RELIABILITY AND VALIDITY OF THE ACTIVE-MINI FOR QUANTIFYING MOVEMENT IN INFANTS WITH SPINAL MUSCULAR ATROPHY

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE GRADUATE SCHOOL OF THE

TEXAS WOMAN'S UNIVERSITY

SCHOOL OF PHYSICAL THERAPY

COLLEGE OF HEALTH SCIENCES

BY

LESLIE NELSON, B. S., M. P. T

DENTON, TEXAS.

DECEMBER 2018

DEDICATION

All the glory to God for this work.

And, with admiration, I dedicate this work to all families with children with SMA.

ACKNOWLEDGEMENTS

There is no way to fully acknowledge all the individuals who facilitated me along this journey. Dr. Thompson, your patience and guidance through these years has been so appreciated. Obviously, I could not have done this without your positive outlook and encouraging words. Dr. Wang, your passion and comprehension of all aspects of research is immeasurable and so very valuable. Dr. Swank, thank you so much for jumping on midway through and embracing it all with such wonderful insight. Dr. Lowes, thank you for your passion for innovation and for your persistence in all things. Without you, this work would have not been possible. All of you made this an amazing learning experience that I will always cherish.

To the Nationwide Department of Research Information Solutions and Innovation, specifically, David Chen, I am extremely grateful for the innovative feature engineering framework that made this project possible.

To my UT Southwestern and Children's colleagues, thank you for putting up with me during this entire process of ups and downs. Your support truly means the world to me and I could not be luckier to work with two amazing groups made up of exceptional people.

And last, but certainly not least, to my family and friends. Your unending love and grace gave me the support and comfort to make it through this entire process. To my Dad, who taught me the meaning of persistence by leading by example all those years growing up. And to my siblings for always having an encouraging word or a way to make me laugh when it was needed.

ABSTRACT

LESLIE NELSON

RELIABILITY AND VALIDITY OF THE ACTIVE-MINI FOR QUANTIFYING MOVEMENT IN INFANTS WITH SPINAL MUSCULAR ATROPHY

DECEMBER 2018

Background: Motor function assessment of individuals with SMA I is challenging due to the low level of function typically obtained and the fragility of the infant. Outcome measures currently used by clinical evaluators, such as the CHOP INTEND, require significant training due to their subjective nature and can be fatiguing to the infant. Outcome measures that can objectively distinguish small changes over time without adding significant stress on the infant with SMA Type I are needed to determine the effectiveness of intervention and change over time. The purposes of this study were to investigate the reliability and validity of the ACTIVE-mini for quantifying movement in infants with SMA, specifically, within-day test-retest reliability, between-day test-retest reliability, convergent validity, and construct validity using the known-groups method.

Methods: This study was a cross-sectional, repeated measure design with two groups. Non-rolling infants with SMA and function-matched non-rolling typically developing infants. The dependent variables included a CHOP INTEND extremity score and a predicted CHOP INTEND extremity score determined by data captured with the ACTIVE-mini. Dependent variables were collected at two time points in a standardized order with standardized assessment. An ICC was calculated to determine within day test-retest reliability and between day test-retest reliability.

To examine the convergent validity of the ACTIVE-mini, a Pearson correlation was used to analyze the relationship between the predicted CHOP INTEND score and the observed CHOP INTEND extremity score. An independent sample *t* test was run to examine the construct validity of the ACTIVE-mini using the known groups method.

Results: There was good reliability for both within day and between day test-retest reliability of the ACTIVE-mini derived score in subjects with SMA. There was a moderate positive correlation of the ACTIVE-mini score with the observed CHOP INTEND extremity score. There was a statistically significant difference of the predicted CHOP INTEND score between the function-matched controls and subjects with SMA.

Conclusion: The results of this study support the use of the ACTIVE-mini for quantifying movement in infants with SMA. There was good test-retest reliability of the tool as well as good convergent and construct validity. The ACTIVE-mini can be used in conjunction with physiologic biomarkers and clinical assessments to offer a more complete report of overall status of the child with SMA I. It may also offer information regarding function over a period of time or at multiple time points that could not be completed with one single clinical assessment. It can be completed in various settings, is quick to administer, and is not burdensome to the infant and the family. While the CHOP INTEND will continue to be the gold standard for measurement of function in infants with SMA, the ACTIVE-mini may be a useful tool that could help resolve the issues of the CHOP INTEND such as fatigue with testing and subjectivity of scoring. Use of the ACTIVE-mini system may aid in understanding disease progression and response to therapeutic agents and interventions in multisite clinical trials and for clinical assessment in patients with SMA I.

TABLE OF CONTENTS

Page

DEDICATION ii

ACKNOWLEDGMENTS iii

ABSTRACT iv

LIST OF TABLES ix

LIST OF FIGURES x

Chapter

I. INTRODUCTION 1

- Statement of the Problem 7
- Purpose of the Study 8
- Research Questions 8
- Research Hypotheses 9
- Operational Definitions 9
- Assumptions 10
- Limitations 11
- Significance of the Study 12

II. REVIEW OF THE LITERATURE 14

- Spinal Muscular Atrophy (SMA) 14
  - Prevalence and Medical Cost of SMA 15
  - Clinical Presentation of SMA 16
- Interventions for Individuals With SMA 18
  - Pharmaceutical Agents 19
  - Non-pharmaceutical Medical Management 21
- Tests and Measures for Individuals With SMA 25
  - Children's Hospital of Philadelphia Test for Neuromuscular Disorders 28
  - Test of Infant Motor Performance, Screening Items 30
  - Other Outcome Measures 31
  - The Ability Captured Through Interactive Video Evaluation-mini 32

Rationale for Choosing Outcome Measures and Chapter Summary 39

III. METHODS 42

Research Design and Study Overview 43
Participants 43
Examiners 44
Instrumentation 45
CHOP INTEND 45
ACTIVE-mini 46
Procedures 49
Data Analysis 52

IV. RESULTS 54

Participants 54
Within Day Reliability of ACTIVE-mini to Quantify Extremity Movements in Children with SMA I 56
Between Day Reliability of ACTIVE-mini to Quantify Extremity Movements in Children with SMA I 58
Convergent Construct Validity 59
Construct Validity 62
Summary 63

V. DISCUSSION 64

Summary of Findings
Hypothesis 1 64
Hypothesis 2 64
Hypothesis 3 65
Hypothesis 4 65
Discussion of Findings 67
Reliability 67
Validity 70
Limitations 78
Recommendations for Future Research 80
Conclusion 81

REFERENCES 83

APPENDICES 101

A. Studies Investigating the use of Physical Therapy Services in Patients with SMA 101

B. CHOP INTEND Scoresheet 105
C. TIMPSI Item List 108
D. CHOP INTEND Manual of Procedures 111
E. CHOP INTEND Extremity Score 119
F. IRB APPROVAL LETTERS 121

LIST OF TABLES

Table Page

1. Classification of Spinal Muscular Atrophy by Type 2
2. Trials Included in Cochran Review Type II and III 20
3. Outcome Measures Used in SMA by Type 26
4. Brazelton Behavioral State 29
5. Definitions of ACTIVE-mini Features 49
6. Participant Characteristics 55
7. Means and Standard Deviation of Recording Session One and Recording Session Two on Day One and Day Two of Testing 57
8. Means and Standard Deviations of the Average ACTIVE-mini scores of Both Days of Testing 58
9. Summary of Research Questions, Analysis Methods, and Results 66
10. *Results of Receiver Operating Curve Analysis for the ACTIVE-mini Score and CHOP INTEND Extremity Score* 77

LIST OF FIGURES

Figure Page

1. Trajectory Plot of Subjects with SMA and Controls 34

2. Total number of voxels accessed with all extremities 36

3. Group average total volume accessed by the upper and lower extremities in infants with SMA I and controls over time as assessed by convex hull analysis 36

