Protocol Number:	AVXS-101-CL-101 (formerly AVXS-101)
IND Number:	15699
Protocol Title:	Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101
Indication Studied:	Spinal muscular atrophy Type 1
Sponsor Address:	2275 Half Day Road, Suite 160 Bannockburn, IL 60015
Protocol Version/Date:	Version 14.0 / 21 April 2016

The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Confidentiality Statement

1 ADMINISTRATIVE INFORMATION

1.1 Summary of Changes

This version of the protocol reflects the change in sponsorship of the study from Sophia's Cure and NCH to AveXis, Inc. This protocol was prepared utilizing the AveXis, Inc. clinical study protocol template, and combines the latest version of the protocol, version 13.0 dated 10 June 2015 and the Protocol Addendum #2 version 1.0 dated 24 June 2015.

The following table outlines the transfer of protocol sections from the previous NCH version(s) of the protocol template to the current AveXis, Inc. protocol template.

Table 1 Summary of Protocol Section Changes and Additions

NCH		AveXis	
Section #	**Section Title**	**Section #**	**Section Title**
Sections Existing in previous versions of protocol(s)			
1.0	Synopsis	2.0	Synopsis
2.0	Abstract	5	Introduction
3.0	Clinical Trial and Principal Investigator	N/A	N/A
3.2	Rationale for Gene Transfer to SMA Type 1 Patients	5.2	Rationale for Gene Transfer to SMA Type 1 Patients
3.3	Background and Preliminary Data	5.1	Background and Preliminary Data
4.0	Preliminary Data	5.3	Non-clinical Studies
5.0	Research	6	Trial Objectives and Purpose
5.2	Pre-Treatment Assessment	8	Selection and Withdrawal of Subjects
5.3	Dosing Plan	9, 10.5, 10.6	Treatment of Subjects, Administration, Dose Escalation
5.4	Clinical Trial Monitoring Plan	11	Assessments
5.5	Outcome Measures	6 (6.1–6.3)	Trial Objectives and Purpose
5.6	Statistical Analysis	13	Statistics
5.7	Timeline of Assessments	Table 6	Schedule of Assessments
6.0	Dose Limiting Toxicity	11.1.1	Dose Limiting Toxicity
6.1	The classification for adverse events	11.1.1	Dose Limiting Toxicity
6.3	Stopping/Discontinuation Rules	8.3	Subject Withdrawal Criteria
6.4	Dose Escalation	10.6	Dose Escalation
7.0	Adverse Event Monitoring and Reporting	12	Adverse and Serious Adverse Events, Relationship to Study Drug, Recording Adverse Events, Reporting Adverse Events
8.0	Study Reports	N/A	N/A Study reports are a sponsor responsibility, outlined in sponsor SOPs
8.3	Data Safety Monitoring Plan	13	Data Safety Monitoring Board
8.4	Clinical Monitoring of the Study	15.1	Study Monitoring
9.0	References	19	References

NCH		AveXis	
Section #	**Section Title**	**Section #**	**Section Title**
Addendum 1	Autopsy Plan	Appendix 2	Autopsy Plan
New Sections that were not present in previous version(s) of protocol(s)			
N/A	N/A	15.2	Audits and Inspections
N/A	N/A	16	Ethics
N/A	N/A	17	Data Handling and Recordkeeping
N/A	N/A	18	Publication Policy
	N/A	Appendix 1	Declaration of Helsinki
	N/A	Appendix 3	CHOP-INTEND
	N/A	Appendix 4	Bayley Scale of Infant Development, version 3
	N/A	Appendix 5	Gross Motor Skills Checklist
The following sections were overhauled to reflect transition in sponsorship of study, supporting AveXis, Inc., as managing sponsor			
N/A	N/A	12	Adverse and Serious Adverse Events
N/A	N/A	13	Data Safety Monitoring Board

The section below highlights content changes represented in this version of the protocol. Language deleted from the previous version of the protocol appears in *italics*. Language added to the previous version of the protocol appears in **bold**.

Section 6.2: Secondary Objectives

A secondary outcome will include time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for >2 weeks in the absence of an acute reversible illness or (b) death.

Secondary outcomes will also include the change in CHOP-INTEND from baseline score and demonstration of improvement of motor function and muscle strength as determined by achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted. Additionally, AveXis, Inc. may opt to provide videos of the physical exams, CHOP-INTEND assessments, and/or Bayley Scale assessments to an independent, blinded reviewer for confirmation of the development milestones.

Rationale for Change

Achievement of motor milestones will serve as a more clinically meaningfully efficacy endpoint.

Section 6.3: Exploratory Objectives

Exploratory outcome measures will be tested during the study as part of the program and product development plan; however if exploratory measurement results show efficacy and primary outcomes do not reach statistical significance, the only interpretation is that the results show a trend toward benefit but can never supersede primary measures. These exploratory outcome measures will include:

- ACTIVE-mini (Ability Captured Through Interactive Video Evaluation-mini) evaluation of infant movement ability.
- Patient functional measures using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). This test has been studied and validated in infants with spinal muscular atrophy and was found to be reliable in this population.[19]
- Bayley Scales of Infant Development version 3 is a standardized, norm-referenced infant assessment. The gross and fine motor portions of this test will administered if the child reaches or exceeds a score of 60 out of 64 on the CHOP-INTEND.
- Motor neuron function will be assessed via evoked compound motor action potentials (CMAP) and motor unit number estimation (MUNE).
- Pathological status of muscles will be quantified by Electrical Impedance Myography (EIM).
- The age at which significant motor milestones are achieved will be assessed using a standard Motor Milestone Development Survey shown in Table 10 in Section 11.1.10.
- **Compelling, demonstrable, documented evidence of efficacy as determined by changes in functional abilities as captured during videotaping sessions during site visits and/or captured by subject/parent/legal guardian at home.**

Rationale for Change

Determination that "compelling evidence" of efficacy may be documented via video-taped physical therapy sessions, showing motor milestone achievement.

Section 7.1: Overall Study Design

The proposed clinical trial is an open-label, single injection ascending dose study of self-complementary AAV9 carrying the SMN gene under the control of a hybrid CMV enhancer/chicken AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein (arm, leg, or scalp) of Type 1 spinal muscular atrophy subjects.

The primary analysis for efficacy will be assessed when all patients reach 13.6 months of age (a database lock will be performed at the time point at which all patients reach 13.6 months of age). A follow-up safety analysis will be completed at the time point at which the last patient reaches 24 months post-dose.

Rationale for Change

In a natural history study of SMA Type 1 survival,[20] the distribution of the age at reaching the combined endpoint of death or respiratory failure differed by SMN2 copy number. The median age at the combined endpoint for subjects with two (2) SMN2 copies was 10.5 (IQR 8.1-13.6). Therefore, 13.6 months is the expected age at which 75% of SMA Type 1 patients with two (2) SMN2 copies will have met the endpoint of death and/or respiratory failure.

The following are procedures that are being conducted for study purposes, but were not described/outlined as appropriate in previous versions of the protocol(s):

Section 8.1 Inclusion Criteria

Subjects must meet all of the following Inclusion Criteria:

1. Six months of age and younger[1] at day of vector infusion with Type 1 SMA as defined by the following features:
   a. Bi-allelic SMN1 gene mutations (deletion or point mutation) with two copies of SMN2 (no more and no fewer).
   b. Patients 6 months and younger with a disease onset up to 6 months of age
   c. Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints.

[1] First nine subjects enrolled under previous version(s) of the protocol could be nine months of age or younger. Inclusion revised to reflect six months of age or younger in 24 Jun 2015 Protocol Addendum #2.

Initial genetic testing and diagnosis completed at an institution/laboratory other than Nationwide Children's Hospital/Ohio State University is acceptable if proper documentation is received at Nationwide Children's Hospital, verified by the PI, and filed in the patient's medical record.

AveXis, Inc. may opt to confirm all genetic diagnoses through a contracted third-party laboratory utilizing an additional blood sample collected during a post-dose visit.

Rationale for Change

For clarification purposes, added notation that baseline diagnostic genetic testing was not completed at Nationwide Children's Hospital in all cases. As noted, AveXis, Inc. may opt to have baseline blood samples for all subjects re-tested at a commercial laboratory to ensure consistent results for all subjects in the trial. As these samples would be run after enrollment/dosing was complete, results would not impact subject eligibility.

Section 11.8.1 CHOP-INTEND

CHOP-INTEND including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions. Anti-gravity movements in assisted rolling, ventral suspension, and supported standing are also measured. **See Appendix 3.**

At such time that a subject achieves two consecutive CHOP-INTEND scores of ≥62, a teleconference will be conducted between PI, physical therapist, and AveXis, Inc. to review the subject status and determine whether or not continued CHOP-INTEND assessments are necessary. A decision will be reached and confirmed in writing following the teleconference. If decided that no further assessments are necessary, the physical therapist will cease completion of the CHOP-INTEND assessment at subsequent visits; otherwise CHOP-INTEND assessments will continue monthly.

CHOP-INTEND examinations will be videotaped in accord with the Videotaping Manual.

Rationale for Change:

As patients on a normal development course age, CHOP-INTEND scores decrease over time as there are portions of the assessment that are specific to infant development. As patients develop out of infancy, they no longer exhibit some motor functions in an appropriate way for some of the assessment sections to be scored. As study subjects achieve a score of 64, more in line with a

normal development course, it would be inappropriate to continue with the CHOP-INTEND for the same reason.

Section 11.8.2 Bayley Scale of Infant Development version 3

Bayley Scales of Infant Development version 3 is a standardized, norm-referenced infant assessment. The gross and fine motor portions and cognition portions of this test will administered if the child reaches or exceeds a score of 60 out of 64 on the CHOP-INTEND. The gross and fine motor portion will be completed monthly during the first year and the cognition portion will be completed every three months. During the second year all required portions of the Bayley Scale will be conducted every three months, except for subjects still being seen monthly for CHOP-INTEND assessments. For those subjects the gross and fine motor and cognition portions will be administered as in Year 1. See Appendix 4.

Bayley scales examinations will be videotaped in accord with the Videotaping Manual.

Section 11.9 Development Milestones Checklist

The age at which significant motor milestones are achieved will be assessed using a standard Motor Milestone Development Survey shown in Table 10 and a Gross Motor Skills Checklist shown in Appendix 5**. The Gross Motor Skills Checklist was designed by physical therapists at Nationwide Children's Hospital specifically to assess SMA Type 1 subjects in this trial; it is source from a collection of existing motor assessments. See Appendix 5.**

Additionally, CHOP-INTEND and Bayley physical therapy assessment videos may be transferred to a centralized reviewer for independent determination of milestones achieved.

Rationale for Change

The Gross Motor Skills Checklist was developed as an assessment and added to the protocol as a method by which to evaluate subjects achieving a maximum CHOP-INTEND score of 64.

Section 11.10 Video Evidence

Physical therapy assessments and physician physical examinations required at each study visit will be videotaped in an effort to produce compelling, demonstrable, documented evidence of efficacy as determined by changes in functional abilities. Parent(s)/legal guardian(s) may also share home videos demonstrating achievement of functional abilities. AveXis, Inc. will provide a secure and confidential upload process for transfer and storage of the videos from NCH to a contracted third-party vendor that will compile and arrange videos as per AveXis, Inc. submission requirements. Any/all videos received at AveXis, Inc. or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis, Inc. AveXis, Inc. and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies and/or the medical community.

Videos will be provided in a blinded fashion to an independent, centralized reviewer for unbiased assessment of milestone achievement.

Section 11.18 Photographs of Infusion Site

Photographs will be taken of the infusion site at the time points specified in Table 6. AveXis, Inc. will provide a secure and confidential upload process for transfer and storage of the photographs from NCH to a contracted third-party vendor that will compile and arrange photographs as per AveXis, Inc. submission requirements. Any/all photographs received at AveXis, Inc. or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis, Inc. AveXis, Inc. and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families in the photographs, which may be shared with regulatory agencies and/or the medical community.

Section 11.19.11 Saliva, Urine, Stool Collection

Saliva, urine, and stool samples will be collected for viral shedding studies. Saliva will be collected from the patient's mouth with a pipette and oral swab. 200–500 µL of urine will be collected from patients' soiled diapers by soaking a cotton ball. Pea-sized fecal samples will be collected from patients' soiled diapers. Each of these samples will be placed in a DNAse/RNAse-free Eppendorf tube with locking top. The tubes will be stored in a -80°C freezer.

Rationale for Change

Saliva, urine, and stool samples will be collected to study viral shedding.

1.2 Contact Information

Table 2 Important Study Contact Information

Role in Study	Name	Address and Telephone number
Clinical Study Leader	Courtney Wells, AveXis Director, Clinical Trials Management - Clinical Operations	2275 Half Day Road, Suite 160 Bannockburn, IL 60015 Office: (847) 572-8405 Mobile: (773) 818-2111 cwells@avexis.com
Responsible Physician	Doug Sproule, MD, AveXis Vice President, Clinical Development	2275 Half Day Road, Suite 160 Bannockburn, IL 60015 Office: (847) 572-8406 Mobile: (978) 505-2524 dsproule@avexis.com

Role in Study	Name	Address and Telephone number
Drug Safety Physician NCH Safety Monitor	Gloria Galloway, MD	OSU Safety Monitor Ohio State University 395 W 12th Avenue Columbus, OH 43210 Office: (614) 293-4969 Mobile: (614) 937-2417 Galloway.58@osu.edu
24-Hour Emergency Contact	Jerry Mendell, MD Samiah Al-Zaidy, MD	NCH 700 Children's Drive- WA 3011 Columbus, OH 43205 Mendell: (614) 355-5247 Al-Zaidy: (614) 355-3682
SAE Reporting	AveXis	safetyreporting@avexis.com FAX: (847) 510-0775
CRO Project Manager	Toni Miller, Sr. Project Manager, Novella Clinical	1700 Perimeter Park Drive Morrisville, NC 27560, United States Office: 919-972-7391 Mobile: 765-481-6257 tmiller@novellaclinical.com

Table 3: Study Vendor Listing

Role in Study	Name	Address
Clinical Research Organization	Novella	1700 Perimeter Park Drive Morrisville, NC 27560
Video	Video 1 Productions	1820 W. Webster Ave., Ste. 201 Chicago, IL 60614
Central Laboratory- confirmatory genetic testing	Q^2 Solutions	200 Forest Street, Suite 200 Marlborough, MA 01752 USA
Autopsy	Regional Pathology and Autopsy Services, Inc.	Oakland, CA 877-330-7727

2 SYNOPSIS

Name of Sponsor/Company: AveXis, Inc.	
Name of Investigational Product: AVXS-101	
Name of Active Ingredient: Survival Motor Neuron Gene by Self-Complementary AAV9	
Title of Study: Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101	
Study center(s): Nationwide Children's Hospital	
Principal Investigator: Jerry Mendell, MD	
Studied period (years): Estimated date first patient enrolled: May 2014 Estimated date last patient completed: Jan 2017	**Phase of development:** 1

Objectives:

Primary:

- Determination of safety based on the development of unacceptable toxicity: defined as the occurrence of any one Grade III or higher, unanticipated, treatment-related toxicity.

Secondary:

- The time from birth until death or until patient requires at least 16-hour per day of ventilation support for breathing for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative use.

Methodology:

Open-label, dose-escalation clinical trial of AVXS-101 injected intravenously through a peripheral limb vein. Short-term safety will be evaluated over a two year period. Patients will be tested at baseline and return for follow up visits on days 7, 14, 21, 30, followed by once every month through 12 months post dose, and then every three months through two (2) years post infusion. Unscheduled visits may occur if the PI determines that they are necessary.

The primary analysis for efficacy will be assessed when all patients reach 13.6 months of age (a database lock will be performed at the time point at which all patients reach 13.6 months of age). A follow-up safety analysis will be completed at the time point at which the last patient reaches 24 months post-dose.

Upon completion of the 2-year study period, patients will be monitored annually as per standard of care for up to 15 years.

Number of patients (planned): 15

Diagnosis and main criteria for inclusion:

Inclusion Criteria

- Six months of age and younger at day of vector infusion with Type 1 SMA as defined by the following features:

- Diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and 2 copies of SMN2.
- Onset of disease at birth: up to 6 months of age.
- Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints

Exclusion Criteria

- Active viral infection (includes HIV or serology positive for hepatitis B or C)
- Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry <95% saturation at the screening visit.
    - Patients may be managed using non-invasive ventilator support (BiPAP) for less than 16 hours per day at the discretion of their physician or study staff.
- Concomitant illness that in the opinion of the PI creates unnecessary risks for gene transfer
- Concomitant use of any of the following drugs: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the trial (eg, corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab)
- Patients with Anti-AAV9 antibody titers >1:50 as determined by ELISA binding immunoassay.
- Abnormal laboratory values considered to be clinically significant (GGT >3 X ULN, Bilirubin ≥3.0 mg/dL , Creatinine ≥1.8 mg/dL, Hgb <8 or >18 g/Dl; WBC >20,000 per cmm)
- Participation in recent SMA treatment clinical trial that in the opinion of the PI creates unnecessary risks for gene transfer.
- Family does not want to disclose patient's study participation with primary care physician and other medical providers.
- Patient with signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding.
- Patients with a single base substitution in SMN2 (c.859G>C in exon 7) will be excluded based on predicted mild phenotype.

Investigational product, dosage and mode of administration:

Cohort 1 will consist of three (3) SMA patients followed by Cohort 2A with a minimum of three (3) and no more than six (6) SMA patients to receive a single infusion at escalating doses.

- Cohort 1 (Low Dose): 6.7×10^{13} vg/kg (n=3)
- Cohort 2A (Intermediate Dose): 2.0×10^{14} vg/kg ($n \geq 3$ and $n \leq 6$)

Cohort 2B and Cohort 3 will each consist of three (3) SMA patients to receive a single infusion at escalating doses.

- Cohort 2B: 2.0×10^{14} vg/kg (n=3)
- Cohort 3 (High Dose): 3.3×10^{14} vg/kg (n=3)

Cohort 2B will be done first and if efficacy is favorable but does not fully improve subjects to normal, Cohort 3 at high dose will be implemented.

Treatment of Cohort 3 is permitted based on safety assessment presented in the IND. A score of 8 or higher on the Bayley Scales of Infant Development will be considered the low end of normal.

Duration of treatment: The vector will be delivered approximately in 10–20 mL/kg of normal saline infused approximately for 60 minutes.

Reference therapy, dosage and mode of administration: N/A

Criteria for evaluation:

Safety:

- Incidence of Grade III or higher, unanticipated, treatment-related toxicity.

Efficacy:

- Time to death or until patient requires at least 16-hour per day of ventilation support for breathing for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative use
- A successful measure for efficacy for this study will be 50% of SMA Type 1 subjects living independently of 16 or more hours of ventilator support at 2 years.
- Change in CHOP-INTEND from baseline measure score of age.
- To determine efficacy by demonstrating improvement of motor function and muscle strength as determined by achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted. Additionally, AveXis, Inc. may opt to provide videos of the physical exams, CHOP-INTEND assessments, and/or Bayley Scale assessments to an independent, blinded reviewer

Statistical methods: This is a Phase I trial, with safety as the primary measure. Sample size was not determined through statistical justification.

