THE VALIDATION OF A NEW DEVELOPMENTAL SCREENING TOOL FOR NEURODEVELOPMENTAL DELAYS AMONG HIV–INFECTED SOUTH AFRICAN CHILDREN

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DECLARATION

I, Dr Ojombo Gbemisola Boyede Student Number BYDOJO001, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background: Over 50% of HIV-infected children in South Africa have developmental delays. Early identification of affected children will lead to early intervention and favourable long-term outcome. Screening for developmental delay is not yet routine by many primary healthcare providers due to lack of locally available, rapid and sensitive screening tools in busy Paediatric HIV clinics. A new screening tool was developed at the Red Cross War Memorial Children's Hospital (RCWMCH) for detecting moderate to severe global developmental delay among very young HIV infected children. The diagnostic accuracy and usefulness of the new tool was evaluated in this study.

Objective: to validate the new RCWMCH developmental screening tool among HIV-infected South African children.

Method: Forty-seven HIV-infected children in the age category 9 – 36 months attending the Infectious Disease Clinic (IDC) of the RCWMCH were screened using the new tool. Full developmental assessments of same children were performed using the Bayley Scale of Infant Development (BSID-III). Developmental Delay (global) was defined as composite scores 2 standard deviations below the mean in two or more developmental domains.

Results: The sensitivity of the RCWMCH tool was 78.5%, specificity 54.6%, positive predictive value was 42.6%, and negative predictive value was 85.7%.

Discussion: The RCWMCH screening tool was found to have sensitivity within the acceptable levels recommended for developmental screening tools. Its high negative predictive value will reduce unnecessary referrals for full developmental assessments in asymptomatic infants and toddlers. It is therefore recommended for screening for developmental delay among HIV-infected children from the age of 9 months to 3years.

Keywords

Developmental delay, Paediatric HIV, Screening, Bayley Scale of Infant development, third edition, Red Cross War Memorial Children's Hospital screening tool, sensitivity, specificity, diagnostic accuracy

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Abbreviations

AAP - American Academy of Paediatrics

AIDS – Acquired Immunodeficiency Disease Syndrome

BSID-III – Bayley Scale of Infant Development, third edition

DNA – Deoxyribonucleic Acid

ELISA – Enzyme-linked Immunosorbent Assay

HAART – Highly Active Antiretroviral Therapy

HIV – Human Immunodeficiency Virus

HREC – Human Research Ethics Committee

IDC – Infectious Disease Clinic

ISID – International Society for Infectious Diseases

PCR – Polymerase Chain Reaction

PI – Principal Investigator

RCWMCH – Red Cross War Memorial Children's Hospital

SCAH – School of Child and Adolescent Health

UCT – University of Cape Town

UNAIDS – Joint United Nation Programme on HIV/AIDS

CHAPTER 1 INTRODUCTION

1.1 Context

Paediatric Human Immunodeficiency Virus/Acquired Immunodeficiency Disease Syndrome (HIV/AIDS) in almost three decades since the first case was diagnosed has remained a significant cause of childhood morbidity and mortality in Africa.[1] In 2014 the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that at the end of 2013, 3.2 million children were living with HIV/AIDS globally and 91% of infected children are resident in Sub-Saharan Africa.[2] In 2012 17% of under-5 mortality in South Africa was caused by HIV infection.[3]

Developmental delays and disabilities among children with vertically transmitted HIV infection have been well documented.[4-7]The developmental deficits are often the clinical manifestations of HIV-associated encephalopathy which is the main neurological complication of HIV/AIDS.[7] Other factors such as poverty, stress, prenatal drug exposure, maternal level of education, age, language have been found to be contributory to developmental delays in HIV-infected children in addition to the viral infection.[6,8] All domains of development can be affected including motor (most commonly affected), language, behaviour and cognitive functioning. This may result in developmental disabilities including learning disabilities and school failure.[7]

Studies on neurodevelopment of HIV-infected African children have reported high prevalence of developmental delays with most reporting prevalence of more than 50%.[8-13] In South Africa, a recent study on development of HIV-infected children reported more than half of the children under the age of two had severe cognitive delay while 72% had severe motor delay.[13] However, despite this high prevalence of developmental disabilities among HIV-infected children in Africa, many paediatric HIV centres do not do routine screening for developmental delays.

Though much effort has been made in recent years to reduce the HIV/AIDS mortality in Africa with the introduction and provision of freely available highly active antiretroviral medications, there has been little effort in improving the poor quality of life that may result from developmental disabilities related to the disease. HIV/AIDS

is fast becoming a chronic illness and the emphasis has shifted from survival to improved quality of life for survivors.

Globally, there has been increasing pressure to identify the children with developmental disabilities as early as possible preferably in infancy so as to commence early intervention. Studies have shown that early intervention programs lead to better long term developmental outcomes for children with developmental disabilities.[14,15] This observation has informed one of the policies of the American Academy of Paediatrics (AAP) in ensuring identification of children with developmental delay before the age of 2 years through standard developmental screening.[15] The current recommendation by AAP is that all children be screened for developmental difficulties during the routine preventive health visits at 9, 18 and 30 months (or at 24 months when a 30-month visit is not included).[16]

Most children with HIV/AIDS in Africa are being followed up at the primary healthcare level where the focus is usually on physical health and prescription of antiretroviral medications. The clinics are usually too busy and the health care providers are usually not skilled in use of standard developmental screening tools. The tendency is for healthcare workers to omit the developmental screening and thereby miss early signs of developmental deficits in HIV-infected children. Only children with obvious gross delays are referred in such settings for specialist review and management and even this is inconsistent. The situation at the secondary and tertiary levels of care is slightly better with most clinicians utilising clinical judgement to identify HIV-infected children with significant developmental delays. Clinical judgement however has been found not to be sensitive in identifying children with developmental delays.[17] The use of standard developmental screening tool is likely to improve the proportion of children that will be identified with delays.[18]

Though there are internationally standardized screening tools, they may not necessarily be valid or appropriate for use among the South African population.[19] Furthermore, most of these tools are time-consuming and complex to administer and may require special kits and training before administration.[19] They therefore lack practical relevance for the African setting with busy clinics and sometimes lower

cadre health care professionals. Without the use of standard screening tools, children with developmental delays will likely go unidentified and miss early interventions and programmes that might have improved their long-term outcome.[14]

There is need for developmental screening for all HIV-infected children during infancy and early childhood. The use of locally available, rapid and sensitive standard developmental screening tools in addition to clinical surveillance will help in identifying children with developmental delays and disabilities for early therapeutic interventions.