4. Kernel density plots of movement velocity and jerk (derivative of acceleration) scaled to most frequent value in an infant with SMA I between days 11 to 78 of life 38

5. ACTIVE-mini set up with Microsoft Kinect® camera platform 47

6. Procedure for Testing 51

7. Flow chart for study enrollment and data analysis 56

8. Scatterplot With Line of Fit Active-mini Score by CHOP INTEND extremity score 59

9. Scatterplot with Line of Fit of ACTIVE-mini Score by CHOP INTEND extremity score with extreme subjects removed 60

10. Bland-Altman Plot with limits of agreement demonstrating agreement between mean ACTIVE-mini and CHOP INTEND extremity scores. The difference between the two scales is plotted on the Y-axis, and the mean ACTIVE-mini and CHOP INTEND extremity score on the X-axis 61

11. Active-mini Score Means by Group 62

12. Receiver Operating Characteristic Curve for ACTIVE-mini Score 76

13. Receiver Operating Characteristic Curve for CHOP INTEND extremity score 76

CHAPTER I

INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular disorder of the anterior horn cell resulting in progressive muscle weakness (Lefebvre et al., 1995). Individuals with SMA exhibit weakness of the neck, trunk, and limbs. The typical pattern of weakness seen in individuals with SMA includes lower limbs affected earlier than upper and proximal weakness greater than distal (Kroksmark, Beckung, & Tulinius, 2001, Thomas & Dubowitz, 1994). One of the most common fatal autosomal recessive disorders, SMA has an estimated incidence of 1 in 6,000 to 11,000 individuals (Arnold, Kassar, & Kissel, 2015; Cobben, de Visser, & Scheffer, 2001; Nicole, Diaz, Frugier, & Melki, 2002). Diagnosis of SMA is confirmed by reduced Survival Motor Neuron (SMN) protein levels located at exon 7 of chromosome 5q as revealed through genetic testing (Mercuri, Bertini, & Iannaccone, 2012). In unaffected individuals, exon 7 codes for the production of SMN protein, which is mostly full-length and functional. When deletions or mutations occur at exon 7, little or no functional SMN protein is produced. This loss can be partially offset by the presence of SMN2 genes, which are similar in structure to SMN1 genes. The number of SMN2 genes varies from person to person. Individuals with earlier onset and fewer SMN copies are typically affected with a more severe form of SMA than those with a later onset and greater number of copies of SMN2 (Prior & Russman, 2000; Swoboda et al., 2005).

The disease is characterized into five subtypes (Type 0, I, II, III, and IV) in individuals based upon age of onset and motor function achieved (see Table 1) (Kroksmark et al.,2001;

Wang, Finkel, & Bertini, 2007; Yuan & Jiang, 2015). SMA 0 is the most severe type exhibiting very little active movement at birth and difficulty in breathing and swallowing (Prior & Russman, 2000). Subtype I is the most common form. Children with SMA I have low tone, poor head and trunk control, and will never be able to sit without support. These infants often develop joint contractures and have bulbar weakness, leading to difficulty with suck and swallow that are necessary for adequate feeding and nutrition (Cobben et al., 2008; Iannaccone, Browne, Samaha, & Buncher, 1993; Thomas & Dubowitz, 1994). The shortened life expectancy in these infants is due to the possibility of a rapid rate of decline due to medical complications including their poor respiratory and nutritional status (Finkel et al., 2014; Griggs et al., 2009).

Table 1

Classification of Spinal Muscular Atrophy by Type

SMA Type	Symptom Onset	Function	Death
0	Birth	Respiratory support	Neonatal
I	0-6 months	Never sit	<2 years
II	7-18 months	Never stand	>2 years
III	>18 months	Stand alone	Adult
IV	>21 years	Stand alone	Adult

The intermediate type, SMA II, is characterized by the functional ability to sit independently, although these individuals are never able to walk without support. Due to their pattern of weakness, they often develop severe orthopedic complications including contractures of the limbs and scoliosis (Bertini et al., 2005). Pulmonary and nutritional status are compromised, but if medically controlled by following recommended standards of care (Finkel et al., 2018; Mercuri et al., 2018; Wang et al., 2007), the children characteristically survive beyond two years and may live into adolescence or longer (Russman, Buncher, White, Samaha, & Iannaccone, 1996; Zerres et al., 1997). The mildest form of juvenile SMA III, may also be further classified into Type IIIa and IIIb. Children diagnosed earlier are classified as Type IIIa and tend to be more severely affected than those diagnosed after 3 years of age (Type IIIb). Children with SMA III develop the ability to walk at some point in their life although many will lose this ability around puberty. Their life expectancy may be normal if respiratory and nutritional health is maintained (Russman. et al., 1992; Zerres et al., 1997). Subtype IV is very rare. Symptoms typically present in adulthood and lead to mild motor impairment (Prior & Russman, 2000). In summary, persons with SMA II, III, and IV typically present with milder symptoms than persons with Type I and therefore can expect fewer adverse events related to nutritional and respiratory status.

Although there are defined subtype classifications, SMA has a broad clinical spectrum with some overlap between classifications. Within each subtype, there are stronger and weaker individuals. For instance, infants classified as SMA I typically do not develop head control, but stronger type I infants may uncharacteristically gain this ability in supported sitting. Another example is children diagnosed earlier than 18 months (characterized as SMA II) who gain the

ability to walk later in life (Russman et al., 1992; Zerres & Rudnik-Schoneborn, 1995). Therefore, experts have found that maximum function achieved by children with SMA predicts the natural course of the disease better than the age of onset (Russman et al., 1996).

Clinical research trials assessing the natural history of the disease and efficacy of interventions in the SMA population are difficult to carry out for many reasons. Challenges include the variability and overlap between and within subtypes, fragility of the infants and children, lack of sensitive and robust outcomes to measure strength and function, the potential rapid rate of decline of the participants, and the rarity of disease (Finkel et al., 2014; Griggs et al., 2009). Nonetheless, stratification for inclusion criteria in the past and current SMA clinical trials have been based upon age and/or disease severity (Darras et al., 2014; Kissel et al., 2013; Mercuri et al., 2007; Swoboda et al., 2010). To measure functional ability in persons with SMA, standardized outcome measures evaluating change are used in clinical research trials and in multidisciplinary clinic settings. Age-specific tests and outcome measures assessing a narrow range of functional abilities make comparisons across subtypes difficult. The overlap of function within SMA subtypes may inflate sample size calculations. Stratification and use of several motor function outcome measures to address subtype and variation in function also generally increase study cost by increasing the time commitment from clinical evaluators and the need for increased evaluator training for the multiple outcomes that must be used. Outcomes used to assess change in patients with SMA must take into consideration the possible overlap of function between types to reduce possible floor and ceiling effects. The measures must also be valid, reliable, and sensitive to change in this population. Ideal measures should be easily administered, require minimal training and equipment, and should minimize patient and family

burden (Kaufmann & Finkel, 2007). Furthermore, clinical outcomes must be meaningful to evaluate treatment effect. Ideally, these qualities would be found in a single outcome measure that would not depend on patients' cooperation or evaluators' skill. Unfortunately, to date no such universal assessment for SMA has been identified and functional or motor status remains the best indicator of change.

Without a universal outcome measure for persons with SMA, or specifically for SMA I which is the most common form of SMA, at this time treatment efficacy is measured based on function achieved by the child as measured by time until respiratory failure (use of assisted ventilation ≥ 16 hours per day) or time until death (Montes, Gordon, Pandya, DeVivo, & Kaufmann, 2009; Wadman et al., 2012). Time until permanent ventilation is a poor endpoint due to the fact that determining when to initiate permanent ventilation is controversial, having no set criteria with varying opinions on how aggressive to be in regard to sustaining or prolonging the life of the child (Ottonello et al., 2011). Time until death is a straightforward outcome in mortality follow-up studies, but has limited usefulness for clinical trials. Although time until death and time until use of permanent ventilation are important endpoints, functional or motor status may be more clinically meaningful when monitoring change over time. Recently, the use of a standardized motor outcome measure, The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP INTEND), has been used as a standard clinical outcome to assess functional status and change over time in infants and young children with SMA I (Glanzman et al., 2010; Krosschell et al., 2013; Montes et al., 2009).