3 TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1 ADMINISTRATIVE INFORMATION 2
1.1 Summary of Changes 2
1.2 Contact Information 7
2 SYNOPSIS 9
3 TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 12
TABLE OF CONTENTS 12
LIST OF TABLES 15
LIST OF FIGURES 15
4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 16
5 INTRODUCTION 18
5.1 Background and Preliminary Data 18
5.2 Rationale for Gene Transfer to SMA Type 1 Patients 18
5.3 Non-Clinical Studies 21
6 TRIAL OBJECTIVES AND PURPOSE 24
6.1 Primary Objective 24
6.2 Secondary Objectives 24
6.3 Exploratory Objectives 24
7 INVESTIGATIONAL PLAN 25
7.1 Overall Study Design 25
7.2 Number of Subjects 25
7.3 Treatment Assignment 26
7.4 Criteria for Study Termination 26
8 SELECTION AND WITHDRAWAL OF SUBJECTS 30
8.1 Subject Inclusion Criteria 30
8.2 Subject Exclusion Criteria 30
8.3 Subject Withdrawal Criteria 31
9 TREATMENT OF SUBJECTS 31
9.1 Description of Study Drug 31
9.2 Concomitant Medications 32
9.2.1 Prophylactic Administration of Prednisolone 32
9.2.2 Prohibited Medications 33
10 STUDY DRUG MATERIALS AND MANAGEMENT 33
10.1 Study Drug 33
10.2 Study Drug Packaging and Labeling 33
10.3 Study Drug Storage 33
10.4 Study Drug Preparation 33

10.5 Administration 35
10.6 Dose Escalation....35
10.7 Study Drug Accountability 36
10.8 Study Drug Handling and Disposal 36
11 ASSESSMENTS....36
11.1 Safety Parameters....36
11.1.1 Dose Limiting Toxicity....36
11.1.2 Discontinuation Rules....37
11.2 Demographic/Medical History....37
11.3 Vital Signs....37
11.4 Pulse Oximetry....37
11.5 Weight and Height 37
11.6 Physical Examination....37
11.7 Vaccination Recommendations 38
11.8 Physical Therapy Assessments 38
11.8.1 CHOP-INTEND....38
11.8.2 Bayley Scale of Infant Development version 3 38
11.9 Development Milestones Checklists....38
11.10 Video Evidence....39
11.11 ACTIVE-mini 39
11.12 Electrophysiology Assessments....39
11.12.1 EIM 39
11.12.2 CMAP 40
11.12.3 MUNE....40
11.13 Chest X-ray 40
11.14 Swallowing Test....40
11.15 Echocardiography 40
11.16 Electrocardiogram (ECG) 40
11.17 Pulmonary Assessment 40
11.18 Photographs of Infusion Site....40
11.19 Laboratory Assessments 41
11.19.1 Hematology....42
11.19.2 Blood Chemistry 42
11.19.3 Urinalysis 42
11.19.4 Coagulation Studies 43
11.19.5 Capillary Blood Gas....43
11.19.6 Virus Serology 43
11.19.7 Research Immunology Blood 43

11.19.8 Baseline Screening of Mother....43
11.19.9 IFN-γ ELISpots....43
11.19.10 Research Blood Sample....43
11.19.11 Saliva, Urine, and Stool Collection....43
12 ADVERSE AND SERIOUS ADVERSE EVENTS....44
12.1 Definition of Adverse Events....44
12.1.1 Adverse Event (AE)....44
12.1.2 Serious Adverse Event (SAE)....44
12.1.3 Other Adverse Event (OAE)....44
12.2 Relationship to Study Drug....44
12.3 Recording Adverse Events....45
12.4 Reporting Adverse Events....45
13 DATA SAFETY MONITORING BOARD....46
13.1 DSMB Reporting and Meetings....46
13.2 DSMB Membership....47
14 STATISTICS....47
15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS....48
15.1 Study Monitoring....48
15.2 Audits and Inspections....48
15.3 Institutional Review Board (IRB)....48
15.4 Quality Control and Quality Assurance....48
16 ETHICS....49
16.1 Ethics Review....49
16.2 Ethical Conduct of the Study....49
16.3 Written Informed Consent....49
17 DATA HANDLING AND RECORDKEEPING....49
17.1 Electronic Case Report Forms....49
17.2 Inspection of Records....50
17.3 Retention of Records....50
17.4 Retention of Samples....50
18 PUBLICATION POLICY....50
19 LIST OF REFERENCES....52
20 APPENDICES....54
Appendix 1 Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects....54
Appendix 2 Autopsy Plan....60
Appendix 3 Chop-intend....61
Appendix 4 Bayley Scale of Infant Development version 3: Gross and Fine Motor Skills Subparts and Speech and cognition subparts....65

Appendix 5 Gross Motor Skills Checklist 81

LIST OF TABLES

Table 1 Summary of Protocol Section Changes and Additions 2
Table 2 Important Study Contact Information 7
Table 3: Study Vendor Listing 8
Table 4 Abbreviations and Specialist Terms 16
Table 5 Spinal Muscular Atrophy Classification 19
Table 6 Schedule of Assessments 28
Table 7 Investigational Product 32
Table 8 Total Dose 34
Table 9 Adverse Event Classification 37
Table 10 Motor Milestone Development Survey 38
Table 11 Total Blood Volume 41
Table 12 Tissue Samples for Analysis 60

LIST OF FIGURES

Figure 1 Kaplan-Meier survival curves and survival probabilities for SMA Type 1, 2, and 3 20
Figure 2 Study results, including staining of transduced spinal motor neurons, SMN expression levels, righting ability, and weight and survival curves 22
Figure 3 Body mass of treated and control mice showed no difference 23
Figure 4 Study Design 27

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 4 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
ACTIVE	Ability Captured Through Interactive Video Evaluation
AE	Adverse event
Alk Phos	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BiPAP	Non-invasive Positive Pressure Ventilator
BUN	Blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CK	Creatine kinase
CMAP	Compound Muscle Action Potentials
cmm	Cubic millimeter
DLT	Dose Limiting Toxicity
DRP	DNAse-Resistant Particle. Titer is based off the original certificate of analysis
DSMB	Data Safety Monitoring Board
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EIM	Electrical Impedance Myography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
mo	months

Abbreviation or Specialist Term	Definition
MUNE	Motor Unit Number Estimation
NHP	Non-human primate
OAE	Other significant adverse event
PI	Principal Investigator. The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
SAE	Serious adverse event
scAAV	Self-complimentary adeno-associated virus
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
WT	Wild type. Wild type mice are those not affected with SMA.
yo	Years old

5 INTRODUCTION

This is the first clinical gene therapy trial for spinal muscular atrophy (SMA). The SMN gene will be transferred using self-complementary adeno-associated virus (scAAV) type 9 under control of the chicken-β-actin hybrid promoter. Pre-clinical studies have demonstrated survival of the SMN-Δ7 mouse model for SMA from a median of 15.5 days to over 1 year, following intravenous delivery to the facial vein. This clinical trial is an open-label, single injection ascending dose study in which AVXS-101 will be delivered one-time through a venous catheter inserted into a peripheral vein (arm, leg, or scalp) in SMA Type 1 subjects with 2 copies of SMN2.

5.1 Background and Preliminary Data

Spinal muscular atrophy is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (SMN1) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. SMA is an autosomal recessive, early childhood disease with an incidence of 1:11,000 live births.[14] SMA is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of SMN2. In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis by 6 months of age and then death due to respiratory failure by age two. SMA Type 1 is the leading genetic cause of infant death. Motor neuron loss in SMA Type 1 is profound in the early postnatal period (or may even start in the pre-natal period), whereas motor neurons in Type 2 and 3 SMA patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early postnatal periods.[10,11,12] From a clinical perspective, these findings emphasize the importance of targeting the SMA Type 1 group for gene transfer of SMN2 in hopes of rescuing neurons at this critical stage. Our goal is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and prolonged survival as seen in SMA Type 2 and 3 patients.

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN levels. These include deacetylase inhibitors, such as, valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the SMN2 promoter, resulting in increased full-length SMN protein in SMA animal models.[15-16] However, clinical trials employing several of these agents, most notably phenylbutyrate, valporic acid, and hydroxyurea, have not resulted in clinical benefit (www.ClinicalTrials.gov, and Darbar, et al[17]). A dose escalation trial of scAAV9.CB.SMN will provide information for the potential gene transfer has in treating Type 1 SMA patients and will hopefully show promise for success in modifying the disease prognosis. This will be a dose escalation study that includes 15 Type 1 patients with 2 copies of SMN2.

5.2 Rationale for Gene Transfer to SMA Type 1 Patients

We have chosen Spinal Muscular Atrophy (SMA) Type 1 as the target for this gene therapy study. We believe there is a strong rationale for this based on studies of the natural history of this disease. The classification of SMA is shown below (Table 5); Type 0 to Type 4 SMA is described. SMA is conventionally classified into four phenotypes on the basis of age of onset

and highest motor function achieved, with an additional phenotype (type 0) to describe the severe forms of antenatal-onset spinal muscular atrophy.[1,2]

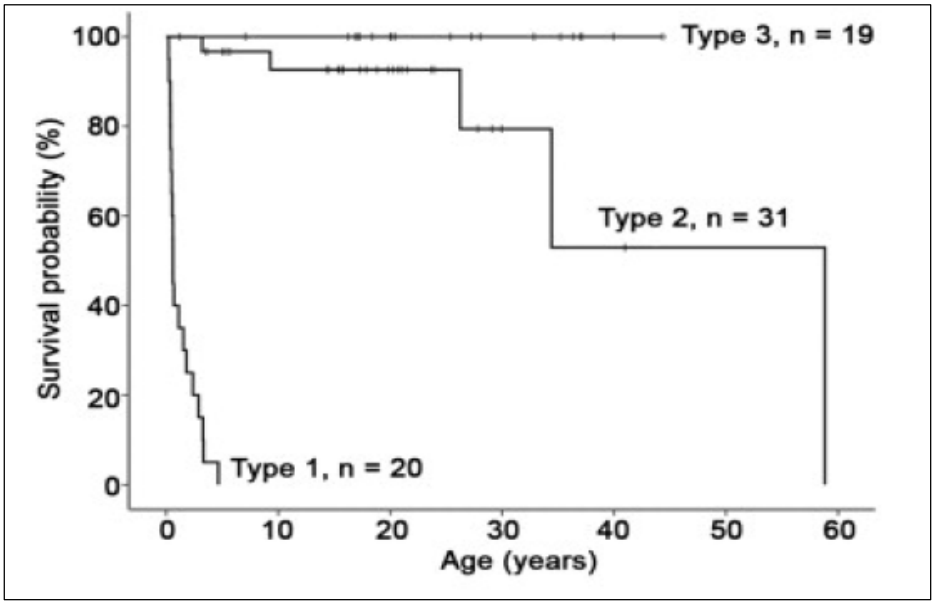
Table 5 Spinal Muscular Atrophy Classification

Type	Age at Onset	Highest Function	Natural Age at Death	*SMN2* No.
0	Prenatal	Respiratory support	<1 mo	1
1	0–6 mo	Never sit	<2 y	2
2	<18 mo	Never stand	>2 y	3, 4
3	>18 mo	Stand alone	Adult	
3a	18 mo–3 y	Stand alone	Adult	3, 4
3b	>3 y	Stand alone	Adult	4
4	>21 y	Stand alone	Adult	4–8

SMA Type 1 patients by definition never attain independent sitting and have hypotonia within the first 6 months of life. SMA Type 1 is the leading genetic cause of infant death. In contrast, SMA Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. SMA Type 3 patients attain the ability to walk unaided [Type 3a have onset <3yo; Type 3b have onset >3 yo]. SMA Type 4 is an adult onset disease. The genetic cause for SMA is well established and is intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by mutations of the survival motor neuron 1 (SMN1) gene. Humans also carry a second nearly identical copy of the SMN1 gene called SMN2.[3] Both the SMN1 and SMN2 genes express SMN protein, however, the amount of functional full-length protein produced by SMN2 is much less (by 10-15%) than that produced by SMN1.[3-5] Although SMN2 cannot completely compensate for the loss of the SMN1 gene, patients with milder forms of SMA generally have higher SMN2 copy numbers.[6-7] Quantitative analysis of SMN2 copies in 375 patients with Type 1, Type 2, or Type 3 SMA showed a significant correlation between SMN2 copy number and SMA type, as well as, duration of survival. 80% of patients with Type 1 SMA carry one or two SMN2 copies, 82% of patients with Type 2 SMA carry three SMN2 copies, and 96% of patients with Type 3 SMA carry three or four SMN2 copies.[8] Among 113 patients with Type 1 SMA, 9 with one SMN2 copy lived <11 months, 88/94 with two SMN2 copies lived <21 months, and 8/10 with three SMN2 copies lived 33–66 months. Even more refined data, describing this relationship, has been generated and has also influenced our choice of the study target group. The median survival for patients with SMA Type 1 is 7.4 months with the age of onset being the most predictive factor in survival.[9]

The severity of SMA type 1 is unequivocally demonstrated by prognosis as illustrated in Kaplan-Meier survival curves shown in Figure 1.

Figure 1 **Kaplan-Meier survival curves and survival probabilities for SMA Type 1, 2, and 3**



In Figure 1, the relative stability of the clinical course of SMA Types 2 and 3 is dramatically illustrated. Perhaps most importantly these findings show that outcome differences are related to the number of SMN2 copies that enable motor neurons to adapt and compensate during the growth of the child and persist into adult life. This contrasts with SMA Type 1 where motor neuron loss is profound in the early postnatal period (or may even start in the pre-natal period, especially for SMA Type 1 patients presenting in first three months of life). The findings in Figure 1 confirm other pieces of evidence from neurophysiological studies and animal studies that also show early loss of motor neurons in the embryonic and early postnatal periods.[10,11,12] From a clinical trials perspective these findings emphasize the importance of targeting SMA Type 1 for gene transfer of SMN2 in hopes of rescuing neurons at this critical stage. Ultimately, the goal is to modify the SMA Type 1 phenotype leading to a milder course and prolonged survival, as we see in SMA Type 2 or 3 patients.

These findings more clearly provide the rationale for a clinical gene transfer trial in the younger patients making it more difficult to justify even Phase I safety trials in older (SMA Type 2 or 3) subjects. Based upon what we know about the natural history of SMA, gene transfer in the older, less severe SMA types (2, 3, and 4), is less likely to have a significant, clinical effect than it would in the younger Type 1 patients. Since the motor neuron pool is stable in older patients due to higher copy number of SMN2, asking Type 2, 3, or 4 patients to undergo safety trials with possibly only minimal benefit is highly unreasonable. It is much more appropriate and safe to prove tolerability in the younger SMA Type 1 group, in which death is the unequivocal outcome. Also, the poor prognosis of the SMA Type 1 patients, who only have 2 copies of SMN2, warrants the rescue of their lives as our top priority at this time.

Factors other than risk-benefit discourage Phase I trials in older SMA patients. The gene transfer viral dose for older patients, which is based on body weight, is much greater than what would be needed for an infant. Not only does this add significantly to the cost of the clinical trial, in some

cases, it could exceed the capacity of the vector manufacturing facility. These added costs, in addition to an increased risk prior to an established proof of principle provide a clear rationale for treating the younger Type 1 patients who have only 2 copies of SMN2. Also present is the issue of a greater chance of encountering pre-existing immunity to AAV in these older, Type 2 and 3 patients.

We also have good reason to believe that there are very few safety issues to be concerned about when targeting the SMA Type 1 group for this clinical gene therapy trial. Overexpression of SMN has been shown to be well tolerated in both mice and non-human primates, and in humans high copy number of SMN2 poses no risk (as seen in Type 2, 3, and 4 patients who have high SMN2 copy number). This allows us to utilize robust, ubiquitous expression systems (like the CB-promoter) to ensure sustained, high-level SMN expression. Additionally, it is important to point out that recombinant scAAV can be employed for this trial because of the small size of the SMN gene. This enables efficient packaging and allows for efficient gene transfer with lower viral titers (a safety consideration), compared with prototypical single-stranded AAV vectors.

Our recent studies using scAAV9.CB.SMN show a robust postnatal rescue of SMA mice with correction of motor function, neuromuscular electrophysiology and survival after a onetime delivery of vector.[13] Intravenous scAAV9 is able to transduce neurons, muscle and vascular endothelium, all of which have been proposed as target cells for SMA treatment.

Taken altogether, our preclinical efficacy and toxicology studies in mice and non-human primates have increased our confidence that our Phase Ib trial will be safe and will have a high potential for success in treating this devastating disease.

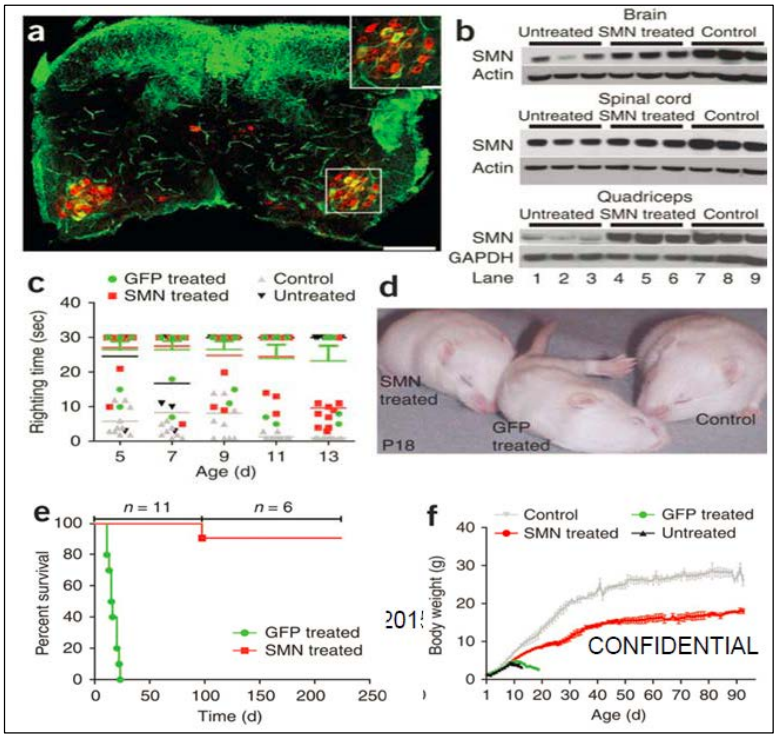
5.3 Non-Clinical Studies

A mouse model was developed by the Arthur Burghes Laboratory after a generation of multiple variants. It was found that the double transgenic, referred to as the SMN-Δ7 mouse, provided the most suitable model to study gene transfer.[18] Studies performed in the Kaspar laboratory have shown that injecting 5 X 10^{11} viral genomes of scAAV9.CB.SMN into the facial vein on day 1 old mice rescues the SMN-Δ7 mouse model.[13] Figure 2 shows the results of these studies, including staining of transduced spinal motor neurons, SMN expression levels, righting ability, and weight and survival curves. Approximately 42 ± 2% of lumbar spinal motor neurons were transduced in scAAV9.CB.SMN treated mice. SMN levels were increased as well, in brain, spinal cord, and muscle of scAAV9.CB.SMN-treated animals, compared to untreated SMA mice (although lower than WT controls). SMA animals treated with either scAAV9.CB.SMN or scAAV9.CB.GFP on P1 were assessed for their righting ability and were compared to WT control mice and untreated mice. WT controls could right themselves quickly, whereas the SMN- and GFP-treated SMA animals showed difficulty at P5. However, by P13, 90% of SMN-treated animals could right themselves compared with 20% of GFP-treated controls and 0% of untreated SMA animals. At P18, SMN-treated animals were larger than GFP-treated animals, but smaller than WT controls. Locomotive ability of the SMN-treated mice was nearly identical to WT controls, as assayed by open field testing and wheel running.

Survival of SMN-treated SMA animals compared with GFP-treated SMA animals was significantly improved. No GFP-treated control animals survived past P22 and had a median life span of 15.5 days. The weights of GFP mice peaked at P10 and then precipitously declined until death, while SMN mice showed a steady weight gain until around P40 with it stabilizing at 17g

(about half the weight of WT controls). The smaller size of corrected animals is likely related to the tropism and incomplete transduction of scAAV9, resulting in a 'chimeric' animal in which some cells were not transduced. Additionally, the smaller size suggests an embryonic role for SMN. Most remarkably, SMN-treated mice survived well past 250 days of age.

Figure 2 Study results, including staining of transduced spinal motor neurons, SMN expression levels, righting ability, and weight and survival curves



a) Shows transduced motor neurons in lumbar spinal cord

b) Western Blots of SMN expression in CNS and muscle

c) Improved righting ability of SMN-treated- similar to WT controls by P13

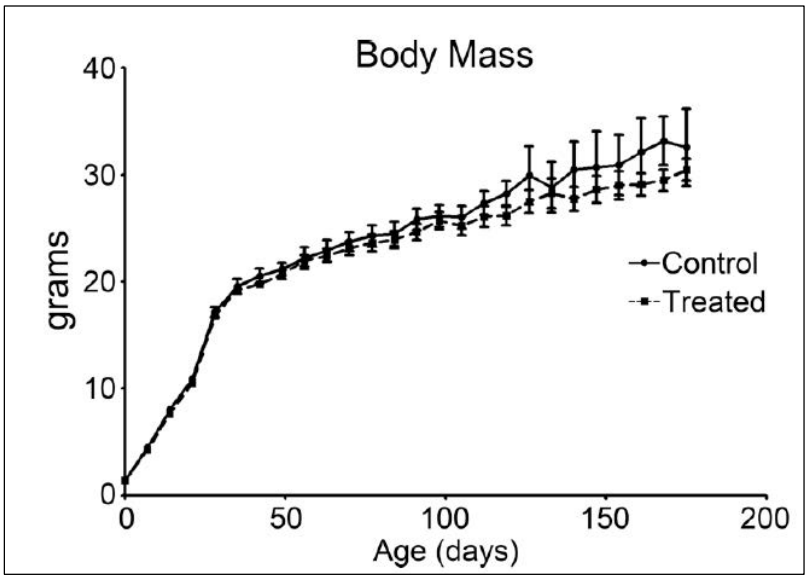
d) SMN- treated are larger than GFP-treated at P18

e) Survival of SMN-treated markedly improved compared to GFP- treated

f) Body weight increased in SMN-treated vs GFP

Toxicology biodistribution studies were generated by the Kaspar laboratory. In the non-GLP studies, 24 mice and 4 non-human primates (NHPs) were injected, by way of vascular delivery, with scAAV9.CB.SMN. To assess toxicity and safety scAAV9.CB.SMN was injected into P1 wild type FVB mice with either vehicle (PBS) (3 males/6 females) or 3.3 x 10^{14} vg/kg of scAAV9.CB.SMN (6 males/9 females) via the facial temporal vein. This dose was previously shown to be most efficacious in the Δ7 mouse model of SMA16. P1 mice were used in anticipation of simulating potential clinical studies in infants, which is the planned population for the first-in-human clinical trial. All mice survived the injection procedure and the initial 24-hour observation period without any signs of distress or weight loss. Body mass was measured and hands-on observations were performed weekly for the remainder of the study; neither revealed any difference between control and treated cohorts (Figure 3).

Figure 3 Body mass of treated and control mice showed no difference



At 60, 90 and 180 days post-injection, blood from the mice was collected for hematology studies and clinical chemistries assessment (ALT, AST, ALK Phos, creatinine, BUN, electrolytes, and CK). All were normal except for one variant at the 90 day time point. This difference appeared to be due to a technical problem relating to the site of blood draw, which differed from that of all other mice. For histopathology, 13 mice were necropsied at 120 days post-injection and 8 mice at 180 days. All organs were normal; in particular there was no inflammation seen in any section from any organ (heart, liver, kidney, muscle, gonads, brain, lung, lymph nodes, and intestines).

In the safety study for the four male Cynomolgus Macaques, subjects were injected at 90 days of age to closely mimic the likely age of administration of treatment in SMA Type 1 infants. The scAAV9.CB.SMN vector was administered one time by catheterization of the saphenous vein with a dose of 6.7×10^{13}/kg, which corresponds to the lowest dose tested for which SMN-Δ7 mice showed a significant increase of survival. Animals were followed for six months until they were sacrificed at approximately 9 months of age. No adverse effects were seen, and all clinical chemistries were normal. T-cell immune response was tested using ELISpot in peripheral blood mononuclear cells (PBMCs), and all were negative at 6 months post injection.

These mouse and monkey studies can be summarized as follows. The serum chemistry and hematology studies were unremarkable as was the histopathology assessment. The NHP subjects mounted appropriate immune responses to capsid (but not to transgene), with very high transgene expression persisting at 6 months post-injection. In conclusion, these studies provide strong evidence that systemically-delivered scAAV9.CB.SMN is safe and well tolerated, even at the high doses required for penetration of the blood-brain barrier.[13]

Formal IND-enabling GLP pharmacology, toxicology, and biodistribution studies were discussed with the FDA at the Pre-IND meeting held January 2012. The toxicology plan discussed with CBER was found to be acceptable for the initiation of this Phase I trial.

6 TRIAL OBJECTIVES AND PURPOSE

6.1 Primary Objective

The primary outcome for this clinical trial is safety. Discontinuation criteria are based on the development of unacceptable toxicity, defined as the occurrence of any one Grade III or higher, unanticipated, treatment-related toxicity that presents with clinical symptoms and requires medical treatment.

6.2 Secondary Objectives

A secondary outcome will include time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death.

Secondary outcomes will also include the change in CHOP-INTEND from baseline score and demonstration of improvement of motor function and muscle strength as determined by achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted. Additionally, sponsor may choose to provide videos of the physical exams, CHOP-INTEND assessments, and/or Bayley Scale assessments to an independent, blinded reviewer for confirmation of the development milestones.

