives, and what it was like to use the tablet device.
- Then, you will be asked to complete the longer assessment that will take 2-3 hours. You can complete it today or come back within 7 days to complete it.
- The longer assessment will ask you questions about how you've been feeling in the past month, and ask you to remember things, draw, tap your finger, put pegs in holes, repeat number sequences, and solve problems.
- Your name will not be attached to any of the forms and results: they will only be identified with a study identification number.

- As part of this research project, the researchers will collect your unique Masivukeni research ID number and get the following information from your Masivukeni research record: your demographic information (age, gender, race, ethnicity, years of education, handedness), information about your ARVs, medical information, such as your most recent CD4 count and viral load. No personal and identifiable information of yours will be collected or stored.

Will you benefit from taking part in this research?

- You will not personally benefit from participating in this new study. Participation could possibly help researchers and scientists understand if the new screening tool works accurately, and this could lead to improved health for people like you.

Are there any risks involved in your taking part in this research?

- During the testing, you may experience emotional upset, embarrassment, or discomfort. If you request it and if you agree, the tests and interview will be stopped and rescheduled. Referral to appropriate counselling or support services can be made if you wish.
- There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

If you do not agree to take part, what alternatives do you have?

- Participation in the study is voluntary. You may withdraw from the study at any time. There are no alternatives to participation. You are free not to participate or to withdraw at any time during the study. Your treatment will not be affected in any way, nor will your participation in the Masivukeni study. You may continue to attend your clinic. It would be helpful for the study team to let us know why you have decided not to take part, but you are free to not give a reason.

Can you be dismissed from the study for any reason?

- Once you begin study participation, study staff may ask you to leave the study before you complete it. This is rare. There are several reasons this could happen such as becoming so medically or mentally sick you cannot attend study visit. If this happens, the study staff will refer you to appropriate health services. If you get better and wish to continue in the study, you may contact the study staff.

What if you decide you no longer want to participate in the study?

- Your participation is completely voluntary. You may withdraw from the study at any time. If you do, you will not lose any benefits to which you are otherwise entitled. Withdrawal will not affect the services provided to you by the clinic.

Who will have access to your medical records?

- The information collected about you will be treated as confidential and protected. If we write about this work, we will not identify you personally. Only the research study team will have full access to the information.

Is the information you provide confidential?

- All research study staff are instructed to keep all of your study information secret. They are not allowed to discuss it with the clinic staff. They are only allowed to discuss it with the research study staff. All study information will be identified by unique ID numbers and will be kept in locked file drawers. These records will only be available to research study staff. Institutional personnel may access it as part of routine audits. A list matching participant names with ID numbers will be kept in a separate locked file drawer. This information will only be available to research study staff. Study results will be reported only as a group. This way, no individual participant can be identified.

Will you be paid to take part in this study and are there any costs involved?

- You will be reimbursed for your transport costs and time to complete the study procedures. You will receive R400 when you complete all of the study questions and evaluations.
- The maximum compensation is R400.

What if you get injured as a direct result of participating in this study?

- Free essential medical treatment is available to you only if you are injured because of your participation in this study. You will not receive any money as compensation for injury.

In case of an emergency or if you feel you need to contact one of the study doctors, you can do so by phoning

Ms Michelle Henry or Dr Hetta Gouse or Dr John Joska at tel no 021-4042164

- You can also contact the Human Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

Information and Consent Summary

Ensure that each participant clearly understands each of the following points:

- You are being asked to partake in a research study linked to the Masivukeni study because you already in the Masivukeni study and have just completed it.
- As a participant in the study, **at one study visit** in the clinic, you will:
  - Allow the study counsellor to administer a screening tool on a tablet device and a brief questionnaire about your experience using the tablet.
  - Allow the study psychometrist to administer a comprehensive neuropsychological battery to you.
- Everything you share during the visits is confidential. Only those people involved in this research study will see your answers to the questions. The clinic staff will not have access to your answers.
- Your participation in this study is completely voluntary.
- Your participation or decision not to participate in the study WILL NOT affect your care at this clinic.
- You can withdraw from the study at any time without negative consequences and you can continue receiving care at this clinic.

DECLARATION BY PARTICIPANT

PARTICIPATION IN RESEARCH STUDY

By signing below, I _____ agree to take part in a research study entitled: *"A Mobile App for LMIC Lay Health Workers to Screen for Neurocognitive Impairment"*

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan as agreed.

Signed at (*place*) _____ on (*date*) _____ 20____.

_____

Signature/Fingerprint of participant

DECLARATION BY INVESTIGATOR/STUDY COORDINATOR

I *(name)* _____declare that:

- I explained the information in this document to _____
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above.

Signed at (*place*) _____ on (*date*) _____ 20____.

_____

Signature of investigator/study coordinator