The CHOP INTEND is a measure of global motor function currently used in the SMA I population as part of standard clinical practice and is recorded as a discrete data set (Montes et

al., 2009). The CHOP INTEND is an assessment instrument that was developed specifically for weak infants with neuromuscular disease (Glanzman et al., 2010). Glanzman et al. (2011) reported in a validation study that the CHOP INTEND related well to participant age, required ventilatory support, and disease severity in the SMA I population. The CHOP INTEND has been used in recent industry sponsored trials as the primary outcome measure and is considered the best assessment of motor function at this time for individuals with SMA I (Chiriboga et al., 2013). Although the CHOP INTEND is clinically meaningful, reliable, and provides discrete sets of information regarding motor function, there are some limitations of its use in research trials. It requires training of the evaluator due to the dependence on the subjective opinion of the assessor. Furthermore, it requires the cooperation of the child and can be fatiguing to the infant, as items require the tester to elicit activity while the child is placed in positions that increase the work of breathing (Glanzman et al., 2011). Rasch analysis also has identified that the scale lacks some psychometric properties that make it less than ideal as outcome measure for clinical trials (Cano et al., 2014). Nevertheless, it is a clinically-valuable outcome measure that provides an understanding of the progression of the disease process in the SMA I population.

The use of video to quantify movement is common in current rehabilitation research. Traditional 3-dimensional (3D) motion capture systems equipped with high-speed cameras have been used to objectively quantify movement (Bhat, Lee, & Galloway, 2007; Chester & Calhoun, 2012; Klotz et al., 2014; Rocha, Silva, & Tudella, 2006). However, 3D motion systems are costly, require significant time for analyzing data, and require travel of the research participant to the site for testing. Recently, the Ability Captured Through Interactive Video Evaluation-seated

system (ACTIVE-seated) was developed to aid in providing an objective and sensitive measure of upper extremities motor function in children with neuromuscular disease (Lowes et al., 2015; Lowes et al., 2013). This system uses the Microsoft Kinect® camera platform that provides a low-cost camera system with the ability to capture video that records both depth and color data. Color-coded data allows the user to differentiate between upper and lower extremity movements for comparison between limbs. Depth data allows the user to differentiate the planes of movement that occur with all extremities. Open source software development kits can be used to process the data stream captured by the Kinect® camera and to automate the process of analyzing the movement data. The Ability Captured Through Interactive Video Evaluation-mini (ACTIVE-mini), was subsequently developed in 2013 by the same research group, using the same concept to examine movement in infants, specifically SMA I individuals. Based on pilot data, the ACTIVE-mini may be beneficial in quantifying movement in infants and may therefore be a useful tool for assessing changes in infants with SMA I (Alfano et al., 2016).

Statement of the Problem

Motor function assessment of individuals with SMA I is challenging due to the low level of function typically obtained and the fragility of the infant. Outcome measures currently used by clinical evaluators, such as the CHOP INTEND, require significant training due to their subjective nature and can be fatiguing to the infant. Outcome measures that can objectively distinguish small changes over time without adding significant stress on the infant with SMA Type I are needed to determine the effectiveness of intervention and change over time.

A recently developed ACTIVE-mini system appears to be an alternative motor outcome measure for weak infants. ACTIVE-mini testing can be completed in various settings (e.g.

laboratory, clinic and home, etc.), is quick to administer, and is minimally burdensome to the infant as it involves collection of natural and spontaneous movements in an uncompromising supine position. Clinical trials in the SMA I population could be advanced by the use of a functional outcome measure such as the ACTIVE-mini that reliably quantifies small changes in movement while minimizing stress on the fragile infants with SMA and their families. However, the reliability and validity of the ACTIVE-mini has not been established for infants with SMA.

Purpose of the Study

The purposes of this study were to investigate the reliability and validity of the ACTIVE-mini for quantifying extremity movement in infants with SMA, specifically, within-day test-retest reliability, between-day test-retest reliability, convergent validity, and construct validity using the known-groups method.

Research Questions

The following research questions were addressed in this study regarding spontaneous extremity movement:

1. Is the within-day test-retest reliability of the ACTIVE-mini good for quantifying movement in infants with SMA?
2. Is the between-day test-retest reliability of the ACTIVE-mini good for quantifying movement in infants with SMA?
3. Does the ACTIVE-mini have good convergent validity for quantifying movement of infants with SMA?
4. Does ACTIVE-mini have good construct validity using the known-groups method for quantifying movement of infants with SMA?

Research Hypotheses

The hypotheses of this study were:

1. There will be good within-day test-retest reliability of the ACTIVE-mini for quantifying movement with intraclass correlation coefficients (ICC) ≥ 75% (Portney & Watkins, 2009).
2. There will be good between-day test-retest reliability of the ACTIVE-mini for quantifying movement with ICC ≥ 75% (Portney & Watkins, 2009).
3. There will be good convergent construct validity of the ACTIVE-mini for assessing motor function level of infants with SMA, with a good to excellent positive correlation ($r \geq 75\%$) (Portney & Watkins, 2009) between the movement score obtained with the ACTIVE-mini and the extremity score of the CHOP INTEND.
4. There will be good construct validity of the ACTIVE-mini using the known-groups method for assessing motor function level, with a significant difference in the movement score obtained with the ACTIVE-mini ($p < 0.05$) between infants with SMA and functional-matched healthy infants (Portney & Watkins, 2009).

Operational Definitions

For the purposes of this study, the following terms were defined:

- Spinal Muscular Atrophy (SMA) I: Subtype of SMA characterized by an infant with genetic confirmation of SMA without the ability to sit independently (Prior & Russman, 2000).
- Behavioral State: Group of characteristic actions and physiologic changes that recur together in a regular pattern in response to a baby's needs (Brazelton & Cramer, 1990).
- Outcome Measure: Standardized tests and measures used early in an episode of care to establish the baseline status of the patient/client, providing a means to quantify change in

the patient's/client's functioning (Montes et al., 2009).Outcome measure results can vary in infants based on their behavioral state.

- CHOP INTEND: Standardized outcome measure of gross motor function currently used in the SMA I population as part of standard clinical practice that measures global function of the patient (Montes et al., 2009).
- CHOP INTEND Extremity Score: Subset of items specifically measuring spontaneous or elicited movement of the upper and lower extremities. Consists of nine items scored bilaterally with a total maximum score of 72.
- ACTIVE-mini: Newly developed evaluation system that uses a motion tracking device to generate color coded positional data that is processed into a scaled score (Alfano et al., 2016; Lowes et al., 2013).
- ACTIVE-mini Score: Generated scaled score examining spontaneous extremity movement of an infant or child using the ACTIVE-mini system and equated to the CHOP INTEND extremity score.

Assumptions

For purposes of this study, the following assumptions were made:

- A difference in behavior state between Brazelton 4 or 5 during test administration will not alter findings.
- The investigator will give consistent verbal instruction and encouragement during the ACTIVE-mini and CHOP INTEND testing.

- Two 2-minute recording times for the ACTIVE-mini will adequately capture spontaneous natural movement of an infant.
- The ACTIVE-mini score calculated from ACTIVE-mini data is accurate.
- The CHOP INTEND is a valid outcome measure for determining the level of motor function for all of the participants.
- The CHOP INTEND extremity score is a valid outcome measure for determining level of motor function in the extremities for all participants.