To overcome the challenge of lack of locally sensitive screening tools for HIV-infected children with developmental delay, a simple developmental screening tool (Appendix I) was devised by the Division of Developmental Paediatrics of RCWMCH for preliminary rapid screen and identification of HIV –infected children with moderate to severe developmental delays. The RCWMCH screening tool was devised with inputs from other professionals in the field of child development such as physiotherapists, occupational and speech therapists. Children identified through this rapid screen can be referred for further detailed assessment at the specialty clinics and/or appropriate early interventions.

The use of a simple screening tool that can be rapidly administered by most healthcare providers without any special equipment, and that is still sensitive enough to identify children with significant developmental delay may result in early identification, referral and interventions with improved outcome for these vulnerable children. The validation of such instrument against a gold standard developmental assessment tool will increase the confidence of healthcare providers and clinicians in its use. The aim of this study is to validate the RCWMCH developmental screening tool by comparing it with a gold standard for infant developmental assessment namely assessment using the Bayley Scale of Infant and Toddler Development, third edition (BSID-III).

1.2 Ethical Consideration

Ethical approval for the study was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (HREC REF 133/2013, Appendix II) and the RCWMCH, Rondebosch, Cape Town (Appendix III). Written Informed consent was obtained at commencement of the study from the parents or legal guardians. The consent forms were translated and made available in the 3 major languages of the region (English, Afrikaans and Xhosa). Interpreters in the hospital setting were available to assist in consent approval in instances of language barrier. The individuals who chose not to be part of the study still received standard care. The children with the possible diagnosis of developmental delays were referred into the Developmental Services at the Hospital as well as the relevant therapies.

The data for the study were obtained during the study participants' routine hospital visits for follow-up. However, the participants had to wait one hour extra for the BSID-III assessments and in some instances came for the BSID-III assessments at a later date. Transport fares for the participants were paid to compensate for the loss of their time.

1.3 Author Guidelines

The dissertation is to be published in the *Journal of Child Neurology* (*JCN*). JCN is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neurosurgery, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavior pediatrics, pediatric neuroscience, and developmental neurobiology. The Journal was chosen because the subject matter of the dissertation on developmental screening is covered by the Journal.

The "Instructions to Authors" of the JCN (Appendix IV) has been appended. The journal is listed in the citation index of the Institute for Scientific Information (ISI).

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CHAPTER 2 PUBLICATION READY MANUSCRIPT

Title Page

The preliminary validation of a new developmental screening tool for neurodevelopmental delay in HIV-infected South African children

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Abstract

The prevalence of developmental delay among HIV-infected children in Africa where 91% of infected children live is over 50% in most studies. Standard screening for developmental delay among infected children is not routine in most Paediatric HIV clinics due to lack of locally adaptable, simple, sensitive and rapid screening tools. The Division of Developmental Paediatrics of the Red Cross War Memorial Children's Hospital (RCWMCH) developed a new tool for rapid screening of moderate to severe global developmental delays among HIV-infected children aged 9 to 36 months. The study's aim was to evaluate the diagnostic accuracy of the novel neurodevelopmental screening tool in HIV-infected children.

Forty-seven HIV-infected children in the age category 9 – 36 months attending the Infectious Disease Clinic (IDC) of the Hospital were screened using the RCWMCH developmental screening tool. Full developmental assessments of same children were performed using the Bayley Scale of Infant Development (BSID-III). Developmental Delay (global) was defined as composite scores 2 standard deviations below the mean in two or more developmental domains.

The sensitivity of the RCWMCH tool was 78.5%, specificity 54.6%, positive predictive value was 42.6% and negative predictive value was 85.4%

The RCWMCH screening tool was found to have acceptable level of sensitivity for a screening tool. The tool also has a high negative predictive value for developmental delay which will limit unnecessary referrals for full developmental assessments. It is recommended for screening for moderate to severe developmental delays among HIV-infected children in the clinical context.

Keywords

Developmental delay, Paediatric HIV, Screening, Bayleys Scale of Infant development, Red Cross War Memorial Children's Hospital screening tool, sensitivity, specificity, diagnostic accuracy

INTRODUCTION

Almost three decades after the first case of Pediatric Human Immunodeficiency Virus/Acquired Immunodeficiency Disease Syndrome (HIV/AIDS) was diagnosed, the disease has remained a significant cause of childhood morbidity and mortality in Africa.[1] In the 2014 report, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that 3.2 million children were living with HIV/AIDS globally and 91% of infected children are resident in Sub-Saharan Africa.[2] In South Africa, HIV/AIDS accounted for 17% of under-five mortality in 2012.[3]

Studies on the neurodevelopment of HIV-infected African children have reported high prevalence of developmental delays with most reporting prevalence over 50%.[4-8] In South Africa with the largest epidemic in the world,[2] a recent study on neurodevelopment of HIV-infected children showed that more than half of infected children under the age of two had severe cognitive delay while 72% had severe motor delay.[8] However, despite this high prevalence of developmental disabilities among HIV-infected children in Africa, infected children are not screened routinely for developmental delays.