6.3 Exploratory Objectives

Exploratory outcome measures will be tested during the study as part of the program and product development plan; however if exploratory measurement results show efficacy and primary outcomes do not reach statistical significance, the only interpretation is that the results show a trend toward benefit but can never supersede primary measures. These exploratory outcome measures will include:

- ACTIVE-mini (Ability Captured Through Interactive Video Evaluation-mini) evaluation of infant movement ability.
- Patient functional measures using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). This test has been studied and validated in infants with spinal muscular atrophy and was found to be reliable in this population.[19]
- Bayley Scale of Infant Development version 3 is a standardized, norm-referenced infant assessment. The gross and fine motor portions as well as speech and cognition portions of this test will administered if the child reaches or exceeds a score of 60 out of 64 on the CHOP-INTEND.
- Motor neuron function will be assessed via evoked compound motor action potentials (CMAP) and motor unit number estimation (MUNE).
- Pathological status of muscles will be quantified by Electrical Impedance Myography (EIM).
- The age at which significant motor milestones are achieved will be assessed using a standard Motor Milestone Development Survey shown in Table 10 in Section 11.1.10.
- Compelling, demonstrable, documented evidence of efficacy as determined by changes in functional abilities as captured during videotaping sessions during site visits and/or captured by subject/parent/legal guardian at home.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design

The proposed clinical trial is an open-label, single injection ascending dose study of self-complementary AAV9 carrying the SMN gene under the control of a hybrid CMV enhancer/chicken AVXS-101 delivered one-time through a venous catheter inserted into a peripheral vein (arm, leg, or scalp) of Type 1 spinal muscular atrophy subjects.

The primary analysis for efficacy will be assessed when all patients reach 13.6 months of age (a database lock will be performed at the time point at which all patients reach 13.6 months of age). A follow-up safety analysis will be completed at the time point at which the last patient reaches 24 months post-dose.

This dose escalation study involves four cohorts. There will be at least a 3 week intra-cohort dosing interval between dosing of patients within a cohort to allow review of the safety analysis from five time points (days 1, 2, 7, 14, and 21) prior to dosing of the next patient. There will be at least a 4-week inter-cohort dosing interval between dosing of patients between cohorts to allow time for review of the safety analysis of at least six time points (days 1, 2, 7, 14, 21, and 30) from all the patients within a cohort. Safety analysis will be done by the investigators and the DSMB, as well as, time for decisions to be made about whether to implement a higher dose group. Dose escalation will be based on dose-limiting toxicity (DLT).

Cohort 1 will consist of three (3) SMA patients followed by Cohort 2A with a minimum of three (3) and no more than six (6) SMA patients to receive a single infusion at escalating doses.

- Cohort 1 (Low Dose): 6.7×10^{13} vg/kg (n=3)
- Cohort 2A (Intermediate Dose): 2.0×10^{14} vg/kg ($n \geq 3$ and $n \leq 6$)

Cohort 2B and Cohort 3 will each consist of three (3) SMA patients to receive a single infusion at escalating doses.

- Cohort 2B: 2.0×10^{14} vg/kg (n=3)
- Cohort 3 (High Dose): 3.3×10^{14} vg/kg (n=3)

Cohort 2B will be done first and if efficacy is favorable but does not fully improve subjects to normal, Cohort 3 at high dose will be implemented.

Treatment of Cohort 3 is permitted based on safety assessment presented in the IND. A score of 8 or higher on the Bayley Scales of Infant Development will be considered the low end of normal. If efficacy (defined as any clinical improvement from baseline of either primary or exploratory outcome measures) is observed at the intermediate dose (2.0×10^{14} vg/kg), the Principal Investigator may continue to enroll at the intermediate dose up to a maximum of 9 patients.

If no clinically significant improvement without toxicity is observed, the possibility of adding an additional escalation cohort at a higher dose will be discussed with the FDA, DSMB and relevant oversight regulatory agencies.

7.2 Number of Subjects

A total of 15 subjects may be enrolled.

7.3 Treatment Assignment

This is an open-label study. Treatment will be assigned in accord with the dose escalation schedule specified in Section 10.6.

7.4 Criteria for Study Termination

An independent Data Safety Monitoring Board (DSMB) and safety monitor will monitor safety data on a continual basis throughout the trial. The DSMB can recommend early termination of the trial for reasons of safety. Study enrollment will be halted by the investigators when any subject experiences a Grade III, or higher adverse event toxicity that is unanticipated and possibly, probably, or definitely related to the study drug that presents with clinical symptoms and requires medical treatment. This will include any patient death, important clinical laboratory finding, or any severe local complication in the injected area related to administration of the study agent. If after review by the DSMB, IRB, IBCSC, NIH-OBA and FDA, the decision is made to continue, the study will proceed according to the dose escalation schedule.

Subjects may be discontinued from further study participation or the trial may be terminated for the following reasons:

- Development of unacceptable toxicity, defined as the occurrence of any one Grade III or higher, unanticipated, treatment-related toxicity that presents with clinical symptoms and requires medical treatment.
- Patient requires at least 16-hour per day of ventilation support for breathing, including BiPAP use, for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative use
- Death
- Failure to comply with protocol-required visits or procedures
- Study is terminated by sponsor
- Subject withdrawal of consent to participate further

Figure 4 Study Design

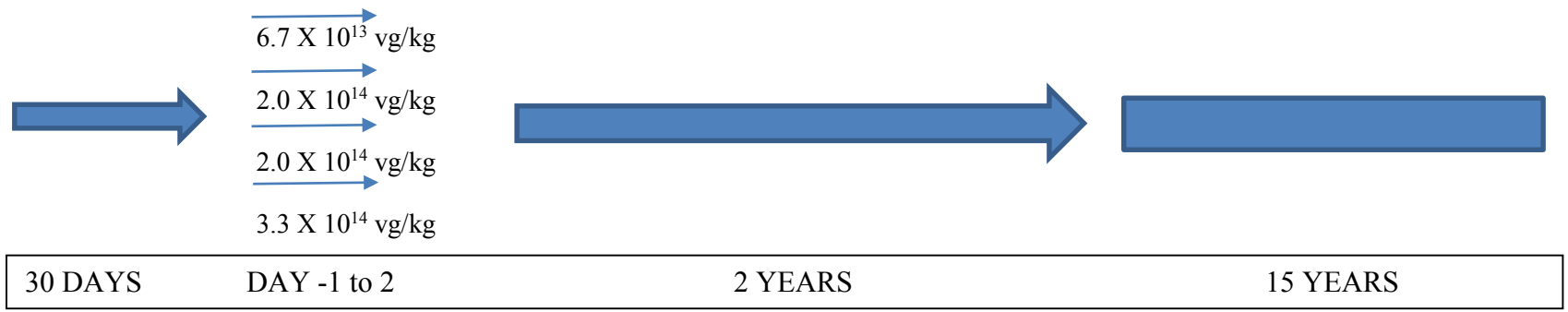


Table 6 Schedule of Assessments

Study Interval	Baseline	Vector Infusion				Follow Up Year 1									Follow Up Year 2			Long Term Monitor
	Screening	(Inpatient)				(Outpatient)												
Visit	1	2				3	4	5	6	7	8	Monthly	Every 3 Months	Every 6 Months	Every Month[g]	Q3 Months	Q6 Months	Annually
Days in Study[a]	-30 (± 7)	-1	0	1	2	7	14	21	30	60	90	Up to 12 Months			13-24 Months			Through 15 years
Informed Consent	X																	
Chest X-Ray	X																	
Medical History	X																	
Physical Exam + Vitals	X	X[c]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	X	X
Pulmonary Assessment	X			X		X	X	X	X	X	X	X	X	X	X[g]	X	X	X
Photograph Injection site	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	X	
Swallowing Test	X													X			X	
Pulse Oximetry[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	X	
Capillary Blood Gas	X	X	X	X	X													
Safety Labs (Blood)	X	X		X	X	X	X	X	X	X	X		X	X	X[g]	X	X	
Coagulation Studies (PT/INR/PTT)											X		X	X		X	X	
Safety Labs (Urinalysis)	X	X		X	X	X	X		X		X		X	X	X[g]	X	X	
Immunology (AntiAAV9/SMN Ab & T-Cells)	X					X	X	X	X	X	X		X	X		X	X	
Research Blood[e]	X							X	X	X	X		X	X		X	X	
CHOP-INTEND[f] (with video)	X	X							X	X	X	X	X	X	X[g]	X	X	

Study Interval	Baseline	Vector Infusion				Follow Up Year 1									Follow Up Year 2			Long Term Monitor
	Screening	(Inpatient)				(Outpatient)												
Visit	1	2				3	4	5	6	7	8	Monthly	Every 3 Months	Every 6 Months	Every Month[g]	Q3 Months	Q6 Months	Annually
Days in Study[a]	-30 (± 7)	-1	0	1	2	7	14	21	30	60	90	Up to 12 Months			13-24 Months			Through 15 years
Bayley[b]	X	X							X	X	X	X[b]	X[b]	X[b]	X[g]	X	X	
ACTIVE-mini	X	X				X	X	X	X	X	X	X	X	X		X	X	
CMAP/MUNE/EIM	X								X		X		X	X		X	X	
Research Urine	X			X	X	X	X	X	X	X	X	X	X	X		X	X	
Research Saliva & Stool	X			X	X	X	X	X	X	X	X	X	X	X		X	X	
Development Milestones/Gross Motor Skills Checklist (with video)	X								X					X	X[g]	X		X
ECHO/ECG	X								X					X		X		X
Prednisolone Dosing		X	X	X	X	X	X											
Gene Transfer			X															
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]	X	X	X
Concomitant Medications	To be collected from 2 weeks before study dose until final study visit, recorded on separate CRF																	X

a Visits on Days 7, 14 and 21 allow a window of ±2 days; all monthly visits following (Visit 6 to 29) allow a window of ±7 days.

b The gross and fine motor portions of this test will be administered monthly through 14 months post-dose if a patient reaches or exceeds a score of 60 out of 64 on the CHOP-INTEND. The cognition portion of this test will be administered every three months if a patient reaches or exceeds a score of 60 out of 64 on the CHOP-INTEND. CHOP-INTEND assessment will be discontinued and only the Bayley will be administered for subjects that achieve two consecutive scores of 64.

c Vital signs recorded every four (4) hours during inpatient hospitalization.

d Continuous monitoring during gene transfer procedure. Axillary temperature to be captured pre- and post- infusion.

e Research blood sample will be used to perform baseline exon 7 modification testing and could also be used to re-confirm SMA Type 1 diagnosis, SMN2 copy number, and exon-7 modification testing through a third-party laboratory.

f Subjects that achieve two consecutive scores of ≥62 may cease further CHOP-INTEND assessments, as per PI, physical therapist, and sponsor decision.

g Subjects for whom the decision is made to continue CHOP-INTEND assessments, or who don't reach score ≥62, will continue to complete monthly visits during Year 2.

8 SELECTION AND WITHDRAWAL OF SUBJECTS

SMA Type 1 subjects, six months and younger with proven mutations of the SMN1 gene will be enrolled in this clinical trial. Patients will be of any racial, ethnic, or gender background. Enrollment will be staggered with at least 4 weeks between patient infusions. The assessment and full treatment plan will be used for all subjects in Cohort 2B (n=3) and potentially for subjects in Cohort 3 (n=6) to be included if subjects in Cohort 2B do not achieve a status of normal: a score of 8 or higher on the Bayley Scales of Infant Development will be considered the low end of normal.

8.1 Subject Inclusion Criteria

Subjects must meet all of the following Inclusion Criteria:

1. Six months of age and younger[1] at day of vector infusion with Type 1 SMA as defined by the following features:
    a. Bi-allelic SMN1 gene mutations (deletion or point mutation) with two copies of SMN2 (no more and no fewer).
    b. Patients 6 months and younger with a disease onset up to 6 months of age.
    c. Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints.

[1] First nine subjects enrolled under previous version(s) of the protocol could be nine months of age or younger. Inclusion revised to reflect six months of age or younger in 24 Jun 2015 Protocol Addendum #2.

Initial genetic testing and diagnosis completed at an institution/laboratory other than Nationwide Children's Hospital/Ohio State University is acceptable if proper documentation is received at Nationwide Children's Hospital, verified by the PI, and filed in the patient's medical record.

AveXis, Inc. may opt to confirm all genetic diagnoses through a contracted third-party laboratory utilizing an additional blood sample collected during a post-dose visit.

8.2 Subject Exclusion Criteria

Subjects must not meet any of the following Exclusion Criteria:

1. Active viral infection (includes HIV or serology positive for hepatitis B or C).
2. Use of invasive ventilatory support (tracheotomy with positive pressure)* or pulse oximetry <95% saturation at the screening visit.
    a. Patients may be managed using non-invasive ventilator support (BiPAP) for less than 16 hours a day at the discretion of their physician or research staff.
3. Concomitant illness that in the opinion of the PI creates unnecessary risks for gene transfer.
4. Concomitant use of any of the following drugs: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the trial (eg, corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab).

5. Patients with Anti-AAV9 antibody titers >1:50 as determined by ELISA binding immunoassay.
6. Abnormal laboratory values considered clinically significant (GGT >3XULN, bilirubin ≥3.0 mg/dL, creatinine ≥1.8 mg/dL, Hgb <8 or >18 g/Dl; WBC >20,000 per cmm).
7. Participation in a recent SMA treatment clinical trial that in the opinion of the PI creates unnecessary risks for gene transfer.
8. Family does not want to disclose patient's study participation with primary care physician and other medical providers.
9. Patient with signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding.
10. Patients with c.859G>c modification in exon 7, based on predicted mild phenotype.

8.3 Subject Withdrawal Criteria

Subjects meeting the following criteria will be withdrawn:

- Development of unacceptable toxicity, defined as the occurrence of any one Grade III or higher, unanticipated, treatment-related toxicity that presents with clinical symptoms and requires medical treatment during the 2-year post-dose period
- Patient requires at least 16-hour per day of ventilation support for breathing, including BiPAP use, for 14 consecutive days in the absence of an acute reversible illness excluding perioperative use
- Death
    - Autopsies will be requested of any subjects that expire following participation in a gene transfer study as per the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules; see Autopsy Plan in Appendix 2.
- Withdrawal of consent from further participation

Further guidance regarding determination of withdrawal criteria is outlined in Section 11.1.

9 TREATMENT OF SUBJECTS

Subjects will receive the gene transfer intravenous infusion under sterile conditions in a PICU patient room. The vector is formulated in the Nationwide Children's Investigational Pharmacy in approximately 10–20 mL/kg of normal saline and delivered to the PICU patient room in pre-labeled syringes sealed in double leak-proof bags, carried in a designated lockable cooler.

The final formulated vector will be administered approximately at 10–20 mL/kg and slowly infused for approximately 60 minutes. The vector will be administered to the patient within 8 hours of preparation.

9.1 Description of Study Drug

The biological product is a non-replicating recombinant self-complementary adeno-associated virus serotype 9 (AAV9) containing the cDNA of the human SMN gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). The AAV inverted

terminal repeat (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed and the resulting protein is produced. The biological product, called scAAV9.CB.hSMN, expresses the human SMN protein.

Table 7 Investigational Product

	Investigational Product
Product Name:	AVXS-101
Dosage Form:	1.96 X 10^{13} DRP/mL (based off supercoiled qPCR) in either a 2 mL vial (with 1 mL fill) or 5 mL vial (with 5 mL fill) All vials are screwcap polypropylene vials
Unit Dose	10–20 mL/kg, in accord with dose escalation schedule
Route of Administration	Peripheral vein intravenous infusion
Physical Description	AVXS-101 is provided in frozen 1 mL and 5 mL vials. Once thawed AVXS-101 is a clear liquid.
Manufacturer	Nationwide Children's Hospital Clinical Manufacturing Facility Center for Gene Therapy 700 Children's Drive Columbus, OH 43205

9.2 Concomitant Medications

Prior and concomitant medications will be captured in the eCRF from two weeks prior to study dosing through the last study visit.

9.2.1 Prophylactic Administration of Prednisolone

In every gene therapy study NCH has completed, including the first SMA patient, an antigen specific T-cell response to the AAV vector has been observed. This is an expected response between 2–4 weeks following gene transfer. One possible consequence to such antigen specific T-cell response is clearance of the transduced cells and loss of transgene expression. In an attempt to dampen the host immune response to the AAV based therapy, patients will be started on prophylactic prednisolone (glucocorticoid) (approximately 1 mg/kg/day) 24 hours prior to the gene transfer as agreed upon with FDA in the revised protocol submitted an IND update Serial No. 004, 31 Oct 2014. Treatment will continue for approximately 30 days with the following guidelines for tapering: When AST and ALT exceed 120 IU/L prednisolone will be maintained until enzymes fall below this level while at the same time monitoring T-cell response for decreases below 100 SFC per 10^6 PBMCs. Discrepancies from these precise recommendations will be at the discretion of the investigator based on potential safety issues for participating patients.

9.2.2 Prohibited Medications

Concomitant use of any of the use of any of the following medications is prohibited:

- Drugs for treatment of myopathy or neuropathy
- Agents used to treat diabetes mellitus
- Ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the trial (e.g, corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab).

10 STUDY DRUG MATERIALS AND MANAGEMENT

AVXS-101 is manufactured in the cGMP facility of the Center for Gene Therapy at the Research Institute at Nationwide Children's Hospital. Only the number of vials required for stability testing and clinical retains will be stored at the cGMP facility.

10.1 Study Drug

AVXS-101

10.2 Study Drug Packaging and Labeling

Each vial is labeled with a specific log number and reagent code.

10.3 Study Drug Storage

AVXS-101 will be maintained at the Investigational Drug Service Pharmacy in the Hazardous Ultralow -80°C freezer located in room D01616 at NCH for the duration of the study.

10.4 Study Drug Preparation

Preparation of the gene vector will be done by the NCH research pharmacist according to the Manual of Operation Procedures. Immediately prior to transportation to the clinical setting, appropriate dilutions of the test article will be completed by the pharmacy. Documentation of the dilution will be completed by the pharmacy following standard pharmacy protocol. The vector will be diluted and manipulated in polypropylene syringes.

The vector is to be filled by the cGMP staff in screw cap vials at volumes of 5.0 mL (5 mL cryovial size) and 1.0 mL (2 mL cryovial size). The appropriate number of vials and volume of each will be determined for each patient based on body weight and specified dose cohort as illustrated in Table 8. The total vector genome dose will be calculated based on patient's body weight and rounded down to the closest 1 kg.

Table 8 Total Dose

Low Dose (6.7e13) vg/kg						
Total Dose (vg)	**Vector Volume (mL)**	**Total Volume (mL)**	**Syringe #**	**Syringe Volume (mL)**	**Vector Volume (mL)**	**Saline Volume (mL)**
2.68E+14	13.7	67.3	1	33.7	6.8	26.8
			2	33.7	6.8	26.8
3.35E+14	17.1	84.2	1	42.1	8.5	33.5
			2	42.1	8.5	33.5
4.02E+14	20.5	101.0	1	50.5	10.3	40.3
			2	50.5	10.3	40.3
4.69E+14	23.9	117.9	1	58.9	12.0	47.0
			2	58.9	12.0	47.0
5.36E+14	27.3	134.7	1	44.9	9.1	35.8
			2	44.9	9.1	35.8
			3	44.9	9.1	35.8
6.03E+14	30.8	151.5	1	50.5	10.3	40.3
			2	50.5	10.3	40.3
			3	50.5	10.3	40.3
6.7E+14	34.2	168.4	1	56.1	11.4	44.7
			2	56.1	11.4	44.7
			3	56.1	11.4	44.7

Intermediate Dose (2.0e14 vg/kg)							
Weight (kg)	**Total Dose (vg)**	**Vector Volume (mL)**	**Total Volume (mL)**	**Syringe #**	**Syringe Volume (mL)**	**Vector Volume (mL)**	**Saline Volume (mL)**
4	8.00E+14	40.8	67.3	1	33.7	20.4	13.3
				2	33.6	20.4	13.2
5	1.00E+15	51.0	84.2	1	42.1	25.5	16.6
				2	42.1	25.5	16.6
6	1.20E+15	61.2	101.0	1	50.5	30.6	19.9
				2	50.5	30.6	19.9
7	1.40E+15	71.4	117.9	1	59.0	35.7	23.3
				2	58.9	35.7	23.2
8	1.60E+15	81.6	134.7	1	44.9	27.2	17.7
				2	44.9	27.2	17.7
				3	44.9	27.2	17.7
9	1.80E+15	91.8	151.5	1	50.5	30.6	19.9
				2	50.5	30.6	19.9
				3	50.5	30.6	19.9
10	2.00E+15	102.0	168.4	1	56.2	34.0	22.2
				2	56.1	34.0	22.1
				3	56.1	34.0	22.1

High Dose (3.3e14 vg/kg)							
Weight (kg)	**Total Dose (vg)**	**Vector Volume (mL)**	**Total Volume (mL)**	**Syringe #**	**Syringe Volume (mL)**	**Vector Volume (mL)**	**Saline Volume (mL)**
4	1.32E+15	67.3	67.3	1	33.7	33.7	0
				2	33.7	33.7	0
5	1.65E+15	84.2	84.2	1	42.1	42.1	0
				2	42.1	42.1	0
6	1.98E+15	101.0	101.0	1	50.5	50.5	0
				2	50.5	50.5	0
7	2.31E+15	117.9	117.9	1	58.9	58.9	0
				2	58.9	58.9	0
8	2.64E+15	134.7	134.7	1	44.9	44.9	0
				2	44.9	44.9	0
				3	44.9	44.9	0
9	2.97E+15	151.5	151.5	1	50.5	50.5	0
				2	50.5	50.5	0
				3	50.5	50.5	0
10	3.3E+15	168.4	168.4	1	56.1	56.1	0
				2	56.1	56.1	0
				3	56.1	56.1	0

In general, the high dose will not be diluted for a total dose of 3.3 X 10^{14} vg/kg. The low doses will be diluted to the same volume as the high dose and split equally. Thus, the vector will be withdrawn from each vial for the low doses, pooled together, and diluted in an amount of normosol-R to equal the total volume used in the high dose cohort in a given weight range for a total dose of 6.7 X 10^{13} vg/kg.

Preparation of the vector will be done aseptically in a class II BSC by the research staff according to the Manual of Operating Procedures. The vector will be allowed to warm to room temperature prior to infusion to avoid the possibility of particle aggregation following product thaw. The vector-containing syringes will be delivered to the designated PICU suite at NCH. It will be delivered inside a sealed leak-proof bag, carried in a designated container at room temperature and administered to the subject within 8 hours from removal from the -80°C freezer.