Limitations

The following were limitations of this study:

- SMA Type I is a rare condition and there are a limited number of subjects.
- There are known psychometric limitations of the CHOP INTEND. To be considered an appropriate measurement instrument for clinical trials, a series of psychometric criteria must be met. Cano et al. (2014) studied Rasch measurement methods and provided a detailed description of the measurement performance of the items on the CHOP INTEND. The scale demonstrated adequate reliability, but did show some internal validity-related problems with the extent to which some items adequately measure motor performance. This study found the CHOP INTEND to have some degree of reversed threshold. This means that their response categories are not working as intended. Adding together items from related but potentially different constructs, for example trunk and extremity function, could contribute to disordered thresholds, lending support to the idea that this may be a significant measurement issue affecting the internal validity of the CHOP INTEND.

- The CHOP INTEND has subjective components that may introduce measurement error. While reliability has been established and there is a standardized manual and scoresheet for the CHOP INTEND, scoring of the items requires the evaluator's interpretation and clinical judgement. In addition to the subjective nature of scoring, the infant's behavior may affect the scoring. For example, an infant that is not displaying his or her best possible movement because he is content, well fed, and rested.
- CHOP INTEND extremity score is derived from the CHOP INTEND and is not a validated measure in persons with SMA.

Significance of the Study

Clinical research trials evaluating therapeutic effects in the SMA I population could be advanced by an outcome measure that reliably and objectively quantifies small changes in function, and minimizes stress on fragile infants (Crawford, 2004). Clinical trials for infants with SMA I pose unique challenges due to their profound weakness, respiratory insufficiency and vulnerability to complications related to participation in trials, such as travel or multiple procedures and examinations required during a research visit (Swoboda et al., 2007). Presently, the most common functional outcome measures used in clinical trials are time until death and time until permanent ventilation. The CHOP INTEND is a functional motor assessment that has emerged as a gold standard for evaluating gross motor function in infants with SMA I. Although it is currently the best indicator of function and is clinically meaningful, it is somewhat limited by its dependence on the subjective opinion of the assessor, and by its lack of psychometric properties that make it ideal as the only necessary tool for use in clinical trials (Cano et al., 2014). Further, it can be fatiguing to the infant, as it requires elicitation of activities while the

child is placed in positions that increase the work of breathing. Development of a more objective assessment of motor function may offer valuable information on functional change in infants with SMA I. The ACTIVE-mini could be used in conjunction with physiologic biomarkers and general clinical assessments performed by physicians and physical therapists to offer a more complete report of overall status of the child with SMA I. This device may also offer information regarding function over a period of time or at multiple time points in a less stressful environment for recording best motor performance, rather than the performance of a single time point in clinic that the investigator can capture with the currently available functional outcome assessments. The central hypothesis, based on pilot data, is that the ACTIVE-mini may be used to quantify movement of the limbs seen in infants with SMA and these values will correlate with the extremity score on the CHOP INTEND. The rationale for this work is that an outcome measure that can quantify small changes in functional abilities and that can be used in a home monitoring setting would optimize outcomes and eliminate some of the barriers to participation in clinical research trials. The contribution of this proposed research may support the use of a user-friendly ACTIVE-mini system to better understand disease progression and response to therapeutic agents and interventions in multisite clinical trials and for clinical assessment.

CHAPTER II

REVIEW OF THE LITERATURE

The purposes of this study were to investigate the reliability and validity of the ACTIVE-mini for assessing movement parameters in infants with SMA. Specifically, the purposes were to examine: (a) the within-day test-retest reliability of the ACTIVE-mini; (b) the between-day test-retest reliability of the ACTIVE-mini; (c) the convergent construct validity of the ACTIVE-mini by correlating the movement parameters obtained using the ACTIVE-mini and the extremity scores obtained using the CHOP INTEND; and (d) the known-groups method construct validity of ACTIVE-mini by comparing the movement parameters obtained using ACTIVE-mini between infants with SMA and function-matched healthy infants.

Spinal Muscular Atrophy (SMA)

SMA is a disorder caused by degeneration of the anterior horn cells of the spinal cord (Dubowitz, 1995) leading to progressive proximal muscle weakness (Mercuri, Bertini, & Iannaccone, 2012). The underlying cause of this commonly fatal autosomal recessive neuromuscular disorder is the absence or mutation of exon 7 confirmed with genetic analysis. The defect within the chromosome region 5q with the absence of exon 7 results in a deletion or mutation of the Survival Motor Neuron 1 (SMN1) gene (Prior & Russman, 2000).

In an unaffected individual, there are generally two copies of the SMN1 gene. This gene is responsible for producing the Survival Motor Neuron (SMN) protein that is an important component of the spliceosomal complex and is necessary for ribonucleic acid (RNA) processing

(Finkel et al., 2014). Therefore, without the SMN protein, there is a loss of function of neuronal cells in the anterior horn of the spinal cord and subsequent system-wide muscle wasting and weakness results. Acting as a homologous copy of SMN1, Survival Motor Neuron 2 (SMN2) plays a role as a phenotypic modifier when SMN1 is missing (Cusco, Barcelo, Baiget, & Tizzano, 2002; Lefebvre et al., 1995). However, most of the SMN protein produced by SMN2 lacks a key building block that is normally produced by SMN1, which means that SMN2 cannot fully make up for the mutated or deleted SMN1 gene (Butchbach, 2016). The number of SMN2 genes can vary from person to person, and individuals with more SMN2 copies typically have a less severe form of SMA than those with fewer copies.

Deficiency of the SMN1 gene may occur in one of two ways. SMN1 may be missing or deleted or SMN1 may be converted to SMN2. Approximately 95% to 98% of individuals with SMA are homozygous for a deletion of the SMN1 gene or a conversion of SMN1 to SMN2. About 2% to 5% are compound heterozygous for an SMN1 deletion or conversion mutation (Prior & Russman, 2000). Most individuals with SMA are homozygous for a deletion of the SMN1 gene or gene conversion from SMN1 to SMN2. Regardless of the mechanism of the SMN1 gene deficiency, the overall estimated incidence of this autosomal recessive disorder is 1 in 6,000 to 11,000 live births (Arnold, Kassar, & Kissel, 2015; Cobben et al., 2008; Lefebvre et al., 1995).

Prevalence and Medical Cost of SMA

While incidence is the rate of occurrence of new disease during a period of time, prevalence is the proportion of the population that has a disease at a point in time. The cost of illness or disease is often examined in relation to disease prevalence. In the case of SMA, prevalence can be estimated in part based on SMA carrier status at birth. Carriers are people

who have inherited a recessive allele for a genetic trait or mutation, but usually do not display that trait or show symptoms of the disease. SMA carrier frequencies are estimated at 1 in 40 to 1 in 60 (Farrar, Vucic, Johnston, du Sart, & Kiernan, 2013). Based on carrier status at birth, SMA birth prevalence, and survival estimates, Lally et al. (2017) estimated the number of prevalent cases of SMA Types I, II, and III to be between 8,526 to 10,333 in the United States during 2016. Using mid-point estimates, the number of SMA Type I cases was 1,610. In a qualitative study of involving 96 participants including individuals with SMA, parents, and clinicians specializing in the care of patients with SMA, pressure on family finances was a common theme (Qian et al., 2015). One clinician estimated that the cost of raising a child with a degenerative neuromuscular disease was "in the millions, per child." Costs associated with SMA are difficult to determine due to small sample sizes and inability to distinguish between early onset and late onset disease, in which the medical costs are very different. In a quantitative study sponsored by the Muscular Dystrophy Association (MDA), the reported total cost of illness to the United States for common neuromuscular diseases was conservatively estimated at $1.37 billion per year (Larkindale et al., 2014). This study examined costs associated with amyotrophic lateral scoliosis, Duchenne muscular dystrophy, and myotonic muscular dystrophy. Amyotrophic lateral scoliosis, a similar disease to SMA in the adult population, had a per-patient annual cost of $63,692 according to the study, which included medical costs, lost income, and non-medical costs of the patient.