Globally, there has been increasing pressure to identify the children with developmental disabilities as early as possible preferably in infancy so as to commence early intervention. Studies have shown that early intervention programs lead to better long term developmental outcomes for children with developmental disabilities.[9,10] This finding has informed a policy by the American Academy of Paediatrics (AAP) which currently recommends that all children be screened, using standardized screening tools, for developmental difficulties during the routine preventive health visits at 9, 18 and 30 months(or at 24 months when a 30-month visit is not included).[11] The use of clinical judgement only for developmental delay surveillance which is often the case in the African setting has been found not to be sensitive in identifying children with significant developmental delays.[12] The use of a standardized developmental screening tool will improve the percentage remarkably.[13]

Though there are internationally standardized screening tools, they may not necessarily be valid for use among the South African population.[14] Furthermore, most of these tools are time-consuming and complex to administer and may require special kits and training

before administration. They therefore lack practical relevance for the African setting with busy clinics and sometimes lower cadre health care professionals. Children with developmental delays will likely go unidentified and miss early interventions and programmes that might have improved their long-term outcome.[10]

To overcome the lack of locally sensitive screening tools for HIV-infected children with developmental delay, a simple developmental screening tool was devised by the Division of Developmental Paediatrics of Red Cross War Memorial Children's Hospital (RCWMCH) for preliminary rapid screen and identification of HIV –infected children with moderate to severe developmental delays. The RCWMCH screening tool was devised with inputs from other professionals in the field of child development such as physiotherapists, occupational and speech therapists. Children identified through this rapid screen can be referred for further detailed assessment at the developmental specialty clinics and/or appropriate early interventions.

In the choice of the gold standard tool to be used for validation of the new screening tool, there was limitation of standard developmental assessment tools developed and validated for the African children. Tools that have been developed in Africa include the Malawi Developmental Assessment Tool (MDAT)[15] and the Kilifi Developmental Inventory.[16] However, though both tools have been shown to have good psychometric properties, neither of these tools have been validated for use in the South African population which limit their use as the gold standard in this study. Among the international gold standard tools, the Bayley Scales are the most widely employed measure of early global development in the cross-cultural context.[14] The Bayley Scales have excellent psychometric properties and had been validated for the South African population.[17] This informed its choice as the gold standard for this study.

The aim of this study is to validate the RCWMCH developmental screening tool by comparing it with a gold standard for infant developmental assessment; Bayley Scale of Infant and Toddler Development, third edition (BSID-III).

The Red Cross War Memorial Children's Hospital (RCWMCH) Developmental Screening Tool

The RCWMCH tool (see Appendix I) was designed to identify children aged 9 to 36 months with moderate and severe developmental delay. The items used under the checklists in the age category of 9 and 18 months were directly adapted from The Western Cape Development Screening Tool[18], a validated screening tool for developmental delay in children in South Africa. For the age category of 24 and 36 months, the authors relied on other international screening tools especially the Denver Developmental tool[19], the Molteno Adapted Scales[20] and their clinical experience to select items believed to be discriminatory in the South African population to diagnose developmental delay.

The new tool consisted of six sections of checklist of items to be ticked depending on the closest age category of the child being evaluated. The age categories in the tool are 9, 18, 24 and 36 months. The age categories used at 18 months and below were deliberately chosen to coincide with that of the South African National Immunization Programme schedules. This is to facilitate the optimal use of the screening tool at the same time the children are seen at the clinics for immunizations. The domains evaluated in the tools are Gross Motor, Fine Motor, Communication, and Social with two additional sections for Warning signs and Action taken.

In its clinical use, the healthcare provider is expected to tick the milestones achieved and warning signs observed during the clinic visit. Failure to attain 2 or more milestones on any of the developmental domains and/or presence of 2 or more warning signs will be interpreted as possibility of developmental delay. The administrator is then expected to tick an action taken depending on which domain(s) is/are affected. Children with two or more gross motor delays are referred to Physiotherapy Clinic while those with 2 or more fine motor delays are referred to Occupational Therapy Clinic. Patients with concerns regarding vision are referred to Eye Clinic and those with speech delay are referred for hearing test and speech therapy.

The tool was developed to be a simple and easy to use instrument by any cadre of healthcare worker. It does not involve the use of any special tools or kits and can be

administered in the clinic consulting rooms. The administration is relatively easy as it involves mainly checklist of items to tick which vary between 2 and 8 items per section with most sections having only 3 items to be checked. The tool can be administered relatively quickly within five to ten minutes and thus will be very useful in busy Paediatric HIV clinics.

Bayley Scale of Infant and Toddler Development, third edition (BSID-III)

Bayley Scales was developed in United States of America and standardized for American children. The Scales have undergone three revisions since its initial release in 1969. The latest revision BSID-III was released in 2006 and is regarded as a gold standard for infant assessment.[21]

BSID-III is an individually administered assessment that measures the developmental functioning of infants and children 1 to 42 months old.[21] The instrument presents children with situations and tasks designed to produce an observable set of behavioural responses that are assessed directly on the following scales: Cognitive Scale, Language with Receptive and Expressive Language subscales, and Motor Composite Scale with Fine- and Gross-Motor subscales. The child's parent or primary caregiver completes two additional scales: Social-Emotional and Adaptive Behaviour.

METHOD

The study, a cross-sectional diagnostic accuracy study, was completed between June 2013 and April 2014. It was conducted at the Infectious Diseases Clinic (IDC) located in the Infectious Disease Unit at RCWMCH, a tertiary level hospital affiliated to the University of Cape Town, Cape Town, South Africa. The hospital provides comprehensive multi-disciplinary care to children in Western Cape, South Africa. During clinics, individual counselling and group counselling sessions are conducted by the clinic lay counsellors or clinic social worker. Most of the HIV-infected children are seen at one to three months intervals and all are on antiretroviral therapy (ART).

Study Population

Vertically infected HIV-infected children aged 9 – 36 months attending the IDC were included. Children were excluded from the study if they had been hospitalised and/or

acutely ill within a one month period prior to the potential enrolment date. Their HIV status was confirmed by HIV DNA polymerase chain reaction (PCR) tests if aged less than 18 months and HIV antibody test (rapitest or enzyme linked immunosorbent assay (ELISA) if older than 18 months at the time of HIV diagnosis.

Ethics

Ethical approval for the study was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (HREC REF 133/2013) and the research committee of RCWMCH. Written Informed consent was obtained at commencement of the study from the parents or legal guardians. Children of caregivers who chose not to be part of the study still received the same standard care. If these children were suspected of having developmental delays they were referred to the Developmental Services at the Hospital for formal assessment and appropriate therapy.