10.5 Administration

The gene transfer infusion procedure will be performed under sterile conditions in a PICU patient room. The final formulated vector will be administered at 10–20 mL/kg and slowly infused for approximately 60 minutes. Patient-specific dosage based on patient weight recorded during hospital admission on Day -1 will be provided by the pharmacy on procedure date.

10.6 Dose Escalation

There will be at least a 3 week intra-cohort dosing interval between dosing of subjects within a cohort to allow review of the safety analysis from five time points (days 1, 2, 7, 14, and 21) prior to dosing of the next subject. There will be at least a 4 week inter-cohort dosing interval

between dosing of subjects in each cohort to allow time for review of the safety analysis of at least six time points (days 1, 2, 7, 14, 21, and 30) from all the subjects within a cohort. Safety analysis will be done by the investigators and the DSMB, as well as, time for decisions to be made about whether to implement a higher dose group. Dose escalation will be based on dose-limiting toxicity (DLT) as described in Section 11.1.1.

The investigators will confer with the IRB and DSMB on all Grade III or higher adverse events with 48 hours that are unanticipated and possibly, probably, or definitely related to the study agent before continuing enrollment. Based on the outcome of the safety and efficacy analysis at the end of each cohort decisions will be made to proceed with dose escalation for the following cohort.

10.7 Study Drug Accountability

Upon withdrawal of a vial, the Investigational Product Accountability Log will be recorded with the specific lot number and code of the reagent.

10.8 Study Drug Handling and Disposal

Handling of scAAV9.CB.SMN gene will follow compliance standards for Biosafety level 1 vectors following the NIH guidelines. Individuals manipulating the vector will be required to wear adequate personal protective equipment.

All materials used for injection, including sterile drapes, needles, and syringes in contact with the vector will be sealed in leak-proof primary and secondary containers. All waste will be double bagged in autoclave bags bearing the biohazard symbol and sealed with autoclave tape. The bag will then be autoclaved and disposed of in a biohazard waste container.

The empty syringes used for delivery of the vector will be resealed in the procedure room and placed into a small labeled box. The empty vials used to prepare the syringes will also be maintained in the pharmacy. Both will be returned to a secure -80°C freezer archival storage separate from the unused vector storage.

11 ASSESSMENTS

11.1 Safety Parameters

The primary outcome for this clinical trial is safety. Withdrawal criteria are based on the development of unacceptable toxicity, defined as the occurrence of any one Grade III or higher treatment-related toxicity.

11.1.1 Dose Limiting Toxicity

Dose limiting toxicity is defined as any adverse event that is possibly, probably, or definitely related to the study agent. This would include any grade III event, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03; these classifications are outlined in Table 9.

Table 9 Adverse Event Classification

1	Mild adverse event; did not require treatment
2	Moderate adverse event; resolved with treatment
3	Severe adverse event; inability to carry on normal activities; required professional medical attention
4	Life-threatening or permanently disabling adverse event
5	Fatal adverse event

Study enrollment will be halted by the investigators when any subject experiences a **Grade III, or higher** adverse event toxicity that is **unanticipated and possibly, probably, or definitely related** to the study drug. The event will then be reviewed by the Data Safety Monitoring Board (DSMB) and an evaluation will be made as to whether the trial should be terminated early following the Discontinuation Rules.

11.1.2 Discontinuation Rules

An independent Data Safety Monitoring Board (DSMB) and safety monitor will monitor safety data on a continual basis throughout the trial. The DSMB can recommend early termination of the trial for reasons of safety. Study enrollment will be halted by the investigators when any subject experiences a **Grade III, or higher** adverse event toxicity that is **unanticipated and possibly, probably, or definitely related** to the study drug that presents with clinical symptoms and requires medical treatment. This will include any patient death, important clinical laboratory finding, or any severe local complication in the injected area related to administration of the study agent. If after review by the DSMB, IRB, IBCSC, NIH-OBA and FDA, the decision is made to continue, the study will proceed according to Section 10.6 of this protocol.

11.2 Demographic/Medical History

Patient demographics and medical history information will be collected at baseline and captured in the CRF.

11.3 Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, and axillary temperature at the time points specified in Table 6.

11.4 Pulse Oximetry

Pulse oximetry will be measured through a small infrared light attached to the end of the patient's finger.

11.5 Weight and Height

Weight and height will be measured as per the time points specified in Table 6.

11.6 Physical Examination

Physical examination will include review of the following systems: HEENT, lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, and genitourinary.

11.7 Vaccination Recommendations

Patients are encouraged to follow all routinely scheduled immunizations as recommended by the Center for Disease Control (CDC). We also recommend seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections.

11.8 Physical Therapy Assessments

11.8.1 CHOP-INTEND

CHOP-INTEND including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions. Anti-gravity movements in assisted rolling, ventral suspension, and supported standing are also measured. See Appendix 3.

At such time that a subject achieves two consecutive CHOP-INTEND scores of ≥62, a teleconference will be conducted between PI, physical therapist, and AveXis, Inc. to review the subject status and determine whether or not continued CHOP-INTEND assessments are necessary. A decision will be reached and confirmed in writing following the teleconference. If decided that no further assessments are necessary, the physical therapist will cease completion of the CHOP-INTEND assessment at subsequent visits; otherwise CHOP-INTEND assessments will continue monthly.

CHOP-INTEND examinations will be videotaped in accord with the Videotaping Manual.

11.8.2 Bayley Scale of Infant Development version 3

Bayley Scales of Infant Development version 3 is a standardized, norm-referenced infant assessment. The gross and fine motor portions as well as the cognition portion of this test will be administered if the child reaches or exceeds a score of 60 out of 64 on the CHOP-INTEND. The gross and fine motor portion will be completed monthly during the first year and the cognition portion will be completed every three months. During the second year all required portions of the Bayley Scale will be conducted every three months, except for subjects still being seen monthly for CHOP-INTEND assessments. For those subjects the gross and fine motor and cognition portions will be administered as in Year 1. See Appendix 4.

Bayley scales examinations will be videotaped in accord with the Videotaping Manual.

11.9 Development Milestones Checklists

The age at which significant motor milestones are achieved will be assessed using a standard Motor Milestone Development Survey shown in Table 10 and a Gross Motor Skills Checklist show in Appendix 5. The Gross Motor Skills Checklist was designed by physical therapists at Nationwide Children's Hospital specifically to assess SMA Type 1 subjects in this trial; it is source from a collection of existing motor assessments.

Additionally, CHOP-INTEND and Bayley physical therapy assessment videos may be transferred to a centralized reviewer for independent determination of milestones achieved.

Table 10 Motor Milestone Development Survey

4 months	Prone: Holds head up to vertical axis and legs extended
6 months	Supine: Rolls over back to front
9 months	Sits alone, with back straight

12 months	Cruises, holding on and may stand without help
15 months	Walks independently
18 months	Runs, walks down stairs one hand held
24 months	Up and down stairs, one step at a time; jumps both feet off floor
30 months	Reciprocal stair climbing; stands on one foot
36 months	Reciprocal stairs going down; rides tricycle
48 months	Hops on one foot; throws ball overhand
60 months	Able to skip

11.10 Video Evidence

Physical therapy assessments and physician physical examinations required at each study visit will be videotaped in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. Parent(s)/legal guardian(s) may also share home videos demonstrating achievement of functional abilities. AveXis, Inc. will provide a secure and confidential upload process for transfer and storage of the videos from NCH to a contracted third-party vendor that will compile and arrange videos as per AveXis, Inc. submission requirements. Any/all videos received at AveXis, Inc. or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis, Inc. AveXis, Inc. and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies and/or the medical community.

Videos will be provided in a blinded fashion to an independent, centralized reviewer for unbiased assessment of milestone achievement.

11.11 ACTIVE-mini

ACTIVE-mini will be conducted to evaluate infant movement ability. This assessment utilizes the Microsoft Kinect camera interface to capture infant movement with an inexpensive, commercially available camera system with real-time quantitative data output provided. Using the 3 cameras built into the Kinect video, depth and color data of an infant's movement is recorded and analyzed. The Kinect's ability to capture images and simultaneously the distance to every point in each image, provides significantly more information for an assessment of infants, than are captured by current post-processed video-based computer vision systems.

11.12 Electrophysiology Assessments

11.12.1 EIM

Pathological status of muscles will be quantified by EIM. Skulpt, Inc., has developed a handheld device specifically for performing EIM measurements in infants. This device will be used to measure EIM in this study. The device is not yet approved by FDA, but has been tested in over 30 other individuals with no adverse events (AEs) (serious or otherwise) reported to date and currently being tested in SMA infants as part of the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) trials. The device has undergone independent electrical safety testing by Intertek (www.intertek.com) to the requirements contained in the following standards:

- IEC 60601-1 Issue 1998/12/01 Ed: 2 Medical Electrical Equipment Part 1: General Requirements and Safety; [Amd. 1-1991(CENELEC EN 60601-1: 1990) (Amd. 2- 1995) (Corrigendum-1995)]

11.12.2 CMAP

The compound muscle action potential (CMAP) size is found using supramaximal stimulation of the motor nerve to the muscle or muscle group (similar to a nerve conduction study). It is recorded using surface electrodes. This is representative of the sum of the surface detected motor unit action potentials from muscles innervated by that nerve.

11.12.3 MUNE

Motor Unit Number Estimation (MUNE) is a technique that uses electromyography to estimate the number of motor units in a muscle. MUNE uses a general formula of:

$$Number\ of\ motor\ units = \frac{compound\ muscle\ action\ potential\ size}{mean\ surface-detected\ motor\ unit\ action\ potential\ size}$$

11.13 Chest X-ray

A chest x-ray will be performed at screening/baseline.

11.14 Swallowing Test

A swallowing test will be performed to determine if the patient has signs of aspiration. If the test is positive for aspiration the patient may be instructed to use an alternative method to oral feeding for the duration of the trial.

11.15 Echocardiography

An ECHO will be performed at screening/baseline and other time points as specified in Table 6.

11.16 Electrocardiogram (ECG)

An ECG will be performed at screening/baseline and other time points as specified in Table 6.

11.17 Pulmonary Assessment

Patients will be assessed by a pulmonologist and may be fitted with a non-invasive positive pressure ventilator (BiPAP) at the discretion of the investigator or study staff.

As part of the pulmonary assessment the parent(s)/legal guardian(s) will be asked by the pulmonologist to recall and report the number of hours per day the subject required ventilation support (including BiPAP) over the two weeks prior to the visit. The response will be recorded in the source documentation.

11.18 Photographs of Infusion Site

Photographs will be taken of the infusion site at the time points specified in Table 6. AveXis, Inc. will provide a secure and confidential upload process for transfer and storage of the photographs from NCH to a contracted third-party vendor that will compile and arrange photographs as per AveXis, Inc. submission requirements. Any/all photographs received at AveXis, Inc. or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis, Inc. AveXis, Inc. and the contracted vendor will provide this secure,

encrypted transfer and storage solution to properly protect the identities of patients/families in the photographs, which may be shared with regulatory agencies and/or the medical community.

11.19 Laboratory Assessments

Biological samples will be collected throughout the trial at the time points specified in Table 6.

Laboratory tests with values within the clinically significant range will be repeated during the same visit whenever possible. If the test result returns after the subject leaves the clinic, they will be immediately contacted. Local residents may be asked to return to the outpatient clinic for a repeat test. For non-local residents, arrangements will be made to have the blood test redrawn in a laboratory close to home or by their primary care physician.

Table 11 Total Blood Volume

Visit	Tests	Total Volume
Screening	Safety, immunology, research	20 mL
Day 0	Safety, immunology	15 mL
Day 7	Safety, immunology	15 mL
Day 14	Safety, immunology	15 mL
Day 21	Safety, immunology, research	20 mL
Day 30	Safety, immunology, research	20 mL
Day 60	Safety, immunology, research	20 mL
Day 90	Safety, immunology, research	20 mL
Day 180	Safety, immunology, research	20 mL
Day 270	Safety, immunology, research	20 mL
Day 360	Safety, immunology, research	20 mL
Day 450	Safety, immunology, research	20 mL
Day 540	Safety, immunology, research	20 mL
Day 630	Safety, immunology, research	20 mL
Last Study Visit	Safety, immunology, research	20 mL
Total Volume for Study 2-Year Duration		**285 mL**

In a case where sufficient blood cannot be collected from a patient, blood will be used in the following priority order with the first having greatest priority and last having the least priority:

1. Safety blood labs
2. Serum antibody to AAV9
3. IFN-γ ELISpots to detect T-cell responses
4. Research Blood sample stored for future purposes

11.19.1 Hematology

Hematology analysis will include a CBC with differential and platelet with smear.

11.19.2 Blood Chemistry

Chemistry analysis will include the following at all study visits:

- serum GGT
- AST/ALT
- serum total bilirubin
- direct bilirubin
- albumin
- glucose
- total creatine kinase and iso-enzyme (CK-MB)
- troponin
- creatinine/BUN
- electrolytes
- alkaline phosphatase
- amylase

Study Visit 2 will also include:

- serum protein electrophoresis (SPEP)

11.19.3 Urinalysis

Urine samples will be collected via cotton swabs. Urinalysis will include the following parameters:

- Color
- Clarity/turbidity
- pH
- Specific gravity
- Glucose
- Ketones
- Nitrites
- Leukocyte esterase
- Bilirubin
- Urobilirubin
- Blood
- Protein
- RBCs
- WBCs
- Squamous epithelial cells
- Casts

- Crystals
- Bacteria
- Yeast

11.19.4 Coagulation Studies

Coagulation studies including prothrombin time (PT), PTT, and INR will be performed at the time points specified in Table 6.

11.19.5 Capillary Blood Gas

A puncture or small incision will be made with a lancet or similar device into the cutaneous layer of the patient's skin at a highly vascularized area (heel, finger, toe). To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area will be warmed prior to the puncture. As the blood flows freely from the puncture site, the sample will be collected in a heparinized glass capillary tube.

11.19.6 Virus Serology

Patients will be tested for HIV and have a serology test for hepatitis B and C.

11.19.7 Research Immunology Blood

Blood samples will be collected to test for serum antibodies to AAV9 and SMN.

11.19.8 Baseline Screening of Mother

There is a potential that the mother of the enrolled infant may have pre-existing antibodies to AAV9 that may be transferred to the patient through breast milk or theoretically via placental transfer in utero. Informed consent will be requested from the mother of the infant to screen the mother for circulating antibodies to AAV9. Once informed consent has been obtained, the mother will have her blood drawn from a peripheral vein for screening of anti-AAV9 antibodies.

11.19.9 IFN-γ ELISpots

Blood will be collected to perform IFN-γ ELISpots to detect T-cell responses to AAV9 and SMN.

11.19.10 Research Blood Sample

Blood samples will be collected for future research purposes, to examine/research potential disease modifiers and/or biomarkers. Research blood will also be used for exon 7 modifier testing at screening. Additionally, blood samples collected for research may be transferred to an independent third-party laboratory contracted by AveXis, Inc. such that genetic testing confirming SMA Type 1 diagnosis can be re-confirmed for each subject.

An additional blood sample may be collected and provided to an independent laboratory for re-confirmatory genetic testing.

11.19.11 Saliva, Urine, and Stool Collection

Saliva, urine, and stool samples will be collected for viral shedding studies. Saliva will be collected from the patient's mouth with a pipette and oral swab. 200-500 µL of urine will be collected from patients' soiled diapers by soaking a cotton ball. Pea-sized fecal samples will be collected from patients' soiled diapers. Each of these samples will be placed in a

DNAse/RNAse-free Eppendorf tube with locking top. The tubes will be stored in a -80°C freezer.

12 ADVERSE AND SERIOUS ADVERSE EVENTS

12.1 Definition of Adverse Events

12.1.1 Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any patient has been enrolled, before treatment, during treatment, or within 30 days of the last study visit, whether or not they are related to the study, must be recorded in the eCRF.

12.1.2 Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any patient has signed informed consent, before treatment, during treatment, or within 30 days following the last study visit, whether or not they are related to the study, must be recorded on forms provided by AveXis, Inc.

12.1.3 Other Adverse Event (OAE)

OAEs may be identified by the Drug Safety Physician and, if applicable, also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient/subject from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

12.2 Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason

exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

12.3 Recording Adverse Events

Adverse events spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from Day -1 until the end of the study. Serious Adverse Event information will be collected from signing of the consent form until 30 days following the last study visit. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Events will be graded in accord with Table 9.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.1.2. An AE of severe intensity may not be considered serious.

12.4 Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of consent form until 30 days following the last study visit. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to AveXis, Inc. within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send notification to AveXis, Inc., as per the Safety Management Plan.

Additional follow-up information, if required or available, should all be provided to AveXis, Inc. within 5 calendar days of receipt for events that are unexpected and/or possibly/probably/definitely related to the investigational product. This information should be provided on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file. Follow-up information for events that are not unexpected and are not related to the investigational product should be provided to AveXis, Inc. within 7 calendar days of receipt.

AveXis, Inc. is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all SAEs that occur at his or her site, as per the IRB's reporting guidelines.

AveXis, Inc. will review the safety database at least quarterly; this data will also be provided to the DSMB for quarterly review. If AveXis or the DSMB determines there are any emerging safety signals and/or trends that may warrant reporting to appropriate regulatory authorities, AveXis will report these events in aggregate.

13 DATA SAFETY MONITORING BOARD

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to review participant safety and study progress for the clinical trial. Responsibilities of the DSMB are to:

- review the research protocol, informed consent documents and plans for data and safety monitoring;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, trial site performance, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on participant safety or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- protect the safety of the study participants;
- review safety data to determine whether to recommend dose escalation;
- review quarterly safety data to determine safety signals or trends;
- ensure the confidentiality of the trial data and the results of monitoring; and,
- assist by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

13.1 DSMB Reporting and Meetings

Reports describing the status of the study will be prepared by AveXis, Inc. and/or the Principal Investigator's staff and sent to the DSMB at least quarterly, or at the DSMB's request. A meeting (either by teleconference or webcast) with the DSMB will be scheduled after Day 30 visit of the last patient in each cohort, or at the DSMB's request. Reports will be submitted prior to a scheduled meeting for review by the DSMB.

Reports will include the following:

- A brief narrative of the study status, including the target enrollment, current and projected time to completing enrollment. Any significant events and/or difficulties should be briefly described in this narrative;
- A brief narrative for each participant describing gender, age, race and ethnicity and other relevant demographic characteristics. The narrative for each participant should briefly describe his/her study status (i.e., dose level, visit number, adverse event information);

- A timeline outlining the study progress relative to visit number for each participant, as well as time points for each SAE/Dose Limiting Toxicity. A total for Adverse Events (AEs) for each participant should be included;
- A summary of AEs by classification;
- A listing of AE details grouped by participant;
- A listing of SAE details grouped by participant;
- A listing of deaths;
- A summary of clinically significant laboratory test results;
- A listing of protocol deviations.

13.2 DSMB Membership

The DSMB membership will consist of persons completely independent of the investigator and sponsor who have no financial, scientific, or other conflicts of interest with the trial. Current or past collaborators or associates of Dr. Mendell or AveXis, Inc. must note any conflict of interest before their eligibility to serve on the DSMB is approved. The DSMB will include experts in or representatives of the fields of:

- Neurology and Neuromuscular Diseases
- Immunology
- Gene Therapy
- Spinal Muscular Atrophy Clinical Care
- Clinical Research and Clinical Trials
- Statistics (non-voting member)

Individuals invited to serve on the DSMB as either voting or non-voting members must disclose any potential conflicts of interest, whether real or perceived. Conflicts of interest can include professional, proprietary, and miscellaneous interests as described in 45 CFR Part 94. Potential conflicts that develop during a member's tenure on a DSMB must also be disclosed. Written documentation attesting to an absence of conflict of interest is required annually.

AveXis, Inc. will employ a third party to provide planning, organization, preparation, and oversight services for the DSMB meetings.

14 STATISTICS

This is a Phase I trial, with safety as the primary measure. A secondary outcome includes the time to death or ≥16-hour respiratory assistance per day continuously for ≥2 weeks in the absence of an acute reversible illness. Only patients with 2 copies of SMN2 will be enrolled. 92% of SMA Type 1 patients with two copies of SMN2 live <21 months. For this study the primary end point for efficacy will be death or ≥16 hour respiratory assistance per day (includes BiPAP). A successful measure for efficacy for this study will be 50% of SMA Type 1 subjects living with less than 16 hour respiratory assistance at 2 years of age.

15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1 Study Monitoring

During the study, a monitor from AveXis, Inc. or representative will have regular contact with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol and ICH/GCP guidelines, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts) including access to the site's Electronic Medical Record (EMR) and the videos captured during specified visit assessments.
- Record and report any protocol deviations not previously sent to AveXis, Inc.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to AveXis, Inc. and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

15.2 Audits and Inspections

Authorized representatives of AveXis, Inc., a regulatory authority, or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an AveXis, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact AveXis, Inc. immediately if contacted by a regulatory agency about an inspection.

15.3 Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15.4 Quality Control and Quality Assurance

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, AveXis, Inc. may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

16 ETHICS

16.1 Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate.

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. AveXis, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

16.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Appendix 1) and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and AveXis, Inc.'s policy on Bioethics.

16.3 Written Informed Consent

The Principal Investigator(s) will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

Per the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (http://oba.od.nih.gov), an autopsy must be requested should a study participant die following participation in a gene transfer trial, no matter what the cause of death. An autopsy is requested to obtain vital information about the safety and efficacy of gene transfer. Patients' parent(s)/legal guardians will be asked to provide consent for an autopsy in advance of any death. Consent is requested at the beginning of the study to relieve the burden of making such a decision at the time of death should such a terrible and unfortunate event occur.

17 DATA HANDLING AND RECORDKEEPING

17.1 Electronic Case Report Forms

Adequate and accurate case records will be maintained and all relevant observations and data related to the study will be recorded. This will include medical history/ physical examination, hematology, clinical chemistry and serology results, a check list of inclusion and exclusion

criteria, urinary screening, drug administration, and a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation.

Electronic CRFs will be used in this study. The eCRF will be electronically signed and dated by the Principal Investigator or his designee after his/her review. After the completion of the study, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the study monitor against the source documentation for accuracy and completeness. Once signed by the Investigator, the monitor will transmit the completed eCRFs to data management for data validation and database analysis.

17.2 Inspection of Records

AveXis, Inc. will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

17.3 Retention of Records

All primary data that are a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not less than 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal discontinuation of the clinical development of the investigational product.