Clinical Presentation of SMA

Characterized by progressive muscle weakness, SMA tends to progress from a proximal to distal distribution of weakness with the lower extremities typically affected before the upper extremities (D'Amico, Mercuri, Tiziano, & Bertini, 2011). Poor weight gain, difficulty with sleep,

episodes of pneumonia, scoliosis and joint contractures are common complications across the spectrum of the disease.

The disease has a variable presentation and therefore is characterized into subtypes (Type 0, I, II, III, and IV) based on age of onset and motor function achieved (Farrar et al., 2013; Kroksmark, Beckung, & Tulinius, 2001; Prior & Russman, 2000; Wang, Finkel, & Bertini, 2007; Yuan & Jiang, 2015). The prenatal form of SMA, SMA 0, is the most severe subtype and is classified with an onset of weakness at birth, facial weakness, breathing difficulty, swallowing difficulty, and arthrogryposis multiplex congenita (Prior & Russman, 2000). Infants typically will not survive past six months of age.

Subtype I is the most common form and is also known as Werdnig-Hoffmann disease, acute SMA, or infantile-onset SMA. Children with SMA I have low tone, poor head and trunk control, and will never be able to sit without support. These infants exhibit joint contractures and have bulbar weakness leading to difficulty with sucking and swallowing that are necessary for adequate feeding and nutrition (Cobben et al., 2008; Iannaccone, Browne, Samaha, & Buncher, 1993; Lally et al., 2017; Mercuri et al., 2012; Thomas & Dubowitz, 1994). SMA I is the most common cause of death due to a genetic disease in childhood (Nicole, Diaz, Frugier, & Melki, 2002). The shortened life expectancy in these infants is due to their fragile nature and the possibility of a rapid rate of decline due to medical complications including poor respiratory and nutritional status (Finkel et al., 2014; Griggs et al., 2009).

The more intermediate type, SMA II, is also known as juvenile SMA or chronic SMA. Subtype II is characterized by an onset after six months of age with the ability to sit independently. Low tone, finger tremors, and absence of reflexes are also present in these

individuals. Children with SMA II are never able to walk without support. Due to their pattern of weakness, they often develop severe orthopedic complications, including contractures of the limbs and scoliosis (Bertini et al., 2005). Pulmonary and nutritional status are compromised, but if medically controlled by following recommended standards of care (Wang et al., 2007), the children characteristically survive beyond two years and may live into adolescence or longer (Russman, Buncher, White, Samaha, & Iannaccone, 1996; Zerres et al., 1997).

Also known as Kugelberg-Welander disease, Wohlfart-Kugelberg-Welander disease, or mild SMA, Type III SMA may also be further classified into Type IIIa and IIIb. Children diagnosed earlier are classified as Type IIIa and tend to be more severely affected than those diagnosed after 3 years of age (Type IIIb). Children with SMA III develop the ability to walk at some point in their life although many will lose this ability around puberty. Weakness in these individuals typically manifests functionally with difficulty with stairs and frequent falls. Their life expectancy may be normal if respiratory health is maintained (Russman et al., 1992; Zerres et al., 1997).

Adult onset SMA, SMA IV, is characterized by an onset of muscle weakness later in life with functional difficulty similar to SMA III (Prior & Russman, 2000). In summary, subtypes of SMA are classified based upon age of onset and function achieved. Typically, earlier onset is indicative of a more severe form of the disease.

Interventions for Individuals with SMA

Until very recently, there were limited treatment options available for individuals with SMA. Both pharmaceutical agents and non-pharmaceutical medical management are reviewed below.

Pharmaceutical Agents

Clinical trials investigating potential pharmaceutical agents that have been completed in SMA are limited, as documented in two Cochrane Reviews for SMA I, SMA II and III published in 2012 (Wadman et al., 2012). All trials, randomized or otherwise, were included in the review for both publications. Although five studies were identified and assessed for review, only one study met inclusion criteria for the review of SMA I a randomized and placebo controlled study of riluzole (Russman, Iannaccone, & Samaha, 2003; Wadman et al., 2012). Conclusions were limited secondary to insufficient power of the study and poor correlation of the two groups at baseline. For SMA II and III, six trials met selection criteria out of 23 that were considered (see Table 2). Included in these studies was one large randomized, but un-blinded and un-controlled trial of gabapentin (Merlini, Solari, & Vita, 2003). Because this un-blinded study did not include a placebo group, conclusions regarding the efficacy of gabapentin could not be drawn (Wadman et al., 2012). Five additional trials that met selection criteria for the Cochrane Review investigated effects of thyrotropin releasing hormone (TRH), phenylbutyrate, creatine, valproic acid, and hydroxyurea. These studies investigating the potential of approved drugs have not shown effects on the SMA population (Kissel et al., 2013; Kissel et al., 2011; Liang et al., 2008; ; Mercuri et al., 2007; Swoboda et al., 2009; Swoboda et al., 2010).

Table 2

Trials Included in Cochran Review for Persons with SMA Type II and III

Therapeutic Agent and Dose	Number of Participants	Age Inclusion Criteria	Number of Study Sites	Duration of Study	Outcomes
Thyrotropin-Releasing Hormone (IV) 0.1 mg/kg/d (Tzeng et al., 2000)	9	4 to 10 years of age	1	35 days	Electromyography, myometry, adverse events
Gabapentin (PO) 1200 mg/d (Miller et al., 2001)	84	≥ 21 years	8	12 months	Several motor function scales, adverse events
Phenylbutyrate (PO) 500 mg/kg/d for 7 days (Mercuri et al., 2007)	107	30 months to 12 years	10	3 months	Motor function scales and myometry, adverse events
Creatine (PO) <5 years: 2 gm/d 5 to 18 years: 5 gm/d (Wong et al,. 2007)	55	2 to 18 years	5	9 months	GMFM, QOL, adverse events; age 5-18 QMT and pulmonary function
Carnitine 50 mg/kg/d in combination with Valproic acid PO (Swoboda et al., 2010)	61	Non-ambulatory SMA II/III 2 to 8 years	5	12 months double cross over	Motor function scales
Hydroxyurea (PO) Escalating dose from 10 mg/kg to 20 mg/kg for 8 wks (Chen et al., 2010)	57	5 to 41 years	1	18 months	Motor function, adverse events

Note. IV = intravenous; PO = by mouth.

Factors limiting these trials were the timing of intervention with regard to disease course and progression or insensitivity of outcome measures used for the study population. Most recently, a new antisense oligonucleotide compound has been tested and reported to have significant therapeutic effects on infants with SMA (Chiriboga et al., 2016, Finkel et al.,

2017a). These findings have resulted in the first U.S. Federal Drug Administration approval for use of Spinraza® (Nusinersen) in patients with SMA (Ottesen, 2017). There is also much optimism for use of adeno-associated virus 9 (AAV9) associated drug therapies, but results are only available for open label protocols with randomized controlled trials pending (Arnold et al., 2015; Chiriboga et al., 2013; Porensky & Burghes, 2013).