Sample size

The sample size was calculated using the appropriate formula designed for diagnostic studies based on expected sensitivity of the new screening tool for a given level of precision and taking into account prevalence of developmental delay in previous studies using the gold standard tool, BSID-III.

Sample size Formula[22]

$$TP + FN = Z^2 \times \frac{SN \times (1 - SN)}{W^2}$$

$$N(sN) = \frac{TP + FN}{P}$$

N (sN) = Sample size, SN = Sensitivity, P = Prevalence, TP=True Positives, FN=False Negatives, W=Accuracy, Z = CI Normal Distribution values (for 95% it is 1.96)

Prevalence, P = 60% based on previous study (for overall developmental delays in HIV positive African children using Bayley Scales)[8] thus P = 0.6, Sensitivity of at least 80% is required for the new RCWCH tool, SN = 0.8, Accuracy of 15% on both sides, W= 0.15, Z for 95% = 1.96

$$TP + FN = (1.96)^2 \times \frac{0.8 \times (1 - 0.8)}{(0.15)^2}$$

$$TP + FN = 27.32$$

$$N = \frac{27.32}{0.6}$$

$$N = 45.5$$

Recruitment and enrolment

Consecutive confirmed HIV-infected children who met the inclusion criteria were recruited into the study. Doctors who routinely consult at the IDC administered the RCWMCH Screening tool and filled the study proforma which collected information on basic demographic data. The doctors were given an orientation on how to properly administer the RCWMCH Developmental Screening Tool in a standardized manner. The time taken by each attending clinician to complete the administration of the screening tool was 4 – 8 minutes.

The Principal Investigator (PI) and a Research Assistant (occupational therapist) conducted the full developmental assessments on all participants. Both were trained and licensed to administer the Bayley Scale of Infant Development, third edition (BSID-III). The PI and Research Assistant were blinded to the outcome of the RCWMCH Screening Tool results. Each full assessment lasted between 45 – 60 minutes. The Bayley record sheet for each subject were pre-numbered with the same study ID number on the study proforma administered to the same subject. Most BSID assessments were administered on the same day as the screening evaluation. Due to a limitation of the number of BSID-III assessments that can be done in one day, some of the full developmental assessments were performed on a later date, within two to four weeks of the screening date.

For the RCWMCH Developmental Screening Tool, failure to have attained 2 or more milestones on any of the developmental domains and/or presence of 2 or more warning signs was interpreted as developmental delay. The BSID-III was administered as stipulated in its manual and recorded in the Record Sheets. The scoring and interpretation of the BSID-III was performed using the Bayley scoring assistant software. Study participants who had borderline or extremely low average scores classification (composite scores less than 70) on 2 or more domains in the BSID-III were diagnosed as having moderate to severe global developmental delay.[21]

Data analysis

Data were entered into statistical software – SPSS 22.0[23] for analysis. The sensitivity, specificity, positive predictive value (PPV), Negative Predictive Value (NPV) of the RCWMCH developmental screening tool compared to BSID-III were calculated using MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium).[24]

RESULTS

The number of children attending the IDC clinic aged 3 years and below during the study period was 925 with an average of 92 children seen monthly. Out of these 88 children were recruited into the study and screened with the new RCWMCH screening tool. 47 had the BSID-III developmental assessments. Children who did not have BSID-III assessments failed to show up on the dates given for assessments despite efforts via phone calls and rescheduling of the assessments dates.

The socio-demographic data of study participants is shown in Table 1. Using the RCWMCH developmental screening tool, 55.3% of study participants were shown to have global developmental delay. The BSID-III developmental assessment confirmed that 29.8% had moderate or severe global developmental delay (Table 2).

The frequency of developmental delay for each of the four developmental domains of both the RCWMCH screening tool and the BSID-III are shown in Table 3 and 4 respectively. The Motor domain (combined gross motor and fine motor) was the domain most frequently delayed with the RCWMCH tool with 26 (54.3%) of the children showing motor delay. This is followed closely by the Communication domain; 20 (42.6%) children had language delay. For the BSID-III, the Motor domain was also the most delayed with 20 (45.2%) having moderate to severe (borderline to extremely low scores) motor delay. It is also followed by the Language domain with 17(36.2%) children having moderate to severe language delay.

The 2X2 table of the RCWMCH screening results with that of the BSID-III is shown in Table 5. Out of the 26 children found to be delayed on the RCWMCH screening, 11 were confirmed delayed on the BSID-III. Conversely, 18 children out of the total 21 who were not delayed on the RCWMCH screening were also confirmed not to have any

developmental delay on the BSID-III. Table 6 shows the diagnostic properties of the RCWMCH screening tool. The tool had a sensitivity of 78.5% and specificity of 54.6%. The positive predictive value was 42.3% and the negative predictive value was 85.7%.

DISCUSSION

The sensitivity of the RCWMCH screening tool was 78.6%. Sensitivity and specificity of 70% to 80% have been deemed acceptable for developmental screening tests.[25] Thus the level of sensitivity of the new screening tool is high enough to be recommended for screening for developmental delay among HIV-infected infants by healthcare providers in busy clinics. The specificity of the tool was low (54.6%). This is due to the design of the tool with high sensitivity being the emphasis and not specificity. The identification of HIV-infected children with possible delays for early intervention is more important especially with the high prevalence of developmental delay in this population of children than exclusion of children who do not need any intervention. The relatively low specificity notwithstanding, the tool should be useful for screening developmental delays among the HIV-infected children.

The positive predictive value of 42.3% for the RCWMCH tool is low but with the high prevalence rate of developmental delay in this population[8], it is important to ensure that no child who could have benefited from intervention is missed. Since the screening is very low-cost and has no risks to the children, it is still worthwhile to screen all children. The high negative predictive value of the RCWMCH tool (87.5%) is reassuring that children who screened negative are highly likely not to have any developmental delay and thus do not require any interventions.