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following: study personnel identification and signature list, subject screening records, subject roster (names omitted), protocol and amendments or administrative changes, FDA Form 1572 (if required), study staff Curricula Vitae, IRB documentation, an approved sample ICF, drug accountability records, correspondence, site monitoring reports, blank Data Documentation form, and lab accreditations and normal values. The site must keep this binder current and available for review by the Sponsor, IRB, and/or FDA.

17.4 Retention of Samples

The identified storage laboratory will be responsible for arranging storage of any remaining or unused biological samples as well as properly documenting the storage procedures, once all study-required analyses are complete, as per sample processing requirements until such time that AveXis, Inc. provides external storage vendor transfer or destruction instructions.

18 PUBLICATION POLICY

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation or as otherwise agreed upon in writing by Sponsor and investigator. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document (in accordance with ICJME). All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

The investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 30 days prior to such presentation or submission for publication. The Sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 30-day period, the investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the investigator will delay the publication or presentation for an additional 60 days to permit the Sponsor to take necessary actions to protect its intellectual property interests. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

19 LIST OF REFERENCES

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20 APPENDICES

APPENDIX 1 DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed,

the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 2 AUTOPSY PLAN

Regional Pathology and Autopsy Services, Inc., a nationwide company that provides autopsy and tissue collection services, will perform autopsy and tissue collection for the patients in the clinical trial. This company will deploy a pathology assistant to the funeral home of the deceased to perform the autopsy and tissue collection. Standard autopsy incisions are used to perform the autopsy and pathology necessary to determine the cause of death, which will be completed by Regional Pathology and Autopsy Services.

During the procedure, multiple tissues along with the entire spinal cord will be collected for research purposes. Up to 7 sections or pieces from each organ and each region of the spinal cord will be collected and returned to the principal investigator of the trial at Nationwide Children's Hospital. Analysis of the tissue will be done to determine whether the vector transduced the expected motor neurons and if the SMN gene was expressed. These results demonstrate whether the vector delivered the therapeutic gene as expected. Tissue samples collected will also be available for histology and immunohistochemistry, allowing the state of the motor neurons and muscles to be examined.

Specifically, tissue samples from the following organs and regions of the spinal cord and brain will be collected (see Table 12 below). Tissue sample will be frozen or fixed (eg. 2% paraformaldehyde) for appropriate analysis.

Families will be asked to consent to the autopsy and tissue collection prior to any sign of moribund or death by the clinical team conducting the trial. There are distinct consent forms for the formal autopsy and for the research tissue collection. This allows the families the flexibility to participate in one or both of the research activities.

Table 12 Tissue Samples for Analysis

Brain	Spinal Cord	Muscles	Organs
Motor cortex	Cervical spinal cord	Diaphragm	Spleen
Layer 5 motor cortex	Thoracic spinal cord	#6/#7 Rib with intercostal muscle and nerve	Kidney
Brain stem	Lumbar spinal cord	Psoas muscle	Small intestine
	Sacral spinal cord		Large intestine
	Dorsal root		Pancreas
	cervical level		Stomach
	Ventral root		Lung
	cervical level		Heart
	DRG root		Liver
	cervical level		Inguinal lymph node
	Cerebrospinal fluid		Gonads

APPENDIX 3 CHOP-INTEND

CHILDREN'S HOSPITAL *of* PHILADELPHIA INFANT TEST OF NEUROMUSCULAR DISORDERS

Time of evaluation:_____ (AM/PM) **Hours off BiPAP at testing: _____(h)**

Item	Position	Test Procedure	Graded Response		Score	
1 Spontaneous movement (Upper extremity)	Supine	Observe throughout testing May unweight limb or stimulate infant to facilitate response	Antigravity shoulder movement (achieves elbow off surface)	4	L	Best side:
			Antigravity elbow movement (achieves hand and forearm off surface)	3		
			Wrist movement	2	R	State:
			Finger movement	1		
			No movement of limbs	0		
2 Spontaneous movement (Lower extremity)	Supine	Observe throughout testing May unweight limb or stimulate infant to facilitate response	Antigravity hip movement (achieves feet and knees off surface)	4	L	Best side:
			Antigravity hip adduction/internal rotation (knees off surface)	3		
			Active gravity eliminated knee movement	2	R	State:
			Ankle movement	1		
			No movement of limbs	0		
3 Hand grip	Supine	Grip strength: place finger in palm and lift until shoulder comes off surface observe when infant loses grasp May use toy of similar diameter for older children	Maintains hand grip with shoulder off bed	4	L	Best side:
			Maintains grip with elbow off surface (shoulders on surface)	3		
			Maintains grip with forearm off surface (elbow supported on surface)	2	R	State:
			Maintains grip only with no traction	1		
			No attempt to maintain grasp	0		
4 Head in midline with visual stimulation*	Supine head midline	Visual stimulation is given with toy. ***If head is maintained in midline for 5 seconds:*** Place head in maximum available rotation and provide visual stimulation to encourage midline	Rotates from maximum rotation to midline	4	L>R	Best side:
			Turns head part way back to midline	3		
			Maintains midline for 5 or more seconds	2	R>L	State:
			Maintains midline, less than 5 seconds	1		
			Head falls to side, no attempts to regain midline	0		

Time of evaluation:_____ (AM/PM) Hours off BiPAP at testing: _____(h)

Item	Position	Test Procedure	Graded Response		Score	
5 Hip adductors	Supine, no diaper	Hips flexed and adducted Feet hip width apart and thighs parallel, knees slightly apart	Keeps knee off surface of bed >5 sec or lifts foot off surface	4	L	Best side:
			Keeps knees off surface of bed 1-5 sec	2		
			No attempt to maintain knees off surface	0	R	State:
6 Rolling: elicited from legs*	Supine (arms at side) Keep side tested up roll away from the Side tested	**1.** Holding infant's lower thigh, flex hip and knee and adduct across midline bringing pelvis vertical maintain traction and ***pause in this position***. **2.** If infant rolls to side apply traction at a 45º diagonal to body and pause to allow infant to attempt to de-rotate body	When traction is applied at the end of the maneuver, rolls to prone with lateral head righting	4	To R	Best side:
			Rolls through side lying into prone without lateral head righting, clears weight-bearing arm to complete roll	3		
			Pelvis, trunk and arm lift from support surface, head turns and rolls onto side, arm comes thru to front of body	2	To L	State:
			Pelvis and trunk lift from support surface and head turns to side. Arm remains behind trunk	1		
			Pelvis lifted passively off support surface.	0		
7 Rolling: elicited from arms*	Supine (arms at side) Keep side tested up roll away from the Side tested	**1.** Hold infant at the elbow move toward opposite shoulder maintain traction on limb and ***pause with the shoulders vertical*** allow infant to de-rotate **2.** if the pelvis achieves vertical continue to provide traction	Rolls to prone with lateral head righting	4	To R	Best side:
			Rolls into prone without lateral head righting; must clear weight-bearing arm completely to finish roll	3		
			Rolls onto side, leg comes thru and adducts, bringing the pelvis vertical	2		
			Head turns to side and shoulder and trunk lift from surface	1	To L	State:
			Head turns to side; body remains limp or shoulder lifts passively	0		
8 Shoulder and elbow flexion And horizontal abduction	Side-lying with upper arm at 30º of shoulder extension and elbow flexion and supported on body (restrain lower arm if needed)	Prompt reach for a toy presented at arm's length at shoulder level (may provide stimulation and ***observe spontaneous movement***)	Clears hand from surface with antigravity arm movement	4	L	Best side:
			Able to flex shoulder to 45 degrees, without antigravity arm movement	3		
			Flexes elbow after arm comes off body	2		
			Able to get arm off body	1	R	State:
			No attempt	0		
9 Shoulder flexion & Elbow flexion	Sitting in lap or on mat with head and trunk support (20º recline)	Present stimulus at midline and at shoulder level at arm's length (may provide stimulation and ***observe spontaneous movement***)	Abducts or flexes shoulder to 60 degrees	4	L	Best side:
			Abducts or flexes shoulder to 30 degrees	3		
			Any shoulder flexion or abduction	2		
			Flexes elbow only	1	R	State:
			No attempt to lift arm	0		

Time of evaluation:_____ (AM/PM) Hours off BiPAP at testing: _____(h)

Item	Position	Test Procedure	Graded Response		Score	
10 Knee extension	Sitting in lap or over edge of mat with head and trunk support (20º recline) thigh horizontal to ground	Tickle plantar surface of foot or gently pinch toe	Extends knee to >45 degrees	4	L	Best side:
			Extends knee 15 to 45 degrees	2		
			Any visible knee extension	1		
			No visible knee extension	0	R	State:
11 Hip flexion and foot dorsiflexion	Hold infant against your body with legs free, facing outward. Support at the abdomen with the child's head resting between your arm and thorax	Stroke the foot or pinch the toe	Hip flexion or knee flexion >30º	4	L	Best side:
			Any hip flexion or knee flexion	3		
			Ankle dorsiflexion only	2		
			No active hip, knee or ankle motion	1	R	State:
			Hip flexion or knee flexion >30º	0		
12 Head control*	Sitting with support at the shoulders and trunk erect	Place the infant in ring sit with head erect and assistance given at the shoulders (front and back) (***may delay scoring a grade of 1 and 4 until end of test***).	Attains head upright from flexion and turns head side to side	4	L	Best side:
			Maintains head upright for >15 sec (for bobbing head control score a 2)	3		
			Maintains head in midline for >5 sec. with the head tipped in up to 30º of forward flexion or extension	2		
			Actively lifts or rotates head twice from flexion within 15 seconds (do not credit if movement is in time with breathing)	1	R	State:
			No response, head hangs	0		
13 Elbow flexion Score with item 14	Supine	**Traction response:** pull to sit extend arms at 45 degree angle, to point of nearly lifting head off surface	Flexes elbow	4	L	Best side:
			Visible biceps contraction without elbow flexion	2		State:
			No visible contraction	0	R	
14 Neck Flexion Score with item 13	Supine	**Traction response:** hold in neutral proximal to wrist and shoulder at 45º, ***to point of nearly lifting head off surface***	Lifts head off bed	4		Score:
			Visible muscle contraction of SCM	2		State:
			No muscle contraction	0		
15 Head/Neck Extension (Landau)	Ventral suspension: Prone, held in one hand upper abdomen	Stoke along spine from neck to sacrum. The coronal axis of the head when parallel to the bed surface = 0 degrees (horizontal)	Extends head ***to*** horizontal plane or above	4		Score:
			Extends head partially, but not to horizontal	2		State:
			No head extension	0		

Time of evaluation:_____ (AM/PM) **Hours off BiPAP at testing: _____(h)**

Item	Position	Test Procedure	Graded Response		Score	
16 Spinal Incurvation (Galant)	Ventral suspension: Prone, held in one hand upper abdomen	Stroke Right then Left throacolumbar paraspinals or tickle abdomen or foot or tilt in infants with For infant over 10 kg knees and head may touch	Twists pelvis towards stimulus off axis	4	L	Best side:
			Visible paraspinal muscle contraction	2		State:
			No response	0	R	

Total score, best score on each side for each item (maximum 64 points):

Comments:

* Adapted from the Test of Infant Motor Performance, Campbell, SK; et al. 2001.

Contractures :

□ None

L □ R □ Knee flexion

L □ R □ Ankle plantar flexion
(Present <20 degrees knee extended)

L □ R □ Hip adductor L □ R □ ITB contracture
(Note if leg cannot abduct and ext. rot. to contact surface in supine)

L □ R □ Shoulder protraction

L □ R □ Elbow flexion

L □ R □ Neck rotation

L □ R □ Neck lateral flexion

□ Plagiocephaly

□ Fixed spinal curve

Behavioral State : (Brazelton, TB.Neonatal Behavioral Assessment Scale, 2nd ed.,1984)

State 1 Deep sleep
State 2 Light sleep
State 3 Drowsy or semi-dozing
State 4 Alert, with bright look
State 5 Eyes open, considerable activity
State 6 Crying

Testing environment:

Ideally test first thing in the AM or same time of day about 1 hour after feeding

Test on a firm padded mat

Diaper /onesie only unless the infant is cold

Test with toys

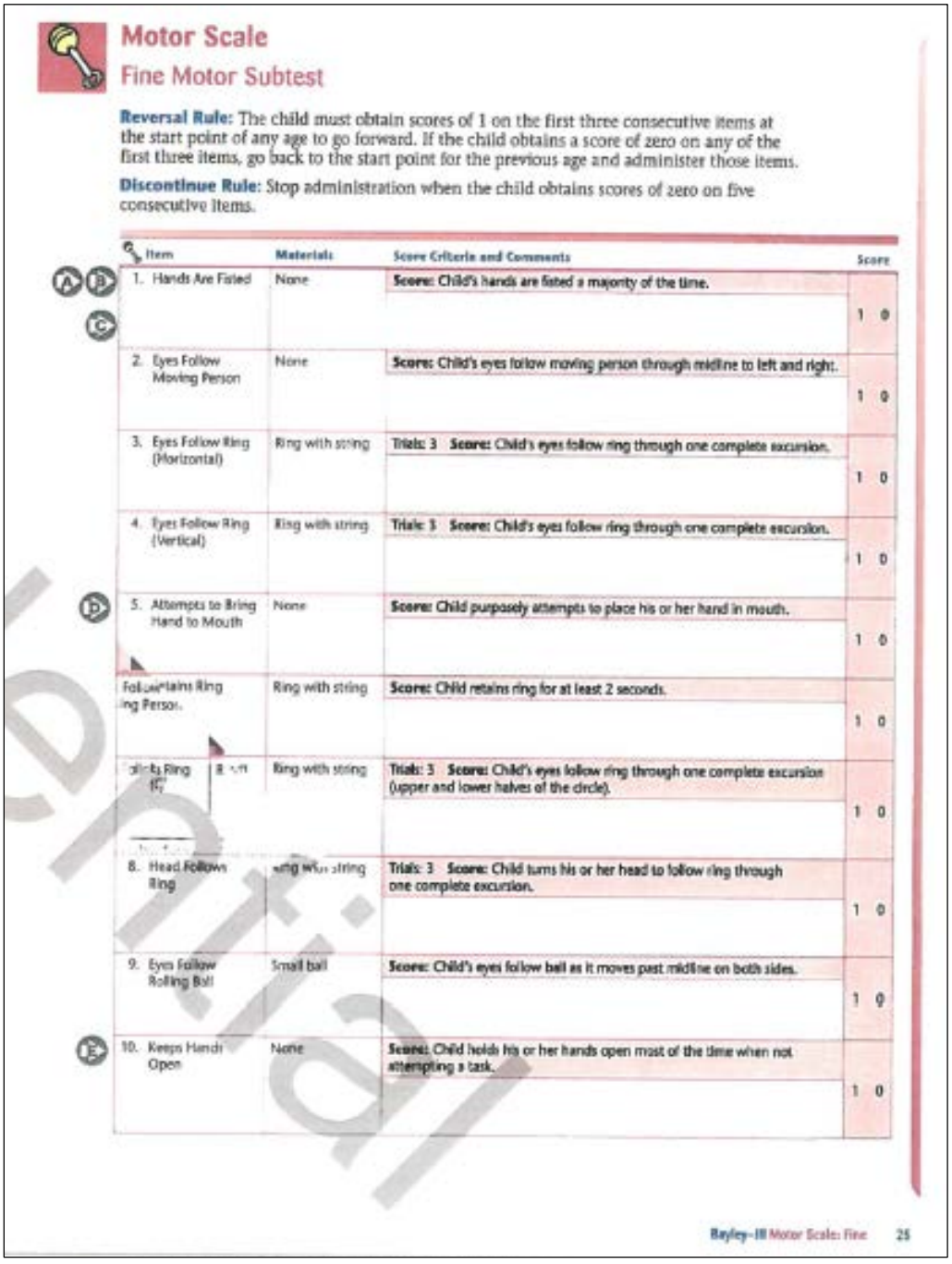
May use pacifier only if needed to maintain state 4 or 5 (see definition).

Mark as CNT (could not test) if patient could not be tested DO NOT MARK 0

SIGNATURE

DATE

APPENDIX 4 BAYLEY SCALE OF INFANT DEVELOPMENT VERSION 3: GROSS AND FINE MOTOR SKILLS SUBPARTS AND SPEECH AND COGNITION SUBPARTS



Motor Scale

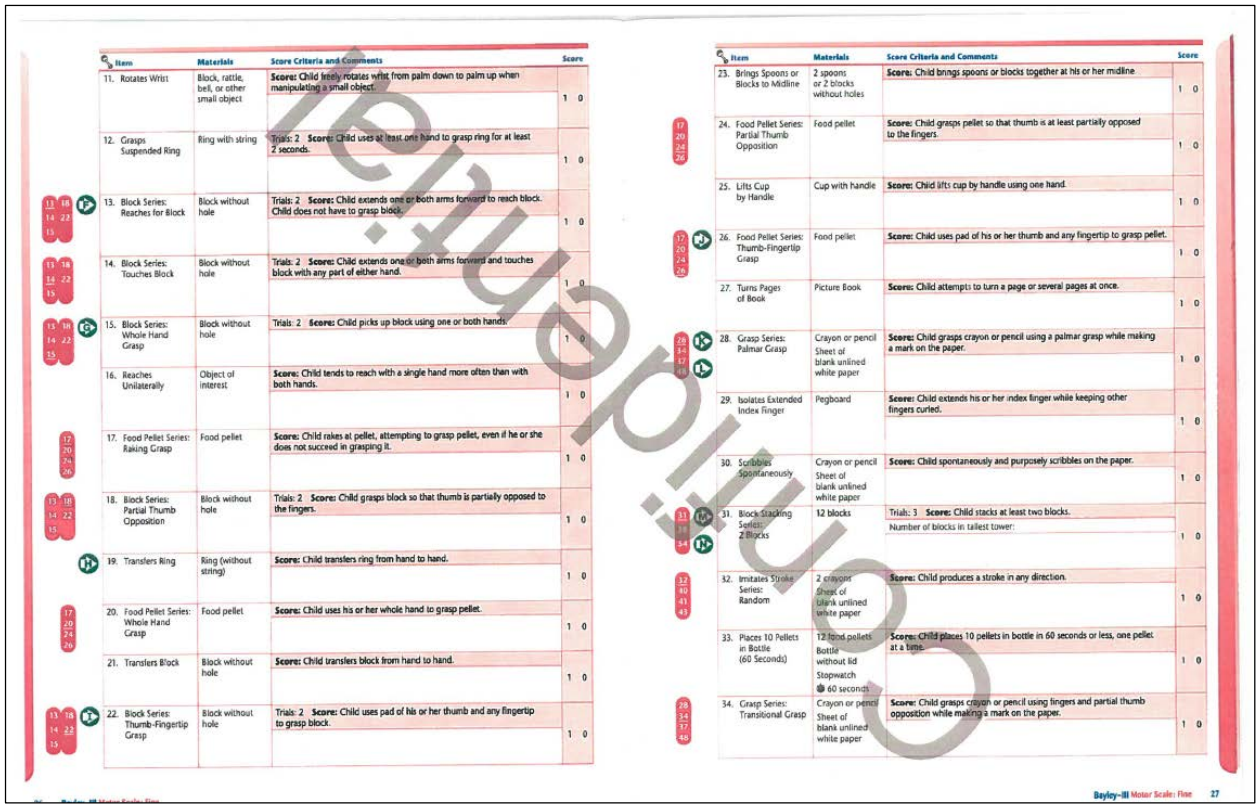
Fine Motor Subtest

Reversal Rule: The child must obtain scores of 1 on the first three consecutive items at the start point of any age to go forward. If the child obtains a score of zero on any of the first three items, go back to the start point for the previous age and administer those items.

Discontinue Rule: Stop administration when the child obtains scores of zero on five consecutive items.