Non-pharmaceutical Medical Management

Although there is promising work underway for pharmaceutical agents that may delay or halt progression of the disease (Darras et al., 2014; Foust et al., 2010), current intervention is based upon the clinical guidelines and standards of care that were originally published in 2007 (D'Amico et al., 2011; Wang et al., 2007) The International Coordinating Committee (ICC) for Standard of Care in SMA was formed in 2005, with a goal of establishing practice guidelines for clinical care of patients with SMA. The core committee members collaborated with more than 60 experts in the care and treatment of persons with SMA to reach consensus for management of the disease. Through various conference calls, a Delphi survey, and two in-person meetings, expert consensus for management of the disease was achieved on five care areas: (a) diagnostic/new interventions, (b) pulmonary, (c) gastrointestinal/nutrition, (d) orthopedics/rehabilitation, and (e) palliative care. Discussion included several topics related to common medical problems in SMA, diagnostic strategies, recommendations for assessment and monitoring the disease, and therapeutic interventions in each care area. A consensus statement was drafted to address the five care areas concerning the three functional levels of patients with SMA: (a) non-sitters; (b) sitters; and (c) walkers. The committee also identified several medical practices that lacked consensus and warranted further investigation. In February of 2016, 26

researchers and industry representatives from 9 different countries (USA, Spain, Italy, France, Germany, Switzerland, Sweden, The Netherlands, United Kingdom), one patient and representatives of SMA Europe and from the SMA Foundation USA met to update and discuss current knowledge on standards of care for SMA (Finkel, Sejersen, & Mercuri, 2017). A similar process was conducted to obtain expert consensus for the workshop report in areas including: (a) diagnosis/genetics, (b) nutrition/growth/bone health care, (c) pulmonary care, (d) orthopedic care, (e) physical therapy and rehabilitation, (f) other organ system involvement, (g) acute care in the hospital setting, (h) medication, and (i) ethics/palliative care. This effort resulted in a recently published updated standards of care document (Mercuri et al., 2018).

Key areas of pulmonary management and nutritional management identified as standards of care for patients with SMA were recognized by the ICC and published in the initial and updated guidelines. Initiating care early on in these areas is integral to the health and life expectancy of those with SMA (Finkel et al., 2018; Wang et al., 2007). Studies have shown that survival beyond one year in patients with SMA I has improved with the introduction of use of non-invasive ventilation and enteral feeding that were set out as standards of care in SMA (Boitano, 2009; Finkel et al., 2018; Oskoui et al., 2007). This earlier intervention in SMA I altered the natural history of the disease in the past decade because of the more proactive approach of feeding tubes and pulmonary management implemented in the medical management of these infants (Mercuri et al., 2012). Non-invasive ventilation is being used early in life when the infant is still relatively healthy. As weakness progresses, the requirement for ventilation may increase from four hours per night to full-time use. With full-time ventilation, damage in the upper airway may result, causing further complications and requiring tracheostomy. Children with

SMA I that undergo tracheostomy will remain dependent on a ventilator for the remainder of their lives. Respiratory support considered standard of care, such as cough assist, may play a role in prevention of infection that further improves the health of the child. Difficulty with feeding and poor weight gain is another aspect of medical management that requires early intervention to maintain the health of the child. Gastrostomy may be indicated when the child is experiencing cough or fatigue with feeding, or prolonged feeding time. The gastrostomy provides supplemental calories as oral feeding becomes more difficult. Implementation of these standards of care have substantially improved life expectancy and quality of life of individuals with SMA I.

Consensus on orthopedic care and rehabilitation were also published in the standards of care documents (Mercuri et al., 2018; Wang et al., 2007). Scoliosis occurs in almost all non-ambulatory patients with SMA (Mercuri et al., 2012). In addition to scoliosis, contractures of the upper and lower limbs are also common issues in patients with SMA. A retrospective study carried out in patients with SMA II and III found that all patients with SMA II developed scoliosis despite the use of orthoses and a rate of progression in contractures of 20^{o} over the course of a year (Rodillo, Marini, Heckmatt, & Dubowitz, 1989). In patients with SMA III, Rodillo et al (1989) found that 63.8% of the patients developed scoliosis with a rate of progression of contractures averaging 5 degrees per year. Surgical spinal fusion is often implemented in children older than 10 years to maintain sitting posture and promote continued function with activities of daily living. Bracing is not used universally due to the negative effect it may have on respiratory function, but could possibly improve stability, reduce the progression rate of the curve or contribute to fewer post-operative complications following spinal fusion (Catteruccia et al.,

2015; Fujak et al., 2013; Tangsrud, Carlsen, Lund-Petersen, & Carlsen, 2001). Bracing to prevent onset and worsening of contractures of the limbs may be beneficial and is recommended based on the standards of care. However, there is limited literature supporting specific guidelines on bracing. Osteoporosis may be related to the reduced mobility that individuals with SMA have or due to the pathophysiological aspects of the disease. Bone mineral density declines in these patients and management such as standing frames for weight bearing or other therapeutic interventions are typically considered in individuals with SMA (Wang et al., 2007). Maintenance of independence for those with SMA is another important aspect of medical management. Recommendations for wheelchairs, adaptive technology for driving or use of communication devices, or home modifications are aspects of care that should be addressed as the child ages according to the standards of care and subsequent studies (Dunaway et al., 2013; Haaker & Fujak, 2013; Jones, McEwen, & Hansen, 2003).

Studies investigating the use of physical therapy services are limited in the SMA population (see Appendix A). A study published in 2014 documents that there might be perceived benefits of participation in equine-assisted activities and therapy, including improved balance, flexibility, and psychological aspects such as improved self-confidence, esteem, and sportsmanship (Lemke, Rothwell, Newcomb, & Swoboda, 2014). Other studies showed that home programs, including aquatic based programs, are safe and feasible and may result in improved stability, stabilization of strength or a delay in progression of weakness, and improved motor function in patient with SMA (Cuhna, Oliveria, Labronici, & Gabbai, 1996; Hartley & Stockley, 2103; Lewelt, Krosschell, & Stoddard, 2015; Montes et al., 2015; Salem & Gropak, 2010). Although there is need for further studies investigating the efficacy of physical therapy

interventions, the existing research demonstrates that exercise is safe and can be beneficial in individuals with SMA. Dunaway et al. (2016) reported on implementation of physical therapy services in a multicenter study. This was the first study to document frequency and impact of therapy services on patients with SMA and further studies are needed to better understand the impact of physical therapy services in this population. In addition to the need for additional studies to determine effects of exercise, choosing valid and meaningful outcome measures to determine change in response to intervention is an important component of establishing treatment efficacy.

Tests and Measures for Individuals with SMA

Tests and measures used in the SMA population are used to determine functional or physiological status. Standardized motor function measures have been developed to address the variance of severity within and between SMA types (Montes, Gordon, Pandya, DeVivo, & Kaufmann, 2009). Physicians or physical therapists often complete these performance- based assessments. Written procedural and scoring manuals are available for all tests, but scoring is somewhat subjective in nature because they are scored based on the examiner's observation and judgement. Collaboration between networks such as the ICC or Translational Research in Europe Assessment and Treatment of Neuromuscular Diseases (TREAT NMD) has resulted in development and validation of disease-specific outcomes that are currently used in the SMA population (see Table 3) (Mercuri, Bertini, & Iannaccone, 2012).

Table 3

Outcome Measures Used in SMA by Type

Outcome	SMA Type or Functional Level	Measure
Myometry or Manual Muscle Testing	II and III	Assessment of Strength
Motor Function Measure	II and III	Functional Scale
Gross Motor Function Measure	II and III	Functional Scale
CHOP Intend	Non sitters or very weak sitters	Functional Scale
TIMPSI	Non sitters or very weak sitters	Functional Scale
Revised Upper Limb Module	Sitters	Functional Scale
Hammersmith functional motor scale for SMA (HFMS)	Sitters and ambulant patients	Functional Scale
Expanded HFMS	Sitters	Functional Scale
Extended HFMS	Sitters	Functional Scale including fine and gross motor and timed tests
Six Minute Walk Test	Ambulant	Measure of endurance
Egen Klassification	Non-ambulant	Questionnaire of functional ability
PedsQL Neuromuscular Module (NMM)	Ambulant	Quality of Life questionnaire

Standards for outcomes set by regulatory agencies, such as the Federal Drug Administration, require psychometric criteria to ensure validity of outcome measures (Cano et al., 2014). In 2014, Cano et al. published findings of Rasch analysis done on scales currently used as clinical outcome measures in SMA. Rasch measurement methods determined that all scales demonstrated adequate reliability, but all had some validity-related problems including misfit, reversed thresholds, and item dependency. Efforts are being made to modify the scales based upon this information and to implement training and improve inter-rater reliability across medical centers for these assessments. Although these outcome measures may lack statistical robustness, they are reliable and invaluable as clinical assessment tools and are clinically meaningful for patients and caregivers.