The RCWMCH screening tool compared favourably with another local South African screening tool, the Infant Gross Motor Screening Test (IGMST) which had a very sensitivity of 97.4% and specificity of 85.7% when validated against the motor component of BSID-III.[26]The IGMST was developed for screening for gross motor delay only since the motor domain is the most commonly delayed domain in HIV-infected infants and toddlers. Additionally, the IGMST is suitable only for children aged 18 months and below. Thus the IGMST function as a screening tool is quite limited to only the motor domain and children aged 18 months and below. The new RCWMCH has the

added advantages of screening all the developmental domains and extending the screening to children aged 36 months. The RCWMCH tool also takes into consideration the age bands at which children are likely to be seen at health facilities usually for immunizations. In addition, the age categories on this tool closely reflect the recommended ages by AAP for standardized developmental screening.[11]

This study had some limitations. There was a high drop-out rate due to limited number of children that could have BSID-III assessments per day. Some children were to have the BSID-III assessments at a later date but defaulted. Though the minimum number of children based on sample size was met, a larger sample perhaps could have yielded better results. Further evaluation of the RCWMCH screening tool for more detailed psychometric properties will also be possible in a larger study. The majority of children were Xhosa speaking. During the BSID-III assessments, the assessors had to rely on parents or hospital staff interpretation of children's words and sentences since the BSID-III was available only in English language. This may have a mild effect on the language scores on BSID-III especially for the older age groups of 24 and 36 months who had items that are more discriminatory for expressive language.

In conclusion with the sufficiently high sensitivity of the RWMCH tool from this validation study, it can be considered for rapid screening for moderate to severe global developmental delay among the HIV-infected children. The tool can be used by low cadre health workers at the primary healthcare level. The additional advantages of the RCWMCH tool include ease of use with no need for tools, rapidity of administration without further prolonging consultation time and incorporation of simple recommendation of immediate interventions when screen is positive for developmental delay. This avoids the loss of therapeutic intervention window while the child is awaiting full developmental assessment by more specialised medical personnel. The RCWMCH screening tool may be a valuable instrument in identification of HIV-infected children with high probability of significant developmental delays. These children are likely to benefit from full developmental assessments and early interventional therapies in this vulnerable age-window and may optimise longterm outcomes.

ACKNOWLEDGEMENT This work was supported by grants from the International Society for Infectious Diseases and the Research Committee of School of Child and Adolescent Health, University of Cape Town. We are grateful to the parents, guardians and children at the IDC for being part of the study. We also thank the staff of the IDC for their support during the course of the study.

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Figure 1 Recruitment Flow diagram

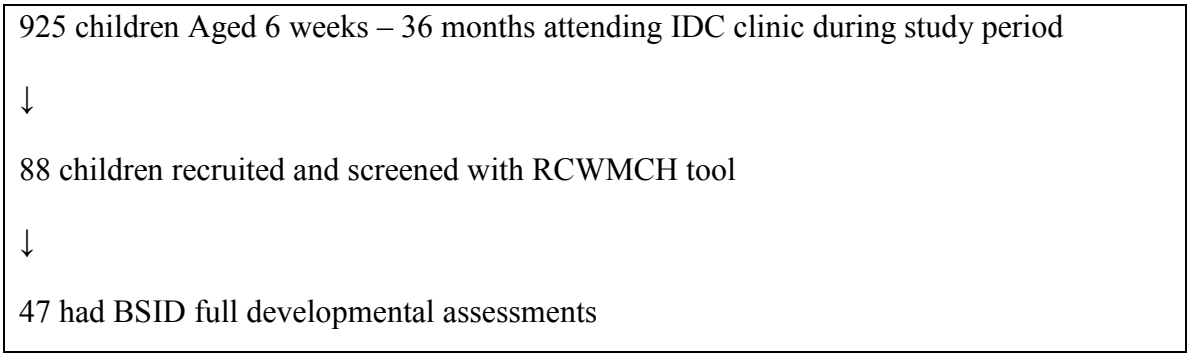

Table 1 Socio-demographic characteristics of study participants

Characteristics	N = 47
Age **(months)**	19.2 ± 9.2
Sex	
Male	22(46.8%)
Female	25(53.2%)
Primary Caregiver	
Mother	41 (87.2%)
Grandmothers	2 (4.3%)
Institution	4 (8.6%)
Mother's level of education	
Tertiary	
Grade 12/Matric	0
Grade 9 - 11	10 (21.3%)
None	13 (27.6%)
Unknown	20 (42.5%)
	2 (4.3%)
Mother's occupation	
unemployed	20 (42.7%)
Unskilled labour	5 (10.5%)
Skilled labour	2 (4.2%)
unknown	19 (40.4%)

Table 2 Prevalence of global developmental delay by RCWMCH screen and BSID-III

	RCWMCH		BSID-III	
	Frequency	Percent	Frequency	Percent
DELAYED	26	55.3	14	29.8
NOT DELAYED	21	44.7	33	70.2
Total	47	100.0	47	100.0

Table 3 Developmental Screen on RCWMCH Screening Tool

	Gross motor	Fine Motor	Communication	Personal-Social
	N (%)	N (%)	N (%)	N (%)
Delayed	17(36.2%)	9 (19.1%)	20 (42.6%)	11(23.4%)
Not delayed	30 (63.8%)	38 (80.9%)	27 (57.4%)	36 (76.6%)
Total	47(100%)	47.0(100%)	47(100%)	47(100%)

Table 4 Developmental Status on the BSID-III

Score Classification	Cognitive N (%)	Motor N (%)	Language N (%)	Socio-emotional N (%)
Very Superior (130 and above)	0	0	0	3 (6.4%)
Superior (120 – 129)	0	1 (2.1%)	0	2(4.2%)
High Average (110–119)	2 (4.3%)	0	0	4 (8.5%)
Average (90 -109)	21(47.7%)	13 (27.7%)	19 (40.4%)	24 (51.1%)
Low Average (80 -89)	0	13 (27.7%)	11 (23.4%)	10 (21.3%)
Borderline (70-79)	2 (4.2%)	11 (23.4%)	11 (23.4%)	4 (8.5%)
Extremely low (69 and below)	9 (19.1%)	9 (19.1%)	6 (12.8%)	0
Total	47 (100%)	47 100%)	47 (100%)	47 (100%)