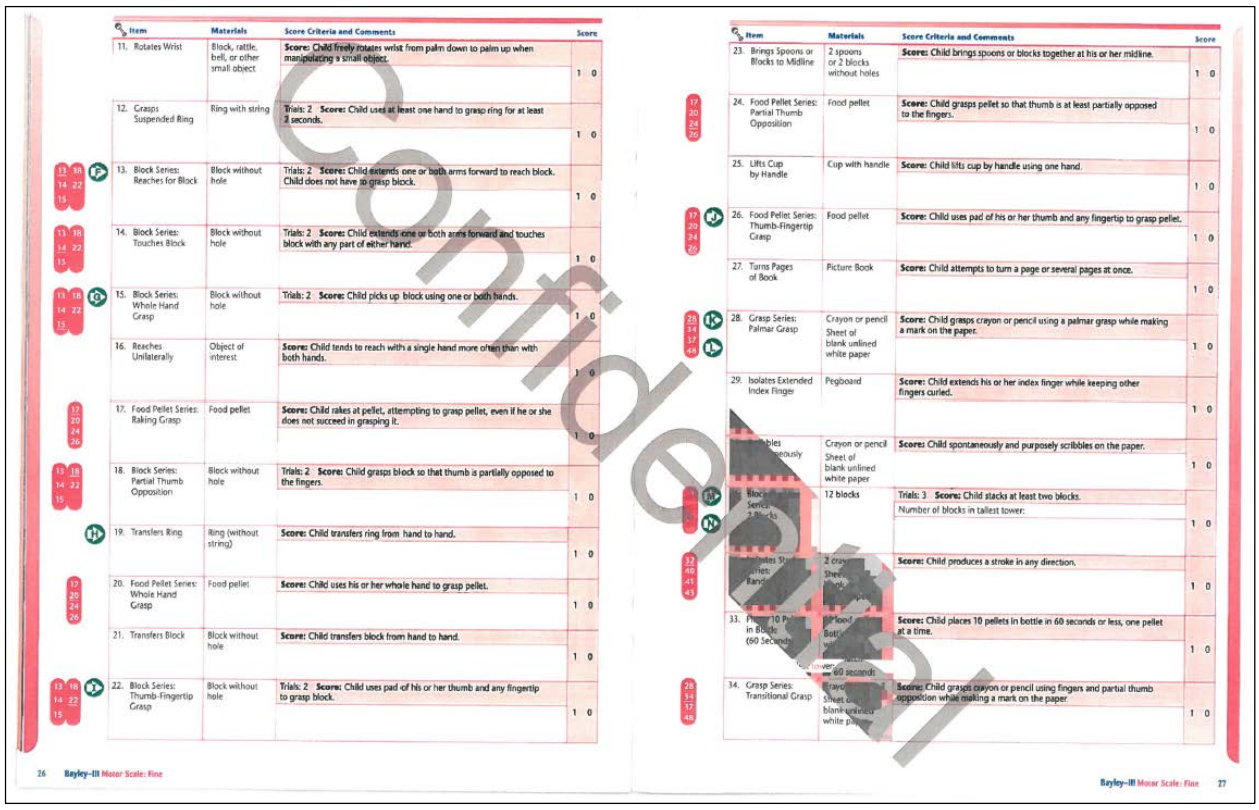
Item	Materials	Score Criteria and Comments	Score
A B C 1. Hands Are Fisted	None	**Score:** Child's hands are fisted a majority of the time.	1 0
2. Eyes Follow Moving Person	None	**Score:** Child's eyes follow moving person through midline to left and right.	1 0
3. Eyes Follow Ring (Horizontal)	Ring with string	**Trials:** 3 **Score:** Child's eyes follow ring through one complete excursion.	1 0
4. Eyes Follow Ring (Vertical)	Ring with string	**Trials:** 3 **Score:** Child's eyes follow ring through one complete excursion.	1 0
D 5. Attempts to Bring Hand to Mouth	None	**Score:** Child purposely attempts to place his or her hand in mouth.	1 0
Follows Ring Retains Ring ing Person	Ring with string	**Score:** Child retains ring for at least 2 seconds.	1 0
Tracks Ring (F)	Ring with string	**Trials:** 3 **Score:** Child's eyes follow ring through one complete excursion (upper and lower halves of the circle).	1 0
8. Head Follows Ring	ring with string	**Trials:** 3 **Score:** Child turns his or her head to follow ring through one complete excursion.	1 0
9. Eyes Follow Rolling Ball	Small ball	**Score:** Child's eyes follow ball as it moves past midline on both sides.	1 0
E 10. Keeps Hands Open	None	**Score:** Child holds his or her hands open most of the time when not attempting a task.	1 0

Bayley-III Motor Scale: Fine 25



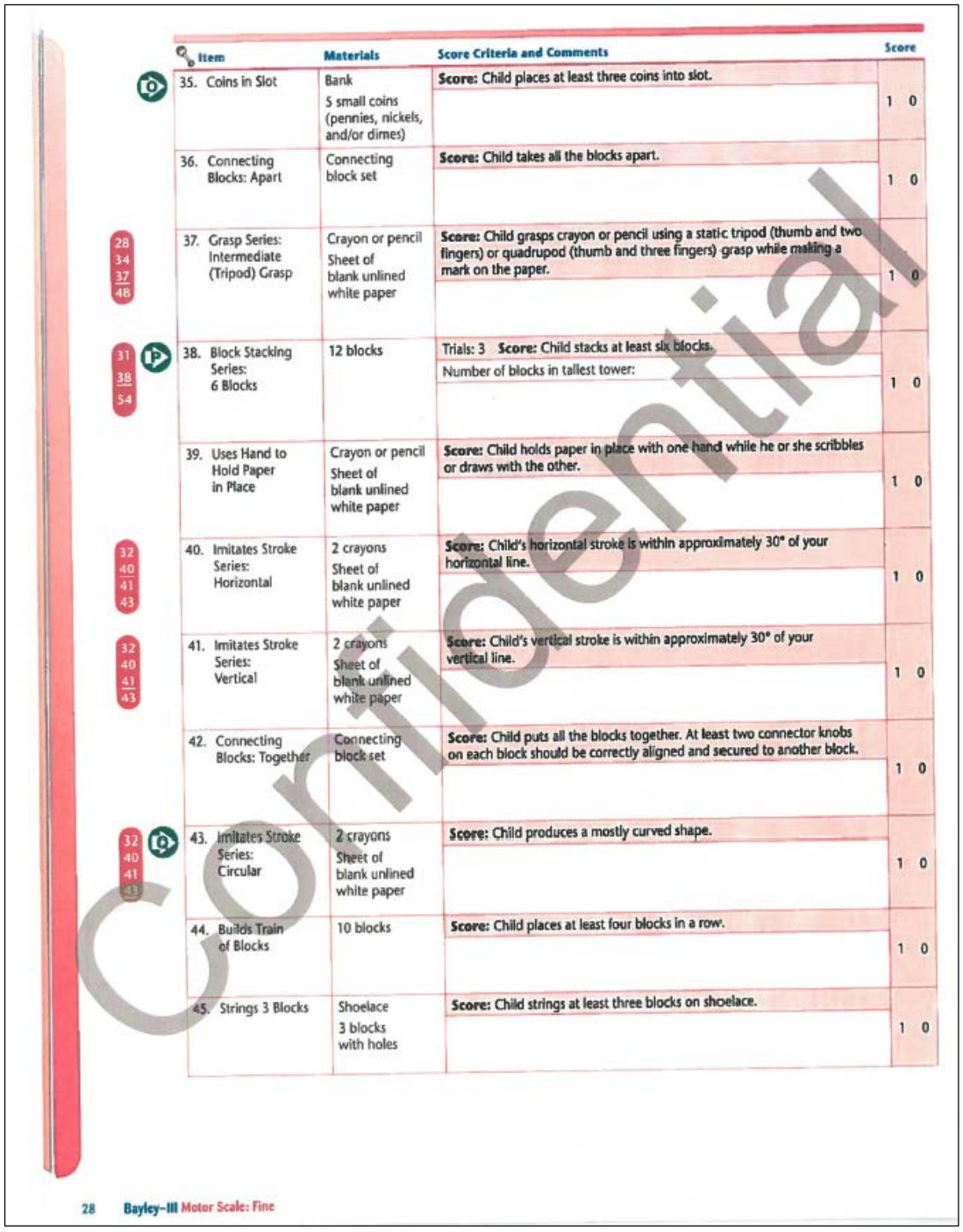
Item	Materials	Score Criteria and Comments	Score
11. Rotates Wrist	Block, rattle, bell, or other small object	**Score:** Child freely rotates wrist from palm down to palm up when manipulating a small object.	1 0
12. Grasps Suspended Ring	Ring with string	Trials: 2 **Score:** Child uses at least one hand to grasp ring for at least 2 seconds.	1 0
13. Block Series: Reaches for Block	Block without hole	Trials: 2 **Score:** Child extends one or both arms forward to reach block. Child does not have to grasp block.	1 0
14. Block Series: Touches Block	Block without hole	Trials: 2 **Score:** Child extends one or both arms forward and touches block with any part of either hand.	1 0
15. Block Series: Whole Hand Grasp	Block without hole	Trials: 2 **Score:** Child picks up block using one or both hands.	1 0
16. Reaches Unilaterally	Object of interest	**Score:** Child tends to reach with a single hand more often than with both hands.	1 0
17. Food Pellet Series: Raking Grasp	Food pellet	**Score:** Child rakes at pellet, attempting to grasp pellet, even if he or she does not succeed in grasping it.	1 0
18. Block Series: Partial Thumb Opposition	Block without hole	Trials: 2 **Score:** Child grasps block so that thumb is partially opposed to the fingers.	1 0
19. Transfers Ring	Ring (without string)	**Score:** Child transfers ring from hand to hand.	1 0
20. Food Pellet Series: Whole Hand Grasp	Food pellet	**Score:** Child uses his or her whole hand to grasp pellet.	1 0
21. Transfers Block	Block without hole	**Score:** Child transfers block from hand to hand.	1 0
22. Block Series: Thumb-Fingertip Grasp	Block without hole	Trials: 2 **Score:** Child uses pad of his or her thumb and any fingertip to grasp block.	1 0

Item	Materials	Score Criteria and Comments	Score
23. Brings Spoons or Blocks to Midline	2 spoons or 2 blocks without holes	**Score:** Child brings spoons or blocks together at his or her midline.	1 0
24. Food Pellet Series: Partial Thumb Opposition	Food pellet	**Score:** Child grasps pellet so that thumb is at least partially opposed to the fingers.	1 0
25. Lifts Cup by Handle	Cup with handle	**Score:** Child lifts cup by handle using one hand.	1 0
26. Food Pellet Series: Thumb-Fingertip Grasp	Food pellet	**Score:** Child uses pad of his or her thumb and any fingertip to grasp pellet.	1 0
27. Turns Pages of Book	Picture Book	**Score:** Child attempts to turn a page or several pages at once.	1 0
28. Grasp Series: Palmar Grasp	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child grasps crayon or pencil using a palmar grasp while making a mark on the paper.	1 0
29. Isolates Extended Index Finger	Pegboard	**Score:** Child extends his or her index finger while keeping other fingers curled.	1 0
30. Scribbles Spontaneously	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child spontaneously and purposely scribbles on the paper.	1 0
31. Block Stacking Series: 2 Blocks	12 blocks	Trials: 3 **Score:** Child stacks at least two blocks. Number of blocks in tallest tower:	1 0
32. Imitates Stroke Series: Random	2 crayons Sheet of blank unlined white paper	**Score:** Child produces a stroke in any direction.	1 0
33. Places 10 Pellets in Bottle (60 Seconds)	12 food pellets Bottle without lid Stopwatch @ 60 seconds	**Score:** Child places 10 pellets in bottle in 60 seconds or less, one pellet at a time.	1 0
34. Grasp Series: Transitional Grasp	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child grasps crayon or pencil using fingers and partial thumb opposition while making a mark on the paper.	1 0



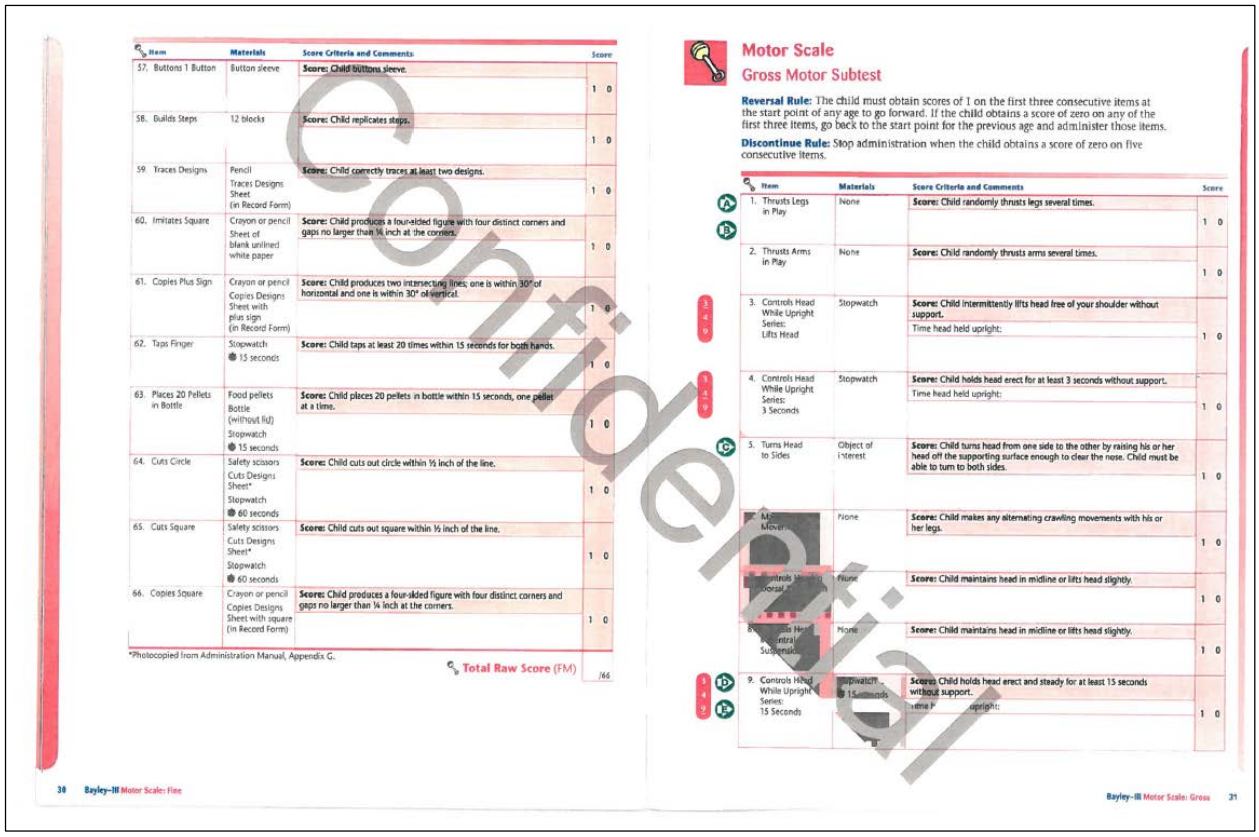
Item	Materials	Score Criteria and Comments	Score
11. Rotates Wrist	Block, rattle, bell, or other small object	**Score:** Child freely rotates wrist from palm down to palm up when manipulating a small object.	1 0
12. Grasps Suspended Ring	Ring with string	Trials: 2 **Score:** Child uses at least one hand to grasp ring for at least 2 seconds.	1 0
13. Block Series: Reaches for Block	Block without hole	Trials: 2 **Score:** Child extends one or both arms forward to reach block. Child does not have to grasp block.	1 0
14. Block Series: Touches Block	Block without hole	Trials: 2 **Score:** Child extends one or both arms forward and touches block with any part of either hand.	1 0
15. Block Series: Whole Hand Grasp	Block without hole	Trials: 2 **Score:** Child picks up block using one or both hands.	1 0
16. Reaches Unilaterally	Object of interest	**Score:** Child tends to reach with a single hand more often than with both hands.	1 0
17. Food Pellet Series: Raking Grasp	Food pellet	**Score:** Child rakes at pellet, attempting to grasp pellet, even if he or she does not succeed in grasping it.	1 0
18. Block Series: Partial Thumb Opposition	Block without hole	Trials: 2 **Score:** Child grasps block so that thumb is partially opposed to the fingers.	1 0
19. Transfers Ring	Ring (without string)	**Score:** Child transfers ring from hand to hand.	1 0
20. Food Pellet Series: Whole Hand Grasp	Food pellet	**Score:** Child uses his or her whole hand to grasp pellet.	1 0
21. Transfers Block	Block without hole	**Score:** Child transfers block from hand to hand.	1 0
22. Block Series: Thumb-Fingertip Grasp	Block without hole	Trials: 2 **Score:** Child uses pad of his or her thumb and any fingertip to grasp block.	1 0

Item	Materials	Score Criteria and Comments	Score
23. Brings Spoons or Blocks to Midline	2 spoons or 2 blocks without holes	**Score:** Child brings spoons or blocks together at his or her midline.	1 0
24. Food Pellet Series: Partial Thumb Opposition	Food pellet	**Score:** Child grasps pellet so that thumb is at least partially opposed to the fingers.	1 0
25. Lifts Cup by Handle	Cup with handle	**Score:** Child lifts cup by handle using one hand.	1 0
26. Food Pellet Series: Thumb-Fingertip Grasp	Food pellet	**Score:** Child uses pad of his or her thumb and any fingertip to grasp pellet.	1 0
27. Turns Pages of Book	Picture Book	**Score:** Child attempts to turn a page or several pages at once.	1 0
28. Grasp Series: Palmar Grasp	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child grasps crayon or pencil using a palmar grasp while making a mark on the paper.	1 0
29. Isolates Extended Index Finger	Pegboard	**Score:** Child extends his or her index finger while keeping other fingers curled.	1 0
30. Scribbles Spontaneously	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child spontaneously and purposely scribbles on the paper.	1 0
31. Block Stacking Series: 2 Blocks	12 blocks	Trials: 3 **Score:** Child stacks at least two blocks. Number of blocks in tallest tower:	1 0
32. Imitates Stroke Series: Random	2 crayons Sheet of blank unlined white paper	**Score:** Child produces a stroke in any direction.	1 0
33. Places 10 Pellets in Bottle (60 Seconds)	12 food pellets Bottle without lid Stopwatch @ 60 seconds	**Score:** Child places 10 pellets in bottle in 60 seconds or less, one pellet at a time.	1 0
34. Grasp Series: Transitional Grasp	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child grasps crayon or pencil using fingers and partial thumb opposition while making a mark on the paper.	1 0



Item	Materials	Score Criteria and Comments	Score
35. Coins in Slot	Bank 5 small coins (pennies, nickels, and/or dimes)	**Score:** Child places at least three coins into slot.	1 0
36. Connecting Blocks: Apart	Connecting block set	**Score:** Child takes all the blocks apart.	1 0
37. Grasp Series: Intermediate (Tripod) Grasp	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child grasps crayon or pencil using a static tripod (thumb and two fingers) or quadrupod (thumb and three fingers) grasp while making a mark on the paper.	1 0
38. Block Stacking Series: 6 Blocks	12 blocks	Trials: 3 **Score:** Child stacks at least six blocks. Number of blocks in tallest tower:	1 0
39. Uses Hand to Hold Paper in Place	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child holds paper in place with one hand while he or she scribbles or draws with the other.	1 0
40. Imitates Stroke Series: Horizontal	2 crayons Sheet of blank unlined white paper	**Score:** Child's horizontal stroke is within approximately 30° of your horizontal line.	1 0
41. Imitates Stroke Series: Vertical	2 crayons Sheet of blank unlined white paper	**Score:** Child's vertical stroke is within approximately 30° of your vertical line.	1 0
42. Connecting Blocks: Together	Connecting block set	**Score:** Child puts all the blocks together. At least two connector knobs on each block should be correctly aligned and secured to another block.	1 0
43. Imitates Stroke Series: Circular	2 crayons Sheet of blank unlined white paper	**Score:** Child produces a mostly curved shape.	1 0
44. Builds Train of Blocks	10 blocks	**Score:** Child places at least four blocks in a row.	1 0
45. Strings 3 Blocks	Shoelace 3 blocks with holes	**Score:** Child strings at least three blocks on shoelace.	1 0

28 Bayley-III Motor Scale: Fine



Item	Materials	Score Criteria and Comments	Score
57. Buttons 1 Button	Button sleeve	**Score:** Child buttons sleeve.	1 0
58. Builds Steps	12 blocks	**Score:** Child replicates steps.	1 0
59. Traces Designs	Pencil Traces Designs Sheet (in Record Form)	**Score:** Child correctly traces at least two designs.	1 0
60. Imitates Square	Crayon or pencil Sheet of blank unlined white paper	**Score:** Child produces a four-sided figure with four distinct corners and gaps no larger than ¼ inch at the corners.	1 0
61. Copies Plus Sign	Crayon or pencil Copies Designs Sheet with plus sign (in Record Form)	**Score:** Child produces two intersecting lines; one is within 30° of horizontal and one is within 30° of vertical.	1 0
62. Taps Finger	Stopwatch ● 15 seconds	**Score:** Child taps at least 20 times within 15 seconds for both hands.	1 0
63. Places 20 Pellets in Bottle	Food pellets Bottle (without lid) Stopwatch ● 15 seconds	**Score:** Child places 20 pellets in bottle within 15 seconds, one pellet at a time.	1 0
64. Cuts Circle	Safety scissors Cuts Designs Sheet* Stopwatch ● 60 seconds	**Score:** Child cuts out circle within ½ inch of the line.	1 0
65. Cuts Square	Safety scissors Cuts Designs Sheet* Stopwatch ● 60 seconds	**Score:** Child cuts out square within ½ inch of the line.	1 0
66. Copies Square	Crayon or pencil Copies Designs Sheet with square (in Record Form)	**Score:** Child produces a four-sided figure with four distinct corners and gaps no larger than ¼ inch at the corners.	1 0

*Photocopied from Administration Manual, Appendix G.

Total Raw Score (FM) /66

30 Bayley-III Motor Scale: Fine

Motor Scale

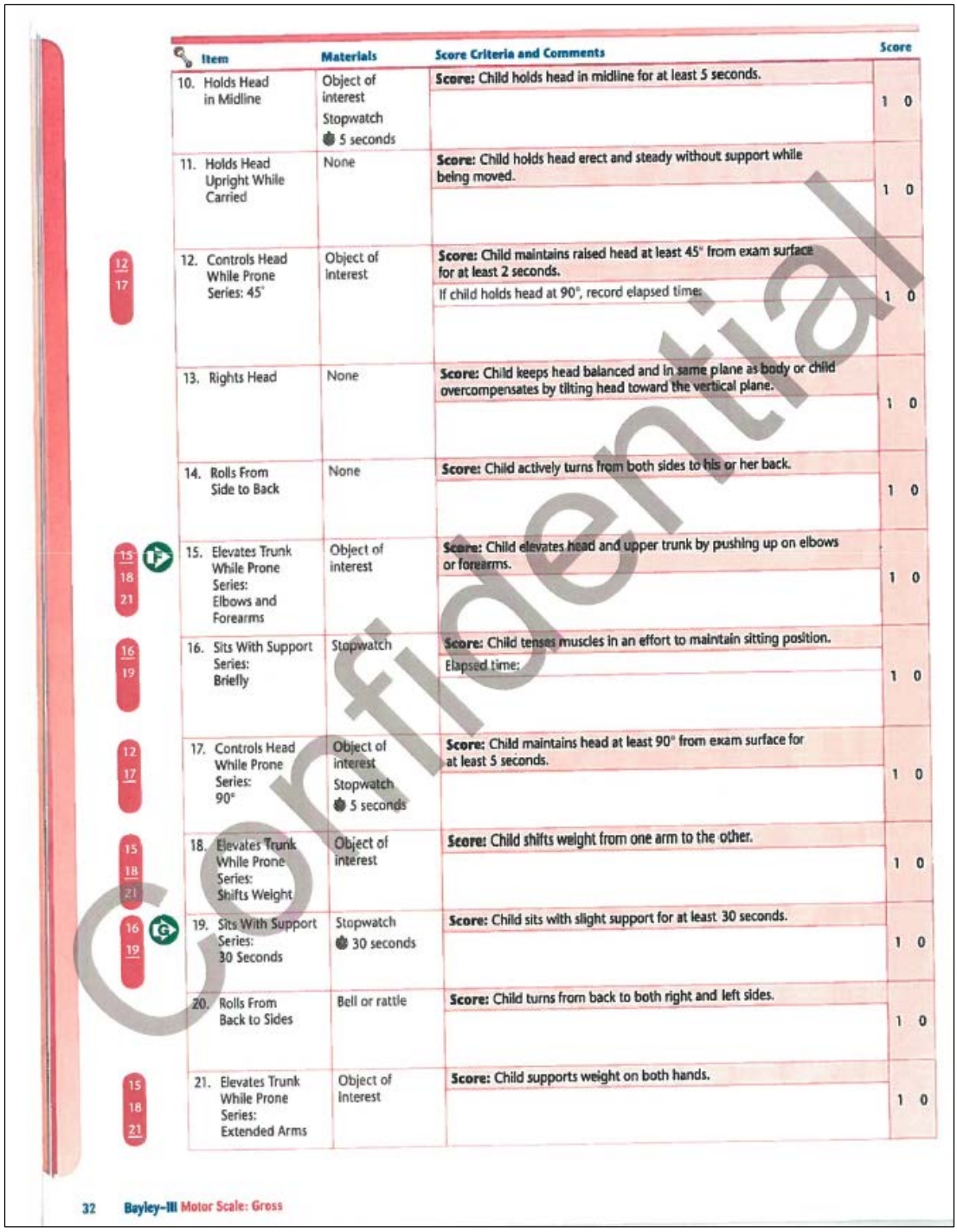
Gross Motor Subtest

Reversal Rule: The child must obtain scores of 1 on the first three consecutive items at the start point of any age to go forward. If the child obtains a score of zero on any of the first three items, go back to the start point for the previous age and administer those items.