The primary outcome used in SMA I infants is typically survival or time to permanent ventilation (Montes et al., 2009; Rudnik-Schoneborn et al., 2009). Standardized motor function outcome assessments for infants and children with SMA Type I are primarily designed to assess motor development in preterm infants (Montes et al., 2009). These motor exams include both elicited and observed movement and document preservation or attainment of developmental milestones. Motor function scales such as the CHOP INTEND and the Test of Infant Motor Performance, Screening Items (TIMPSI) are the two most commonly used assessments in clinical practice. The CHOP INTEND has become the gold standard for functional assessment in published industry-sponsored clinical trials. Both of these functional outcome measures are clinically meaningful and are valuable as they may identify the small changes seen functionally in patients with SMA I and in patients with weak SMA II (Kolb, 2013).

Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders

The CHOP INTEND is a measure of motor function currently used in the SMA I population as part of standard clinical practice that measure global function of the participant (Montes et al., 2009). The CHOP INTEND is an assessment instrument that was developed and validated in infants with SMA in 2010, specifically for infants with neuromuscular disease (Glanzman et al., 2010). Glanzman et al. (2011) reported in a validation study that the CHOP INTEND relates well to participant age, required ventilatory support, and disease severity in the SMA I population. This test is a 16-item evaluation that assesses trunk and limb functional movement using both observational and elicited movements. Each item is scored bilaterally with a 4-point rating scale with a higher score indicative of a higher level of motor function observed. (see Appendix B) The total score is derived from the sum of the best score from both extremities with a maximum score of 64. A score of zero indicates no active movement. A score of 15.5 indicates a significantly weak infant and strongly correlates with infants with SMA I who require respiratory support (Glanzman et al., 2011). The test is intended to be conducted on an alert, content and reactive infant as scored by the Brazelton scale with a state of four (alert with bright look, minimal activity) or five (eyes open, considerable activity) to optimize consistency of results and the state at the time at which each item is recorded (see Table 4) (Brazelton, 1995). The assessment can be completed in approximately 20 to 30 minutes. Written procedure and scoring instructions are available.

Table 4

Brazelton Behavioral State

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

The CHOP-INTEND has excellent inter-rater and intra-rater reliability in participants with SMA I as well as good face validity (Glanzman et al., 2010). Intra-rater reliability of the resulting test was established by test-retest of nine infants with SMA-I over a two-month period ($ICC_{3,1}$ = 0.96). Interrater reliability was conducted by video analysis of a mixed group of infants with neuromuscular disease by four evaluators ($ICC_{3,4}$ = 0.98) and in a group of eight typically developing infants by five evaluators ($ICC_{3,5}$ = 0.93). The face validity of the CHOP INTEND is supported by the use of an expert panel in item selection. Cano et al. (2014) performed a Rasch analysis to examine the psychometric properties of the CHOP INTEND. Analysis found adequate targeting of the scale. Adequate targeting implies that the range of items on the CHOP INTEND appears to envelop the variable range of motor performance seen in the patient samples that were examined. This also implies that the scale does not exhibit a floor or ceiling effect. However, the analysis also demonstrated that this assessment has some issues with fit and dependency in at least one pair of items. Issues with fit suggests that the items on the scale may not work together to give a valid summed score as an overall measure of motor performance.

Items that have issues with dependency suggest that the response to one item is directly influenced by another item. This may artificially inflate the reliability of the scale. Although there may be some need for slight modification to improve the statistical robustness of the assessment because of the limitations found with Rasch analysis, the CHOP INTEND is a valuable clinical assessment tool that can be reliably used in infants with SMA.

The CHOP INTEND provides an assessment of gross motor function of extremities as well as trunk and neck. For purposes of this study the research team chose to evaluate a subset of items exclusively assessing extremity function. The CHOP INTEND Extremity Score is composed of nine items taken from the CHOP INTEND excluding items that measure trunk or neck motor function (see Appendix E). Items such as rolling and head control were not included in the CHOP INTEND extremity score. To date this subset of items has not been validated in the SMA population and is exploratory in nature.

Test of Infant Motor Performance, Screening Items

Another tool, the TIMPSI, has been used in natural history studies and industry sponsored pharmaceutical trials in the SMA I population, and is a shorter, screening version of the Test of Infant Motor Performance (TIMP) (Krosschell et al., 2013). The TIMP is a functional outcome measure that was designed to assess infants born from 34 weeks postmenstrual age to term and could be used to follow their motor development up to four months of chronological age (Finkel et al., 2008). Krosschell et al. (2013) found the TIMPSI to have excellent inter-rater, intra-rater, and test-retest reliability and good convergent validity when compared to reaching items from the Project Cure Functional Rating Scale for SMA Type I: A Primary Caregiver Questionnaire (PCFRS-I). The TIMPSI is a 29-item evaluation that contains three item sets: a

screening set, an easy set, and a hard set. The test can be completed in approximately 30 to 45 minutes. The screening set consists of 11 items from the original version of the TIMP, each with a 5- or 7-point rating scale. The easy set has 6 items with 5-or 6-point rating scales and 4 dichotomously scored items. The hard set has 8 items, 3 items scored with 5-point rating scales and 5 items that are scored dichotomously (see Appendix C). The total score is derived from all subset scores and is the sum of those subset scores with a maximum score of 99. A score of zero indicates a child with no active movement. A score ≤ 41 is considered less than ideal for functional motor movement of an infant and this has been used as a cutoff score in one current clinical trial to determine weaker versus stronger infants (Kolb, 2013). Rasch analysis performed on TIMPSI data showed adequate scale targeting but problems with fit (Cano et al., 2014). The data set examined for Rasch analysis was small (< 300) and therefore to confirm these findings, further evaluation with larger data sets is needed. The TIMPSI is a clinically meaningful outcome assessment, and has been used in a multi-center natural history study, but to date no published clinical trials have used the TIMPSI (Kolb et al., 2016).

Other Outcome Measures

Outcomes used in Type II and III include strength assessments as well as motor function standardized assessments (Iannaccone & AmSMART Group, 2002; Iannaccone, Hynan, & AMSMART Group, 2003; Mercuri et al., 2012; Montes et al., 2009). Strength measures such as quantitative and hand-held dynamometry muscle testing can be used in patients with Type II and III age five and up, whereas functional exams are feasible in patients two years and older. Gait assessments to determine changes in endurance such as the Six Minute Walk Test are also used in individuals with Type III (Montes et al., 2010; Young et al., 2016). Standardized outcomes

such as the Gross Motor Function Measure (GMFM), Hammersmith Motor Function Scale (HFMS), Motor Function Measure (MFM) and the Egan Klassifikation Scale (EK) have all been used in patients with Type II and III (Berard, Payan, Hodgkinson, & Fermanian, 2005; Main, Kairon, Mercuri, & Muntoni, 2003; Nelson, Owens, Hynan, & Iannaccone, 2006; Steffensen, Lyager, Werge, Rahbek, & Mattsson, 2002). Rasch analysis performed on all four of these assessments indicated that all need slight modifications to improve their psychometric properties due to problems with fit and dependency (Cano et al., 2014). Quantitative muscle testing has been shown to correlate with function when compared to the items on the GMFM (Nelson et al., 2006). Hand-held or manual muscle strength testing does not appear to directly correlate with function and therefor may be less clinically meaningful (Merlini, Mazzone, Solari, & Morandi, 2002), but may still provide valuable information regarding changes in strength.