Table 5 2X2 Table of the RCWCH and the BSID-III

		BSD-III		Total
		DELAYED	NOT DELAYED	
RCWMCH	DELAYED	11	15	26
	NOT DELAYED	3	18	21
Total		14	33	47

Table 6: Diagnostic properties of the RCWMCH screening tool

Sensitivity	78.57 %	95% CI: 49.2% - 95.1%
Specificity	54.55 %	95% CI: 36.4% - 71.9%
Positive Likelihood Ratio	1.73	95% CI: 1.09 - 2.75
Negative Likelihood Ratio	0.39	95% CI: 0.14 - 1.12
Disease prevalence	29.79 %	95% CI: 17.4% - 44.9%
Positive Predictive Value	42.31 %	95% CI: 23.4% - 63.1%
Negative Predictive Value	85.71 %	95% CI: 63.6% - 96.8%

APPENDIX 1

RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL DEVELOPMENTAL SCREENING TOOL

1. Please tick milestones achieved and warning signs observed at clinic visit closest to screening age
2. Please refer patients with 2 or more gross motor item delays/ warning signs to Physiotherapy (local clinic)
3. Please refer all patients with 2 or more fine motor item delays/ warning signs to Occupational Therapy (local clinic)
4. Discuss any patient with concerns regarding vision with ***Eye Clinic:***
   Please refer patients with speech delay for a hearing test as well as Speech Therapy

Age in months	Head Circumference (cm) + percentile on HC chart	GROSS MOTOR	Fine Motor	Communication	Social	**Warning Signs:** ***PLEASE TICK IF PRESENT***	**Action Taken:** ***PLEASE TICK***
9		Crawls ☐ Sits alone ☐ Pulls to stand ☐	Points to objects ☐ Holds small object in each hand ☐	**Babbles:** mamma or dadda without meaning ☐ **Understands** "bye" and "no" ☐ **Waves** bye, shakes head for "no" ☐	Holds and eats biscuit or chips ☐ Stranger anxiety ☐	No head control ☐ Not sitting ☐ Fisting ☐ Hand preference ☐ Persisting Primitive reflexes ☐ Head Circumference <3P or >97P ☐ No visual fixation ☐ Squint ☐ No response to sound ☐	Physio referral ☐ OT referral ☐ Speech referral ☐ Hearing ☐ Vision test ☐

18		Walks alone ☐ Throws a ball ☐ Kicks a ball ☐	Builds a 3-4 cube tower ☐ Holds pen (palmar grasp) and scribbles ☐	6 or 7 clear words ☐ Two word utterences ☐ Points to one Body part ☐	Uses spoon ☐ Pulls socks off ☐ Domestic mimicry ☐	Not walking ☐ No pincer grasp ☐ Unable to understand simple commands ☐ No words ☐	Physio referral ☐ OT referral ☐ Speech referral ☐ Hearing ☐ Vision test ☐

24		Jumps off step – two feet together ☐ Stands on one leg (either) briefly ☐	Tried to copy vertical line ☐ Hand preference usually present ☐	Points to 5 body parts ☐ Uses pronouns –I, You, Me ☐ Combines 3 words ☐	Spoon feeds well ☐ Handles cup very well ☐ Clean and dry by day ☐	Single words or less ☐ Not following simple commands ☐	Physio referral ☐ OT referral ☐ Speech referral ☐ Hearing ☐ Vision test ☐
36		Up stairs ☐ One foot per step Down stairs ☐ Two feet per step	Copies circle, horizontal and vertical lines ☐ Able to complete a simple puzzle (2-3 pieces) ☐	Names 10 pictures 3-digit repetition ☐	Parallel play ☐ Washes and dries hands ☐ Dresses – needs help with buttons ☐ Dry at night ☐	Single words or echolalia ☐ Single words or echolalia ☐	Physio referral ☐ OT referral ☐ Speech referral ☐ Hearing ☐ Vision test ☐

APPENDIX II

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

28 June 2013

HREC REF: 133/2013

Dr G Boyede
c/o Dr K Donald & Prof B Eley
Developmental Paediatrics
Out-Patients Building
Red Cross War Memorial Children's Hospital

Dear Dr Boyede

PROJECT TITLE: THE VALIDATION OF A NEW DEVELOPMENTAL SCREENING TOOL FOR NEURODEVELOPMENTAL DELAYS AMONG HIV-INFECTED SOUTH AFRICAN CHILDREN

Thank you for your response to the Faculty of Health Sciences Human Research Ethics Committee dated 24th June 2013.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 30th June 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

pp T Burgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised

APPENDIX III

Dr TA Blake
Manager: Medical Services
Email: Thomas.Blake@pgwc.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166
2 July 2013

DR G BOYEDE
SCAH
UCT

Dear Dr Boyede,

Your application to do research at the Red Cross War Memorial Children's Hospital has been approved.

I need to remind you that you need to inform the Operational Manager of the area in which you will be working of this.

Yours faithfully,

Signature Removed

DR T A BLAKE
CHAIRPERSON
HOSPITAL RESEARCH REVIEW COMMITTEE
RCWMCH

APPENDIX IV

Instructions for Authors

Aims and Scopes

The *Journal of Child Neurology* (*JCN*) is an interdisciplinary peer-reviewed biomedical journal publishing articles in the fields of child neurology, pediatric neurosurgery, pediatric neuroradiology, child psychiatry, pediatric neuropsychology, developmental and behavior pediatrics, pediatric neuroscience, and developmental neurobiology.

General Instructions

All submissions (including invited material) are subjected to peer review. Authors are invited to submit original articles of all types for consideration. Case reports can be submitted as brief communications. All material must be submitted online at the SAGETRACK ScholarOne website http://mc.manuscriptcentral.com/childneurology. New authors should use the "Create Account: New users click here" button at the submission website. After entering the website, go to the "Corresponding Author Center" to submit manuscripts, using the "Click here to submit a new manuscript" button. Manuscript text and tables must be prepared and submitted only in Microsoft Office Word (MSWord) document format (saved as ".doc" files). Files to be uploaded should be complete final versions of text of the article (including abstract and keywords), tables, and figures (photographs, art work, or line drawings); do not insert existing figures into the MSWord document file. At the completion of the upload of each file, a confirmation window will appear asking for a description of the file (for the main document, use language such as "article text" or "main document"; for figures, indicate a figure number, such as "Figure 1"; and for other supporting materials, indicate clearly what the file is).