Discontinue Rule: Stop administration when the child obtains a score of zero on five consecutive items.

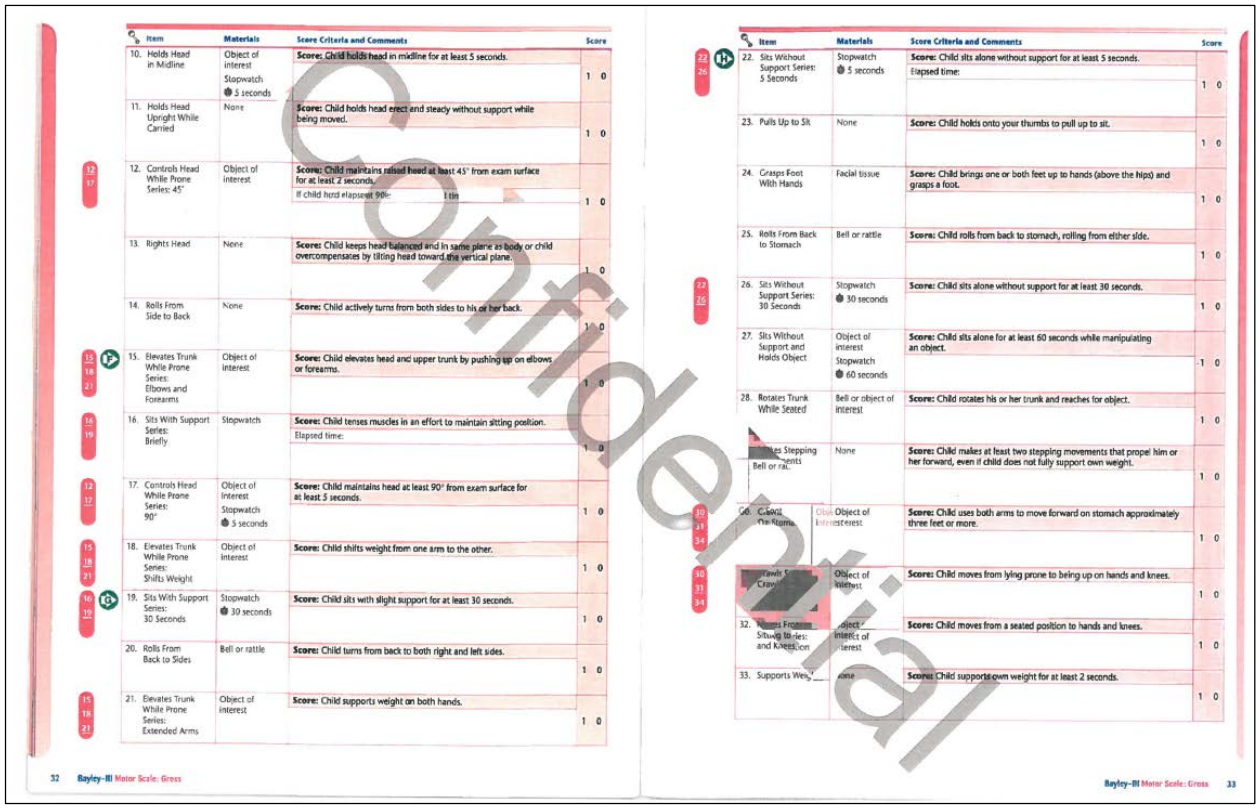
Item	Materials	Score Criteria and Comments	Score
A B 1. Thrusts Legs in Play	None	**Score:** Child randomly thrusts legs several times.	1 0
2. Thrusts Arms in Play	None	**Score:** Child randomly thrusts arms several times.	1 0
3 4 5 6 3. Controls Head While Upright Series: Lifts Head	Stopwatch	**Score:** Child intermittently lifts head free of your shoulder without support. Time head held upright:	1 0
3 4 5 6 4. Controls Head While Upright Series: 3 Seconds	Stopwatch	**Score:** Child holds head erect for at least 3 seconds without support. Time head held upright:	1 0
C 5. Turns Head to Sides	Object of interest	**Score:** Child turns head from one side to the other by raising his or her head off the supporting surface enough to clear the nose. Child must be able to turn to both sides.	1 0
[illegible]	None	**Score:** Child makes any alternating crawling movements with his or her legs.	1 0
[illegible]	None	**Score:** Child maintains head in midline or lifts head slightly.	1 0
[illegible]	None	**Score:** Child maintains head in midline or lifts head slightly.	1 0
3 4 5 6 D E 9. Controls Head While Upright Series: 15 Seconds	Stopwatch ● 15 seconds	**Score:** Child holds head erect and steady for at least 15 seconds without support. Time head held upright:	1 0

Bayley-III Motor Scale: Gross 31



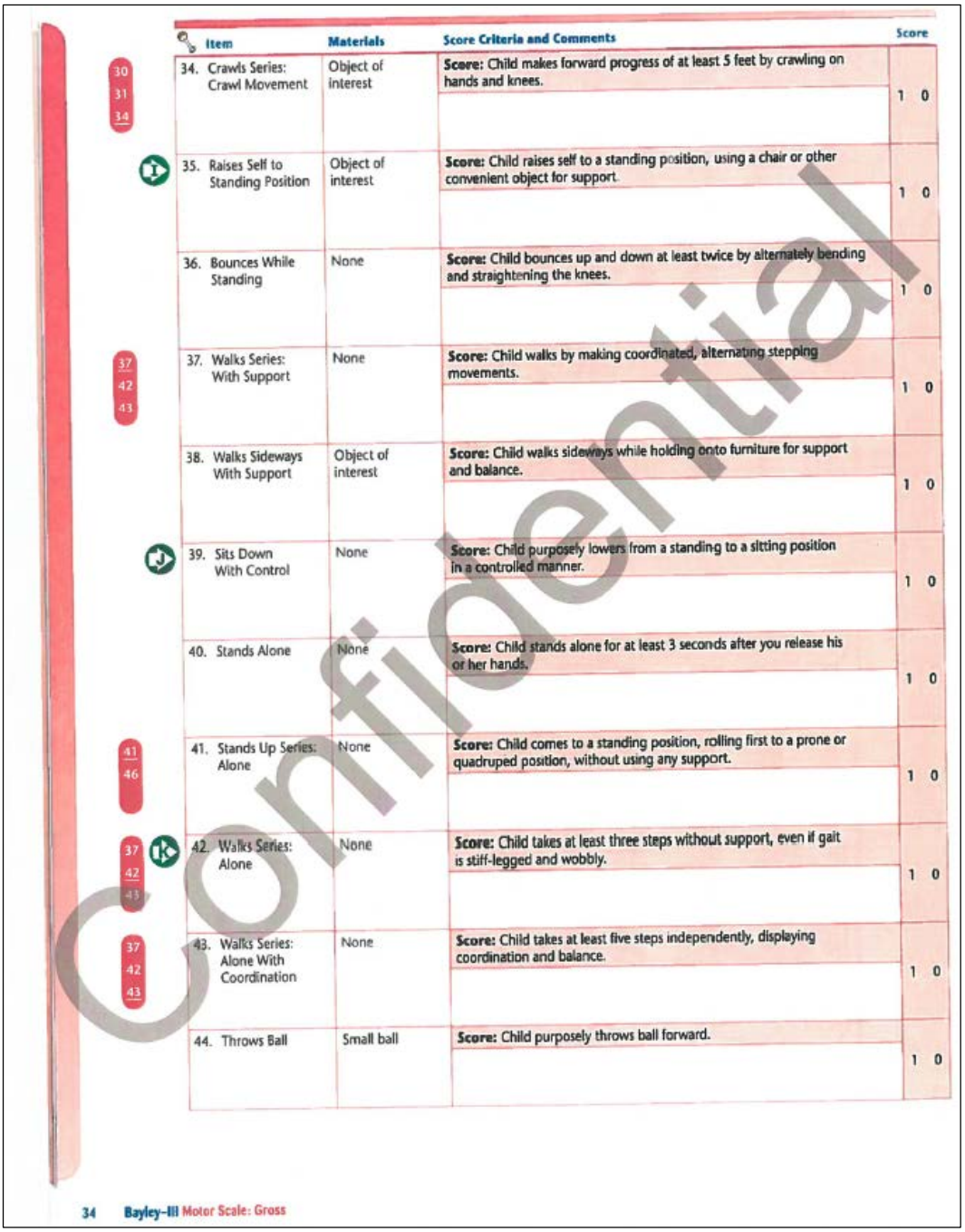
Item	Materials	Score Criteria and Comments	Score
10. Holds Head in Midline	Object of interest Stopwatch 5 seconds	**Score:** Child holds head in midline for at least 5 seconds.	1 0
11. Holds Head Upright While Carried	None	**Score:** Child holds head erect and steady without support while being moved.	1 0
12. Controls Head While Prone Series: 45° (12 17)	Object of interest	**Score:** Child maintains raised head at least 45° from exam surface for at least 2 seconds. If child holds head at 90°, record elapsed time:	1 0
13. Rights Head	None	**Score:** Child keeps head balanced and in same plane as body or child overcompensates by tilting head toward the vertical plane.	1 0
14. Rolls From Side to Back	None	**Score:** Child actively turns from both sides to his or her back.	1 0
15. Elevates Trunk While Prone Series: Elbows and Forearms (15 18 21)	Object of interest	**Score:** Child elevates head and upper trunk by pushing up on elbows or forearms.	1 0
16. Sits With Support Series: Briefly (16 19)	Stopwatch	**Score:** Child tenses muscles in an effort to maintain sitting position. Elapsed time:	1 0
17. Controls Head While Prone Series: 90° (12 17)	Object of interest Stopwatch 5 seconds	**Score:** Child maintains head at least 90° from exam surface for at least 5 seconds.	1 0
18. Elevates Trunk While Prone Series: Shifts Weight (15 18 21)	Object of interest	**Score:** Child shifts weight from one arm to the other.	1 0
19. Sits With Support Series: 30 Seconds (16 19)	Stopwatch 30 seconds	**Score:** Child sits with slight support for at least 30 seconds.	1 0
20. Rolls From Back to Sides	Bell or rattle	**Score:** Child turns from back to both right and left sides.	1 0
21. Elevates Trunk While Prone Series: Extended Arms (15 18 21)	Object of interest	**Score:** Child supports weight on both hands.	1 0

32 Bayley-III Motor Scale: Gross



Item	Materials	Score Criteria and Comments	Score
10. Holds Head in Midline	Object of interest Stopwatch 5 seconds	**Score:** Child holds head in midline for at least 5 seconds.	1 0
11. Holds Head Upright While Carried	None	**Score:** Child holds head erect and steady without support while being moved.	1 0
12. Controls Head While Prone Series: 45°	Object of interest	**Score:** Child maintains raised head at least 45° from exam surface for at least 2 seconds. If child head elapsed at 90° time	1 0
13. Rights Head	None	**Score:** Child keeps head balanced and in same plane as body or child overcompensates by tilting head toward the vertical plane.	1 0
14. Rolls From Side to Back	None	**Score:** Child actively turns from both sides to his or her back.	1 0
15. Elevates Trunk While Prone Series: Elbows and Forearms	Object of interest	**Score:** Child elevates head and upper trunk by pushing up on elbows or forearms.	1 0
16. Sits With Support Series: Briefly	Stopwatch	**Score:** Child tenses muscles in an effort to maintain sitting position. Elapsed time:	1 0
17. Controls Head While Prone Series: 90°	Object of interest Stopwatch 5 seconds	**Score:** Child maintains head at least 90° from exam surface for at least 5 seconds.	1 0
18. Elevates Trunk While Prone Series: Shifts Weight	Object of interest	**Score:** Child shifts weight from one arm to the other.	1 0
19. Sits With Support Series: 30 Seconds	Stopwatch 30 seconds	**Score:** Child sits with slight support for at least 30 seconds.	1 0
20. Rolls From Back to Sides	Bell or rattle	**Score:** Child turns from back to both right and left sides.	1 0
21. Elevates Trunk While Prone Series: Extended Arms	Object of interest	**Score:** Child supports weight on both hands.	1 0

Item	Materials	Score Criteria and Comments	Score
22. Sits Without Support Series: 5 Seconds	Stopwatch 5 seconds	**Score:** Child sits alone without support for at least 5 seconds. Elapsed time:	1 0
23. Pulls Up to Sit	None	**Score:** Child holds onto your thumbs to pull up to sit.	1 0
24. Grasps Foot With Hands	Facial tissue	**Score:** Child brings one or both feet up to hands (above the hips) and grasps a foot.	1 0
25. Rolls From Back to Stomach	Bell or rattle	**Score:** Child rolls from back to stomach, rolling from either side.	1 0
26. Sits Without Support Series: 30 Seconds	Stopwatch 30 seconds	**Score:** Child sits alone without support for at least 30 seconds.	1 0
27. Sits Without Support and Holds Object	Object of interest Stopwatch 60 seconds	**Score:** Child sits alone for at least 60 seconds while manipulating an object.	1 0
28. Rotates Trunk While Seated	Bell or object of interest	**Score:** Child rotates his or her trunk and reaches for object.	1 0
[illegible] Stepping [illegible]	None	**Score:** Child makes at least two stepping movements that propel him or her forward, even if child does not fully support own weight.	1 0
[illegible] Crawl the Room	Object of interest	**Score:** Child uses both arms to move forward on stomach approximately three feet or more.	1 0
[illegible] Crawl	Object of interest	**Score:** Child moves from lying prone to being up on hands and knees.	1 0
32. [illegible] Sitting Series: and Kneeling	[illegible] interest	**Score:** Child moves from a seated position to hands and knees.	1 0
33. Supports Weight	None	**Score:** Child supports own weight for at least 2 seconds.	1 0



	Item	Materials	Score Criteria and Comments	Score
30 31 34	34. Crawls Series: Crawl Movement	Object of interest	**Score:** Child makes forward progress of at least 5 feet by crawling on hands and knees.	1 0
	35. Raises Self to Standing Position	Object of interest	**Score:** Child raises self to a standing position, using a chair or other convenient object for support.	1 0
	36. Bounces While Standing	None	**Score:** Child bounces up and down at least twice by alternately bending and straightening the knees.	1 0
37 42 43	37. Walks Series: With Support	None	**Score:** Child walks by making coordinated, alternating stepping movements.	1 0
	38. Walks Sideways With Support	Object of interest	**Score:** Child walks sideways while holding onto furniture for support and balance.	1 0
	39. Sits Down With Control	None	**Score:** Child purposely lowers from a standing to a sitting position in a controlled manner.	1 0
	40. Stands Alone	None	**Score:** Child stands alone for at least 3 seconds after you release his or her hands.	1 0
41 46	41. Stands Up Series: Alone	None	**Score:** Child comes to a standing position, rolling first to a prone or quadruped position, without using any support.	1 0
37 42 43	42. Walks Series: Alone	None	**Score:** Child takes at least three steps without support, even if gait is stiff-legged and wobbly.	1 0
37 42 43	43. Walks Series: Alone With Coordination	None	**Score:** Child takes at least five steps independently, displaying coordination and balance.	1 0
	44. Throws Ball	Small ball	**Score:** Child purposely throws ball forward.	1 0

34 Bayley-III Motor Scale: Gross

Cognitive Scale

Reversal Rule: The child must obtain scores of 1 on the first three consecutive items at the start point of any age to go forward. If the child obtains a score of zero on any of the first three items, go back to the start point for the previous age and administer those items.

Discontinue Rule: Stop administration when the child obtains scores of zero on five consecutive items.

Item	Materials	Score Criteria and Comments	Score
A 1. Calms When Picked Up	None	**Score:** Child calms when picked up by either you or caregiver.	1 0
2. Responds to Surroundings Series: Inspects	None	**Score:** Child freely turns eyes or head in visual exploration of surroundings.	1 0
B C 3. Regards Object for 3 Seconds	Ring with string, ball, or other small object of interest	**Score:** Child gazes continuously at object for at least 3 seconds.	1 0
4. Habituates to Rattle	Rattle	Trials: 5 **Score:** Child displays orienting response to stimulus, then habituates during any of the remaining trials.	1 0
5. Discriminates Between Objects	Bell Stopwatch 5 seconds	**Score:** Child responds to bell by displaying a marked behavioral change within 5 seconds after you ring bell.	1 0
6. Recognizes Caregiver	None	**Score:** Child's expression changes to indicate recognition of the caregiver.	1 0
D 7. Becomes Excited in Anticipation	None	**Score:** Child displays anticipatory excitement.	1 0
8. Regards Object for 5 Seconds	Block or other small object of interest Stopwatch 5 seconds	**Score:** Child regards object continuously for at least 5 seconds.	1 0
9. Reacts to Disappearance of Face	None	**Score:** Child changes facial expression or displays other reaction to caregiver's disappearance.	1 0
10. Shifts Attention	Bell Rattle	Trials: 3 **Score:** Child's eyes move from one object to another in response to sound or movement of object(s).	1 0

2 20

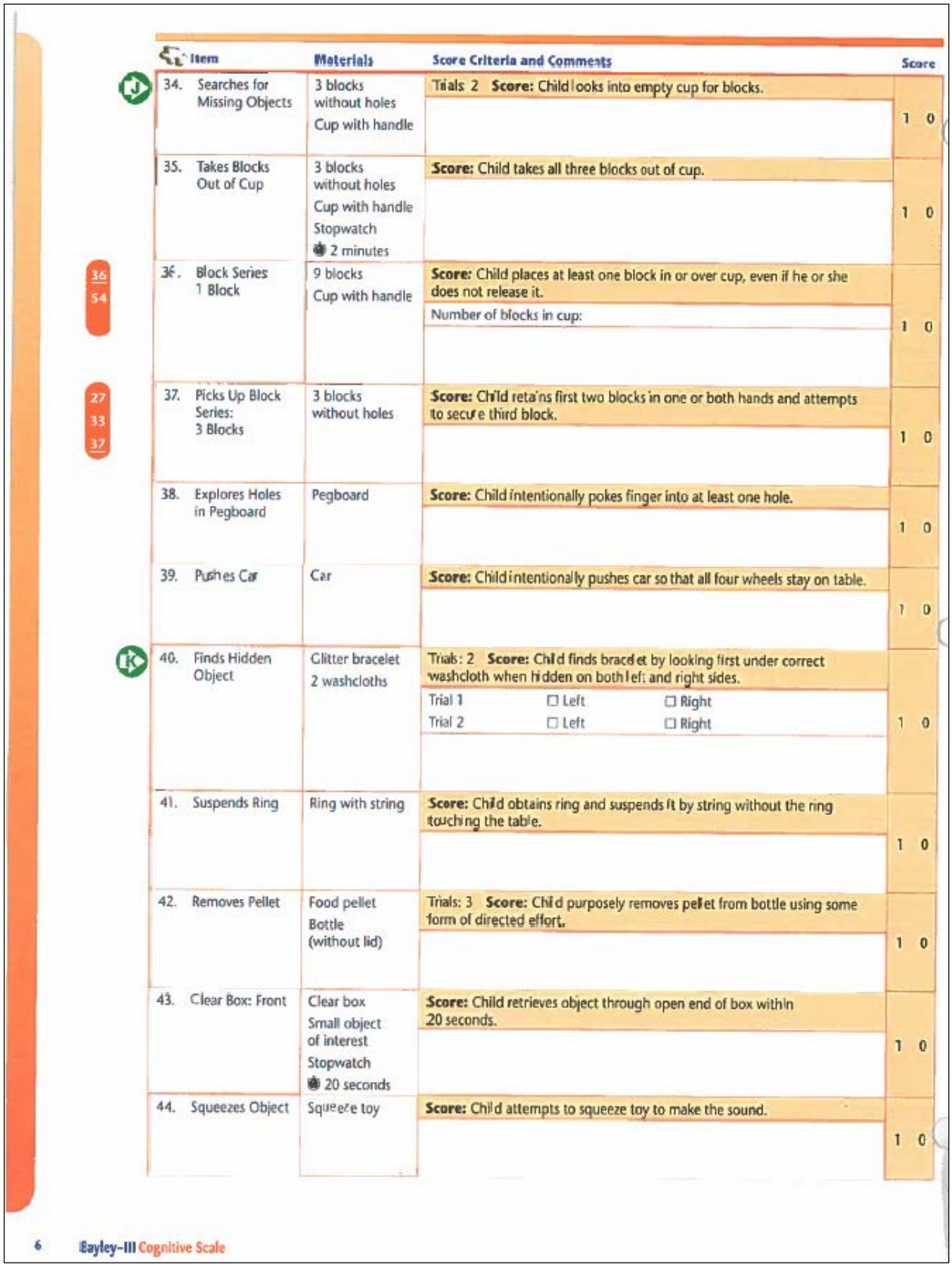
Bayley-III Cognitive Scale 3

Item	Materials	Score Criteria and Comments	Score
11. Shows Visual Preference	Stimulus Book (pp. 7–9) Stopwatch 15 seconds per page	**Score:** Child looks longer at striped pattern on both pages.	1 0
12. Habituates to Object	2 blocks without holes Stopwatch 30 seconds	**Score:** Child habituates within 30 seconds, displaying decrease in attention and interest.	1 0
13. Prefers Novel Object	Block without hole Small ball Stopwatch 15 seconds per presentation	**Score:** Child looks longer at ball than block in both presentations.	1 0
14. Habituates to Picture (Balloons)	Stimulus Book (p. 11) Stopwatch 30 seconds	**Score:** Child habituates within 30 seconds, displaying decrease in attention and interest.	1 0
15. Prefers Novel Picture (Ball)	Stimulus Book (pp. 13–15) Stopwatch 15 seconds per page	**Score:** Child looks longer at ball than balloons in both presentations.	1 0
16. Explores Object	Rattle or other small object of interest	**Score:** Child attends to sight, sound, or feel of object by shaking, mouthing, or other activity.	1 0
17. Carries Object to Mouth	Glitter bracelet or other small object of interest	**Score:** Child purposely carries object to mouth.	1 0
18. Inspects Own Hand	None	**Score:** Child visually inspects one or both hands.	1 0
19. Mirror Image Series: Approaches	Mirror	**Score:** Child approaches mirror image with head, body, or hands, or purposely touches mirror image.	1 0
20. Responds to Surroundings Series: Awareness of Novelty	None	**Score:** Child displays awareness of being in novel surroundings (e.g., startles, looks around).	1 0
21. Persistent Reach	Block without hole or other small object of interest	**Score:** Child persistently reaches for object, even if he or she fails to obtain it.	1 0