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Text

Manuscripts should follow the usual format for scientific articles and articles recently published in JCN (examples can be found at the SAGE Journals Online website http://jcn.sagepub.com/. Authors must assure that manuscripts conform to the style guidelines of the *AMA Manual of Style*. Manuscript pages should be double-spaced and numbered consecutively with the appropriate subheadings used to designate different sections in the following order: title page, abstract, keywords, text, references, tables, and figure legends. Avoid use of any abbreviations or acronyms unless the abbreviation or acronym itself has become a word (e.g., DNA). Only generic names of drugs should be used. Clinical laboratory data (including normal ranges) should be expressed in conventional units rather than SI (Système International) units, although SI units can be provided in parentheses. Authors whose native language is not English must have manuscripts carefully proofread and corrected for proper American English spelling, grammar, and syntax by a professional editor or colleague who is a native English speaker. Authors should retain for their own files at least one complete copy of all material submitted. Additional information on manuscript preparation can be obtained from the website http://www.icmje.org/ or from the following references:

1. *AMA Manual of Style: A Guide for Authors and Editors*. 10th ed. New York, NY: Oxford Press; 2007.
2. Brumback RA. Success at publishing in biomedical journals: hints from a journal editor. *J Child Neurol*. 2009;24:370-378.
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Title page. The title should be brief and meaningful. Following the title, there should be a listing of first and last names of all authors, along with highest academic or medical degrees and affiliations. Authorship should be limited to direct participants. List the complete name, address, telephone number, fax number, and e-mail address for the corresponding author (authors who do not have an e-mail account can obtain one from among the free sites such as "gmail.com," "hotmail.com,"' or "yahoo.com"'). For multi-authored submissions, up to three authors can be designated as "first authors who contributed equally to this work" if the contributions of those individuals essentially constituted the majority of the work on the project. In addition, "mentors who contributed equally to this work" can be used to define a category of authorship for senior investigators, clinicians, or directors who equally provided the support and mentorship necessary for the success of the work. A separate paragraph of "acknowledgements" should identify where the work was done, the meeting, if any, at which the material was presented, and any assistance in writing the manuscript or other help that did not merit authorship (including "ghost authorship"). A separate "declaration of conflicting interests" should describe all potential conflicts of interest or commercial or other financial relationships of the authors and a separate paragraph of "funding" should list all financial support for the studies.

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References. Authors are responsible for correctness and completeness of reference citations. The reference list should be typed double-spaced and begin on a separate page. Reference citations should be arranged according to their order of appearance in the text, and indicated by superscript numbers in the text. References should be typed generally in accordance with the style of the AMA Manual of Style (examples shown below). Only the first four authors should be listed; when there are more than four authors, list only the first three followed by "et al." Abbreviations of journal names should conform to the style in PubMed. Abstracts should be noted as such. Citation of websites should list the complete URL address and the date and month accessed. Sample references are given below.

1. Liptak GS, Bloss JW, Briskin H, et al. The management of children with spinal dysraphism. *J Child Neurol*. 1988;3(1):3-20.
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4. Volpe JJ. *Neurology of the Newborn*. 2nd ed. Philadelphia, PA: WB Saunders; 1987.

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Artwork Submissions

Artwork includes charts and graphs, maps, photographs, line art, and tables with 17 or more columns. Electronic art should be prepared as sharp high-quality computer images with a minimum width of 2100 pixels and saved in uncompressed TIFF and JPEG file formats. Microsoft application files are acceptable for vector art (line art). For all scanned images, line art (black and white) images should be scanned as a bitmap at 900ppi and photos should be scanned as grayscale or CMYK at 300ppi. Graphs should be submitted as figure files and should be finished drawings, not requiring further artwork. All patient identifiers must be removed from pictures of radiographs or other imaging modalities. Recognizable photographs of patients must be accompanied by written permission for publication. Reproduction of any previously published illustration must be accompanied by written permission from both the original author and publisher. Figure legends should include full explanations of the figures and be typewritten double-spaced with numbers corresponding to those on the figure files themselves. Abbreviations appearing in figures must be fully identified in the legend. All figures must be specifically referred to in the text and numbered in order of appearance in the text. Color photographs or illustrations will be published in the online version at no cost to the authors; however publication of color images in the print version will be charged to the author at a cost of $800 for the first figure and $200 for each additional figure.

Tables

Tables should be numbered consecutively corresponding to in-text citation. Each table should be prepared on a separate page at the end of the text document and preferably should be no larger than a single page. Include a brief descriptive title of the table and a footnote with explanation of any abbreviations. All tables must be specifically referred to in the text and numbered in order of appearance in the text.

Conflict of Interest

Authors must disclose any commercial, financial, or other associations that could pose a conflict of interest in connection with their submitted article and these must be disclosed on the title page at the time of submission.

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- ☐ Cover letter describing manuscript; responses to reviewers and all corrections and changes to manuscript detailed for a revision or resubmission.

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- ☐ Title page in main document contains complete and current information for all authors: first (given) and last (family) names, highest degrees earned, institutional affiliations, and e-mail addresses; for all authors, complete postal address, e-mail address, phone number, and fax number also included on title page.

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- ☐ Abbreviations and acronyms eliminated from manuscript text, except those abbreviations or acronyms that have become words themselves (such as DNA); all abbreviations and acronyms used in tables or figures are identified and fully spelled out in legend.

- ☐ Reference citations checked for accuracy, completeness, and proper format; references cited as superscript in text in numerical order, making sure each is cited in sequence in text.

- ☐ Legends for all figures included on separate manuscript page in main document.

- ☐ Each table prepared on separate manuscript page in main document.

- ☐ Figures properly prepared and formatted as sharp high-quality computer images with minimum width of 2100 pixels and saved as uncompressed TIFF or JPEG computer files; payment for printing of color figures arranged with SAGE Publications.

- ☐ Manuscript text file, all figure files, and any associated document files uploaded to SAGETRACK ScholarOne website (http://mc.manuscriptcentral.com/childneurology).

- ☐ Signed informed consent forms (in English) for identifiable patient photographs or previously copyrighted materials uploaded to SAGETRACK ScholarOne website as scanned PDF files or faxed to journal editorial office.

APPENDIX V

The validation of a new developmental screening tool for neurodevelopmental delays among HIV–infected South African children

INFORMATION SHEET AND CONSENT FORM

Dear Parent/Guardian,

Thank you for your time in reading this document. I am Dr Gbemisola Boyede. I am a Masters Student at the University of Cape Town and also a doctor at Red Cross Children's Hospital. I am doing a study titled '**the** v**alidation of a new screening tool for neurodevelopmental delays among HIV –infected South African children'**

What we are doing

We are conducting research on screening tool to help us identify early HIV positive children who have developmental delays. HIV has been known to cause developmental delays among infected children. Children who are identified early will benefit from early treatments that will improve their quality of life in the long-term. However, many children with HIV in our clinics are not being screened because the tools usually needed for the assessment like the Bayleys Scales can only be used by specially trained healthcare workers and also take some time to do. We are conducting a study to see if our new tool is as effective as the well-known Bayleys Scales. If the new tool we are testing is also very effective then it can be useful in the busy clinics for identifying the HIV positive children who have developmental delays without wasting so much time by the health care workers.

Your participation

We are asking you whether you will allow us to assess your child/ward with our new tool and the Bayley Scale. If you agree, we will want your child/ward to have a developmental assessment using the Bayley Scale for approximately one hour.

Please understand that **the participation of your child/ward is voluntary** and they are not being forced to take part in this study. The choice of whether to allow your child/ward to participate or not, is yours alone. If you choose not to allow your child/ward to take part, he/she will not be affected in any way whatsoever. If you agree your ward/child may participate, you may stop him/her from participating in the research at any time and tell me that you don't want to continue. If you do this, there will be no penalties and you will not be prejudiced in any way.

Confidentiality

Any study records that identify your child/ward will be kept confidential to the extent possible by law. The records from your participation may be reviewed only by people responsible for making sure that research is done properly. (All of these people are required to keep your identity confidential.) Otherwise, records that identify you will be available only to people working on the study, unless you give permission for other people to see the records. All identifying information will be kept in a locked file cabinet and will not be available to others. We will refer to you by a code number in any publication.

Risks/discomforts

At the present time, we do not see any risks in your participation. The risks associated with participation in this study are no greater than those encountered in daily life.

Benefits

The immediate benefit to your child/ward from participating in this study is that of having his/her full developmental assessment done at no cost to you. Additionally, this study may be contributory to current knowledge in validating a tool that may become useful in clinical practice in identifying children with HIV who have developmental delays early so they can benefit from early treatments that may improve their quality of life in long-term.

We will give you the report of your child's developmental assessment. If you would like to receive feedback on our study, we will record your phone number on a separate sheet of paper and can send you the results of the study when it is completed.

Who to contact if you have been harmed or have any concerns

If you have concerns or questions about the research you may call me directly on this mobile number 0791150729 or my Supervisor Dr Kirsty Donald on 021 6585535.

If you have any complaints about ethical aspects of the research or feel that you have been harmed in any way by participating in this study, please call the **Faculty of Health Sciences Human Research Ethic Committee**, University of Cape Town on 021 406 6338.

CONSENT

I .....the parent/legal guardian of.....hereby agree for my child/ward to participate in research on the validation of a new screening tool for neurodevelopmental delays among HIV –infected South African children. I understand that I am participating freely and without being forced in any way to do so. I also understand that I can stop participating at any point should I not want to continue and that this decision will not in any way affect me negatively. I understand that this is a research project whose purpose is not necessarily to benefit me or my child personally in the immediate or short term. I understand that my child/ward participation will remain confidential.

……..

Signature of parent/legal guardian **Date**:……..

APPENDIX VI

The validation of a new developmental screening tool for neurodevelopmental delays among HIV–infected South African children

STUDY PROFORMA/DATA SHEET

Study Number ------ Hospital Number ---------- Date of Assessment----------

Interpreter Y/N

A. SOCIO-DEMOGRAPHIC DATA

1. Date of birth ---------- 2. Age in months.....

2. Sex a. male b. Female 4. Age at diagnosis of HIV infection ----------

5. Level of education of parents Father Mother

6. Occupation of parents Father Mother

7. Primary care-giver----------

B. RCWMCH SCREENING TOOL

Domains	Number of unattained milestones/warning signs
Gross motor	
Fine Motor	
Communication	
Personal Social	
Warning Signs	

RCWMCH TOOL Assessment: 1. Delay development 2. No delay development

C. Bayleys Scales Assessment

Domain	Total Raw scores	Composite Scores	Percentile
Cognitive			
Language			
Motor			
Social- Emotional			
Adaptive			

BSID-III Assessment:

APPENDIX VII

STARD checklist for reporting of studies of diagnostic accuracy
(version January 2003)

Section and Topic	**Item #**		**On page #**
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	15,17
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	18
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	21
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	22,23
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	22
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	23
Test methods	7	The reference standard and its rationale.	20,21
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	23
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	23
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	23
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	23
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	23
	13	Methods for calculating test reproducibility, if done.	-
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	21

	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	24, 30 (Table 1)
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	24, 29 (Fig 1)
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	23
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	24, 31 (Table 2)
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	34 (Table 5)
	20	Any adverse events from performing the index tests or the reference standard.	-
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	35 (Table 6)
	22	How indeterminate results, missing data and outliers of the index tests were handled.	23
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	-
	24	Estimates of test reproducibility, if done.	-
DISCUSSION	25	Discuss the clinical applicability of the study findings.	24,25