4 Bayley-III Cognitive Scale

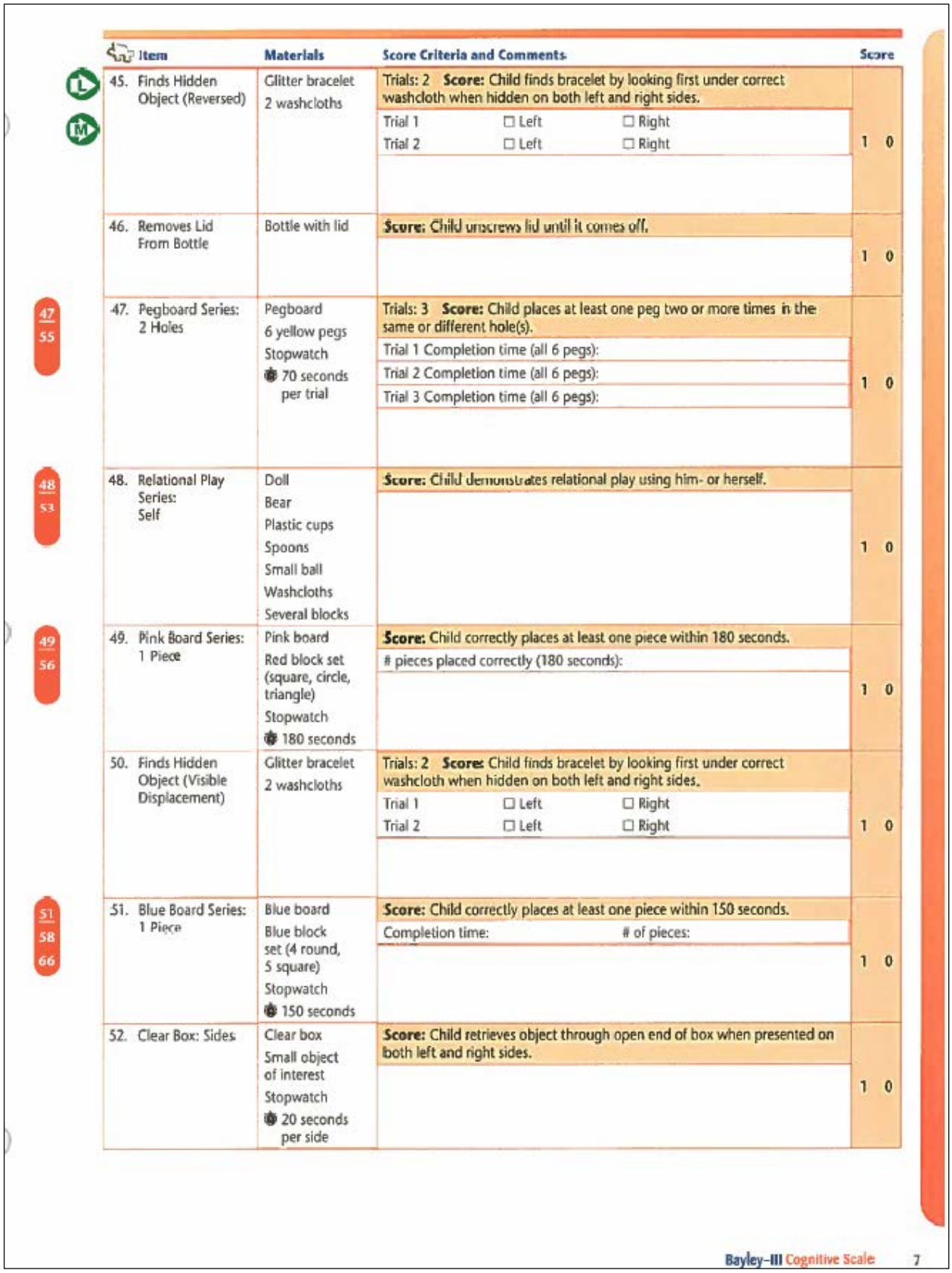
	Item	Materials	Score Criteria and Comments	Score
19 22 G	22. Mirror Image Series: Responds Positively	Mirror	**Score:** Child plays with image by looking and smiling/laughing, patting, banging, reaching playfully, or mouthing.	1 0
	23. Plays With String	Ring with string	**Score:** Child plays with string by picking it up, chewing it, pulling on it, or manipulating it.	1 0
	24. Bangs in Play	Block without hole, spoon, or other suitable hard object	**Score:** Child purposely bangs in play at any time during testing.	1 0
H	25. Searches for Fallen Object	Squeeze toy	**Score:** Child looks for fallen toy by looking toward floor.	1 0
26 31	26. Bell Series: Manipulates	Bell	**Score:** Child manipulates bell while looking at it with interest.	1 0
27 33 37	27. Picks Up Block Series: Reaches for Second Block	3 blocks without holes	**Score:** Child holds first block and reaches for second block.	1 0
	28. Pulls Cloth to Obtain Object	Washcloth Object of interest	**Score:** Child pulls washcloth purposely toward him or her to obtain object.	1 0
	29. Pulls String Adaptively	Ring with string	**Score:** Child picks up string, purposely pulls to secure ring, and grasps ring.	1 0
	30. Retains Both Blocks	2 blocks without holes	**Score:** Child holds both blocks simultaneously for at least 3 seconds.	1 0
26 31 I	31. Bell Series: Rings Purposely	Bell	**Score:** Child holds bell by handle and purposely rings it.	1 0
	32. Looks at Pictures	Picture Book	**Score:** Child regards one or more specific pictures with interest or recognition.	1 0
27 33 37	33. Picks Up Block Series: Retains 2 of 3 Blocks	3 blocks without holes	**Score:** Child retains first two blocks for at least 3 seconds after visually attending to third block	1 0

Bayley-III Cognitive Scale 5



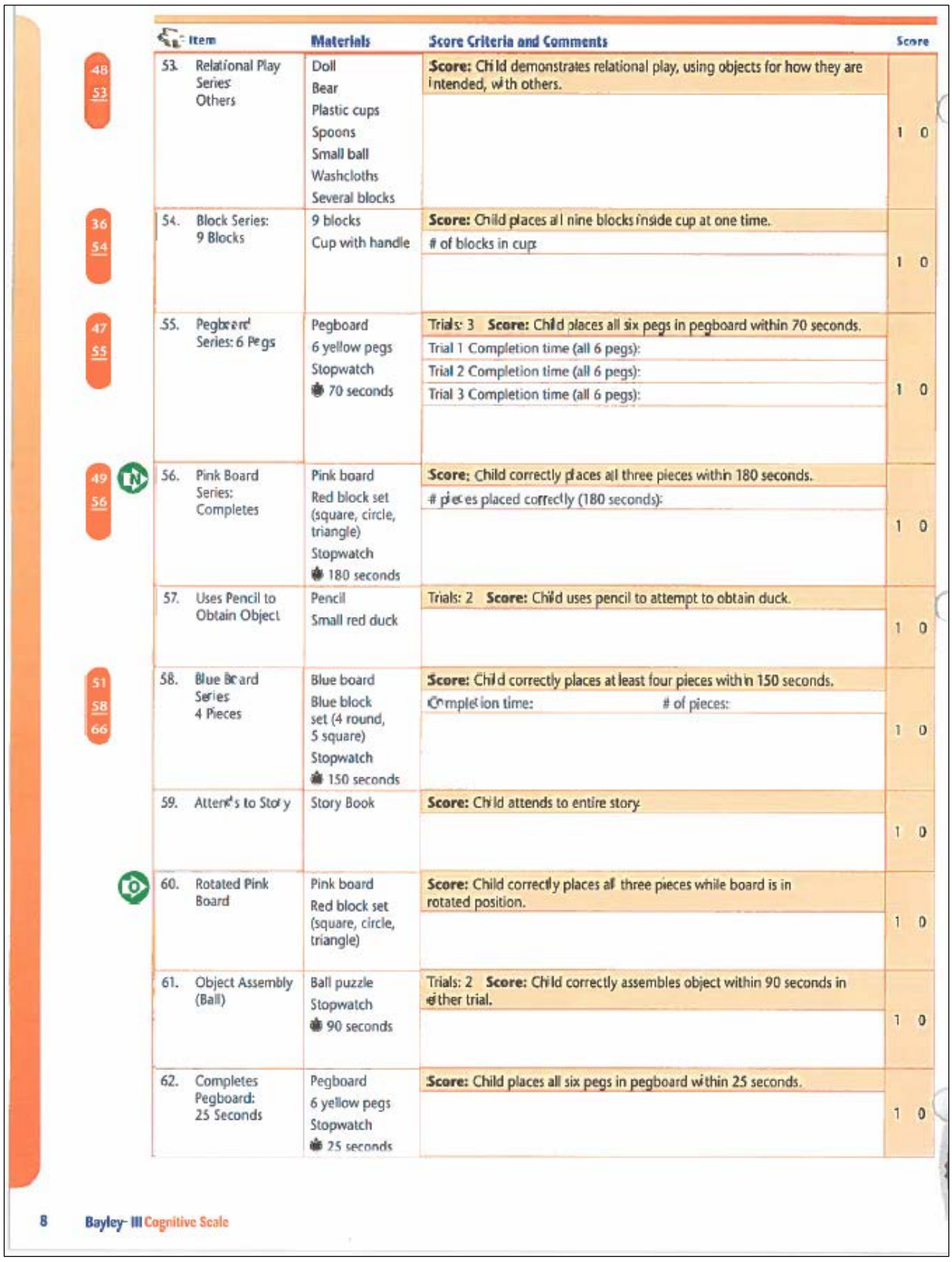
	Item	Materials	Score Criteria and Comments	Score
J	34. Searches for Missing Objects	3 blocks without holes Cup with handle	Trials 2 **Score:** Child looks into empty cup for blocks.	1 0
	35. Takes Blocks Out of Cup	3 blocks without holes Cup with handle Stopwatch 2 minutes	**Score:** Child takes all three blocks out of cup.	1 0
36 54	36. Block Series 1 Block	9 blocks Cup with handle	**Score:** Child places at least one block in or over cup, even if he or she does not release it. Number of blocks in cup:	1 0
27 33 37	37. Picks Up Block Series: 3 Blocks	3 blocks without holes	**Score:** Child retains first two blocks in one or both hands and attempts to secure third block.	1 0
	38. Explores Holes in Pegboard	Pegboard	**Score:** Child intentionally pokes finger into at least one hole.	1 0
	39. Pushes Car	Car	**Score:** Child intentionally pushes car so that all four wheels stay on table.	1 0
K	40. Finds Hidden Object	Glitter bracelet 2 washcloths	Trials: 2 **Score:** Child finds bracelet by looking first under correct washcloth when hidden on both left and right sides. Trial 1 ☐ Left ☐ Right Trial 2 ☐ Left ☐ Right	1 0
	41. Suspends Ring	Ring with string	**Score:** Child obtains ring and suspends it by string without the ring touching the table.	1 0
	42. Removes Pellet	Food pellet Bottle (without lid)	Trials: 3 **Score:** Child purposely removes pellet from bottle using some form of directed effort.	1 0
	43. Clear Box: Front	Clear box Small object of interest Stopwatch 20 seconds	**Score:** Child retrieves object through open end of box within 20 seconds.	1 0
	44. Squeezes Object	Squeeze toy	**Score:** Child attempts to squeeze toy to make the sound.	1 0

6 Bayley-III Cognitive Scale



Item	Materials	Score Criteria and Comments	Score
45. Finds Hidden Object (Reversed)	Glitter bracelet 2 washcloths	Trials: 2 **Score:** Child finds bracelet by looking first under correct washcloth when hidden on both left and right sides. Trial 1 ☐ Left ☐ Right Trial 2 ☐ Left ☐ Right	1 0
46. Removes Lid From Bottle	Bottle with lid	**Score:** Child unscrews lid until it comes off.	1 0
47 / 55 47. Pegboard Series: 2 Holes	Pegboard 6 yellow pegs Stopwatch 70 seconds per trial	Trials: 3 **Score:** Child places at least one peg two or more times in the same or different hole(s). Trial 1 Completion time (all 6 pegs): Trial 2 Completion time (all 6 pegs): Trial 3 Completion time (all 6 pegs):	1 0
48 / 53 48. Relational Play Series: Self	Doll Bear Plastic cups Spoons Small ball Washcloths Several blocks	**Score:** Child demonstrates relational play using him- or herself.	1 0
49 / 56 49. Pink Board Series: 1 Piece	Pink board Red block set (square, circle, triangle) Stopwatch 180 seconds	**Score:** Child correctly places at least one piece within 180 seconds. # pieces placed correctly (180 seconds):	1 0
50. Finds Hidden Object (Visible Displacement)	Glitter bracelet 2 washcloths	Trials: 2 **Score:** Child finds bracelet by looking first under correct washcloth when hidden on both left and right sides. Trial 1 ☐ Left ☐ Right Trial 2 ☐ Left ☐ Right	1 0
51 / 58 / 66 51. Blue Board Series: 1 Piece	Blue board Blue block set (4 round, 5 square) Stopwatch 150 seconds	**Score:** Child correctly places at least one piece within 150 seconds. Completion time: # of pieces:	1 0
52. Clear Box: Sides	Clear box Small object of interest Stopwatch 20 seconds per side	**Score:** Child retrieves object through open end of box when presented on both left and right sides.	1 0

Bayley-III Cognitive Scale 7



	Item	Materials	Score Criteria and Comments	Score
48 53	53. Relational Play Series: Others	Doll Bear Plastic cups Spoons Small ball Washcloths Several blocks	**Score:** Child demonstrates relational play, using objects for how they are intended, with others.	1 0
36 54	54. Block Series: 9 Blocks	9 blocks Cup with handle	**Score:** Child places all nine blocks inside cup at one time. # of blocks in cup:	1 0
47 55	55. Pegboard Series: 6 Pegs	Pegboard 6 yellow pegs Stopwatch 70 seconds	Trials: 3 **Score:** Child places all six pegs in pegboard within 70 seconds. Trial 1 Completion time (all 6 pegs): Trial 2 Completion time (all 6 pegs): Trial 3 Completion time (all 6 pegs):	1 0
49 56	56. Pink Board Series: Completes	Pink board Red block set (square, circle, triangle) Stopwatch 180 seconds	**Score:** Child correctly places all three pieces within 180 seconds. # pieces placed correctly (180 seconds):	1 0
	57. Uses Pencil to Obtain Object	Pencil Small red duck	Trials: 2 **Score:** Child uses pencil to attempt to obtain duck.	1 0
51 58 66	58. Blue Board Series: 4 Pieces	Blue board Blue block set (4 round, 5 square) Stopwatch 150 seconds	**Score:** Child correctly places at least four pieces within 150 seconds. Completion time: # of pieces:	1 0
	59. Attends to Story	Story Book	**Score:** Child attends to entire story.	1 0
	60. Rotated Pink Board	Pink board Red block set (square, circle, triangle)	**Score:** Child correctly places all three pieces while board is in rotated position.	1 0
	61. Object Assembly (Ball)	Ball puzzle Stopwatch 90 seconds	Trials: 2 **Score:** Child correctly assembles object within 90 seconds in either trial.	1 0
	62. Completes Pegboard: 25 Seconds	Pegboard 6 yellow pegs Stopwatch 25 seconds	**Score:** Child places all six pegs in pegboard within 25 seconds.	1 0

8 Bayley-III Cognitive Scale

Item	Materials	Score Criteria and Comments	Score
63. Object Assembly (Ice Cream Cone)	Ice cream cone puzzle Stopwatch 90 seconds	Trials: 2 **Score:** Child correctly assembles object within 90 seconds in either trial.	1 0
64. Matches Pictures	Stimulus Book (pp. 17–23)	**Score:** Child correctly identifies matching picture on at least three pages. ☐ Airplane ☐ Tricycle ☐ Tree ☐ Telephone	1 0
65. Representational Play	Plastic cups Spoon Doll Washcloths Block Other objects of interest	**Score:** Child takes an object and pretends it is something else.	1 0
66. Blue Board Series: Completes (75 Seconds) (51 58 66)	Blue board Blue block set (4 round, 5 square) Stopwatch 75 seconds	**Score:** Child correctly places all nine pieces within 75 seconds.	1 0
67. Imitates a Two-Step Action	Small yellow duck Spoon	Trials: 3 **Score:** Child correctly imitates both steps.	1 0
68. Matches 3 Colors	Stimulus Book (p. 25) Red, yellow, blue, and green disks	**Score:** Child places yellow, blue, and green disks on or near matching crayons in Stimulus Book, or points to matching crayons. ☐ Yellow ☐ Blue ☐ Green	1 0
69. Imaginary Play	Plastic cups Spoon Doll Bear Washcloths Small ball Other objects of interest	**Score:** Child uses imaginary objects in play.	1 0
70. Understands Concept of One	3 blocks without holes Stopwatch 5 seconds	**Score:** Child hands you only one block within 5 seconds.	1 0
71. Multischeme Combination Play	Plastic cups Spoon Doll Bear Washcloths Small ball Other objects of interest	**Score:** Child demonstrates multischeme combination play involving at least two steps.	1 0

Bayley-III Cognitive Scale 9

Item	Materials	Score Criteria and Comments	Score
72. Concept Grouping: Color	Big and little ducks (blue and yellow)	**Score:** Child correctly identifies both blue ducks.	1 0
73. Concept Grouping: Size	Big and little ducks (red and yellow)	**Score:** Child correctly identifies both little ducks and both big ducks.	1 0
74. Compares Masses	2 big blue ducks	Trials: 2 **Score:** Child correctly identifies heavy duck when placed in both left and right hands.	1 0
75. Matches Size	Big red duck Big blue duck Little yellow duck	**Score:** Child correctly identifies big blue duck.	1 0
76. Discriminates Pictures	Stimulus Book (pp. 27–37)	**Score:** Child correctly identifies calf and donkey.	1 0
77. Simple Pattern	Big and little ducks	**Score:** Child correctly identifies big yellow duck.	1 0
78. Sorts Pegs by Color	4 red pegs 4 yellow pegs 4 blue pegs 3 plastic cups	**Score:** Child sorts pegs by color, placing them in appropriate cups or in separate piles.	1 0
79. Counts (One-to-One Correspondence)	5 blocks	**Score:** Child assigns only one number to each block when counting. Child must count to at least 3 in proper sequence.	1 0
80. Discriminates Sizes	Stimulus Book (pp. 39–43)	**Score:** Child identifies correctly-sized object for at least two of three pages. ☐ Box lid ☐ Bowl ☐ Shoe	1 0
81. Identifies 3 Incomplete Pictures	Stimulus Book (pp. 45–61)	**Score:** For all three series, child correctly identifies image when presented with first or second page of the series. ☐ Face ☐ Cat ☐ Flower	1 0
82. Object Assembly (Dog)	Dog puzzle Stopwatch 90 seconds	Trials: 2 **Score:** Child correctly assembles object within 90 seconds in either trial.	1 0
83. Discriminates Patterns	Stimulus Book (pp. 63–67)	**Score:** Child correctly identifies out-of-place object for all three pages. ☐ Square ☐ Triangle ☐ E	1 0

10 Bayley-III Cognitive Scale

Item	Materials	Score Criteria and Comments	Score
84. Spatial Memory	Memory Cards	**Score:** Child correctly identifies the correct pairs of cards for the first two objects. ☐ Tops ☐ Flowers ☐ Cars	1 0
85. Counts (Cardinality)	10 blocks	**Score:** Child correctly responds to both parts.	1 0
86. Number Constancy	5 blocks	**Score:** Child correctly answers both questions.	1 0
87. Laces Card	Lacing card Shoelace	**Score:** Child laces shoelace through entire lacing card, in proper order without skipping holes or lacing around side of card.	1 0
88. Classifies Objects	Stimulus Book (pp. 69–73)	**Score:** Child correctly identifies all three objects that don't belong. ☐ Banana ☐ Lamp ☐ Train	1 0
89. Understands Concept of More	9 blocks 1 red disc 3 red pegs	**Score:** Child correctly responds to all four administrations. ☐ First ☐ Second ☐ Third ☐ Fourth	1 0
90. Repeats Number Sequences	None	**Score:** Child correctly repeats at least four number sequences. ☐ A: 4–2–5 ☐ B: 3–1–4–2 ☐ C: 7–9–1–3 ☐ D: 5–3–7–1–6 ☐ E: 8–1–9–6–4	1 0
91. Completes Patterns	Pegboard Red, blue, and yellow pegs	**Score:** Child places correct pegs in pegboard for all three patterns. Pattern 1 ☐ R–B–R–B–R–**B** Pattern 2 ☐ Y–B–R–Y–**B**–R Pattern 3 ☐ Y–Y–B–Y–**Y**–**B**	1 0
		Total Raw Score (Cog)	/91

APPENDIX 5 GROSS MOTOR SKILLS CHECKLIST

Gross Motor Skills Checklist

Subject: Date: Evaluator:

Item Description	Image	Able to Perform?	
1. Hands to midline in supine		Yes	No
2. Holds head upright while carried		Yes	No
3. Lifts head in prone		Yes	No
4. Rolls from side to back		Yes	No
5. Rolls from back to side		Yes	No
6. Props on hands in prone		Yes	No
7. Sits with support		Yes	No
8. Rolls from back to stomach		Yes	No
9. Rolls from stomach to back		Yes	No
10. Sits without support		Yes	No

Item Description	Image	Able to Perform?	
11. Sits without support and plays		Yes	No
12. Holds hands and knees position		Yes	No
13. Pulls to Stand		Yes	No
14. Cruises at support surface		Yes	No
15. Walks with support		Yes	No
16. Takes independent steps		Yes	No