The Ability Captured Through Interactive Video Evaluation-mini

The use of video to quantify movement is not a novel concept. Traditional 3-dimensional (3D) motion capture system equipped with high-speed cameras are often used to objectively quantify movement in clinical and research settings (Bhat et al., 2007; Chester & Calhoun, 2012; Klotz et al., 2014; Rocha et al., 2006). However, these 3D motion systems are costly, require significant training and time to complete analyses of data, and are not portable requiring travel of the research participant or patient to the site for testing (Chang, Chen, & Huang, 2011; Llorens, Alcaniz, Colomer, & Navarro, 2012; Taylor, McCormick, Shawis, Impson, & Griffin, 2011). Video-based assessments have the potential to collect data precisely while removing the examiner bias of existing functional motor scales.

The Microsoft Kinect® is a gaming device interface that can be used to document an individual's movement. In recent years, the Microsoft Kinect® system has been applied in many areas in the health care field to enhance motivation in rehabilitation sessions, increase exposure to tele-rehabilitation options, individualize treatment options, and measure and quantify movement due to its relatively low cost (Chang et al., 2011; Kurillo, Chen, Bajcsy, & Han, 2013; Llorens et al., 2012; Mentiplay et al., 2015; Taylor et al., 2011). The Kinect® has the ability to track participant motion using an imbedded infrared camera to record positional data over time. Data collected may be post processed to quantify a participant's movement parameters based upon mathematical algorithms (Lowes et al., 2013).

In 2013, Lowes et al. developed the Ability Captured Through Interactive Video Evaluation-seated (ACTIVE-Seated) system using the Microsoft Kinect® to gather upper extremity positional data, specifically in individuals with dystrophinopathy. The system was developed to aid in providing an objective and sensitive measure of upper extremity motor function in children with neuromuscular disease that is not always fully captured with current standardized functional assessments (Lowes et al., 2013; Lowes et al., 2015). The ACTIVE-mini was subsequently developed in 2013 by the same group using the same concept to examine spontaneous extremity movement in infants, specifically in individuals with SMA I.

Using the Microsoft Kinect® system, the ACTIVE-mini collects color-coded data with video recordings. Color coded data allows the user to differentiate between upper and lower extremity movements for comparison between limbs. The color tracking system tracks each limb over the 2-minute recording. Depth data allows the user to differentiate the planes of movement that occur with all extremities. Open-source software development kits can then be

used to process the data stream collected to automate the process of analyzing the movement data mathematically. This process leads to the calculation of various aspects of movement per unit time, such as direction change, velocity, and acceleration. Initially, to understand the ACTIVE-mini's ability to quantify total volume of movement, pilot data gathered by the developers of the tool were first visualized using trajectory plots (see Figure 1).

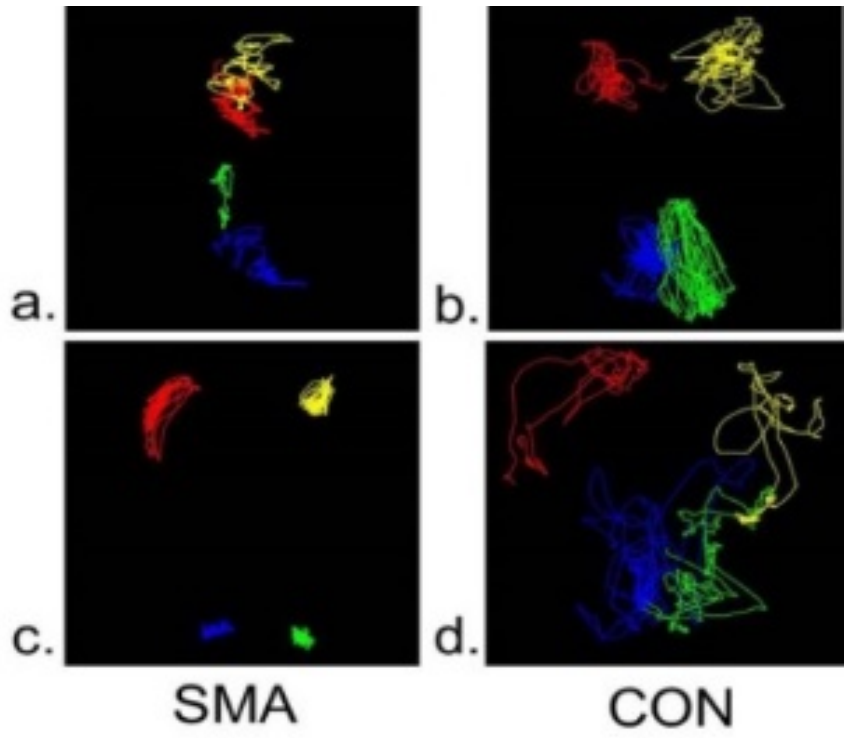

Figure 1. Trajectory Plot of Subjects with SMA and Controls (CON). The left column (a and c) is an infant with SMA Type I at an age of 11 days and again at 69 days, respectively. The right column (b and d) illustrates an age-matched healthy control infant recorded at and age of 12 days and 68 days, respectively.

These plots illustrate the total distance covered by each extremity (red=right arm, yellow=left arm, green=left foot, blue=right foot) during a recording. Based on this data, the researchers concluded the overall trajectory of movement was decreased for the infant with SMA Type I as compared to the control infant even as early as the 11-day time point (a and b). This difference becomes much more apparent at the 69-day (c and d) visit for the subject with SMA. This was demonstrated by analysis of the space occupied by the extremity trajectory. All extremity movement decreased in size for the infant with SMA I, as compared to the control whose space was increasing in size. This decrease in movement was also much more apparent in the lower extremities as compared to the upper extremities, which correlated to natural history and expected presentation of an infant with SMA I (D'Amico et al., 2011). To quantify this difference in movement volume accurately, the total number of voxels accessed with all extremities was calculated (see Figure 2). A voxel represents a defined value on a regular grid in three-dimensional space. The voxel analysis depicted in Figure 2, calculates the total number of unique voxels (3D pixels) that infants accessed during a trial. Based upon this pilot data, the researchers concluded that infants with SMA I typically accessed a lower number of voxels in a given trial compared to typically-developing controls. This was illustrated by the fact that the infants with SMA I never accessed more than 300 voxels in one recording, as compared to control infants who had approximately 400 voxels in one recording across the first 100 days of life. This point is further emphasized when viewing Figure 3, which accentuates the change in average volume accessed for each group (SMA Type I or control) over time as measured by convex hull analysis. This analysis determines the total movement volume of the furthest excursion of all extremities in space in all directions.

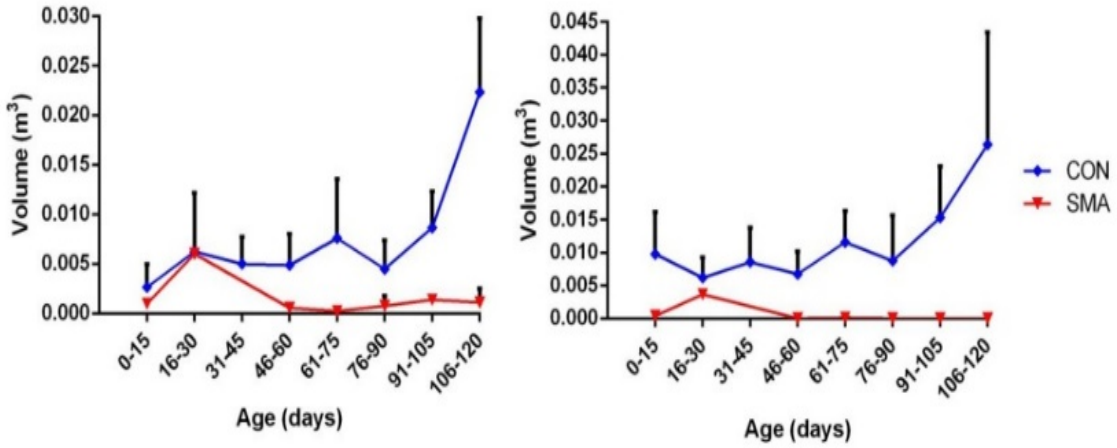

Figure 2. Total number of voxels accessed with all extremities

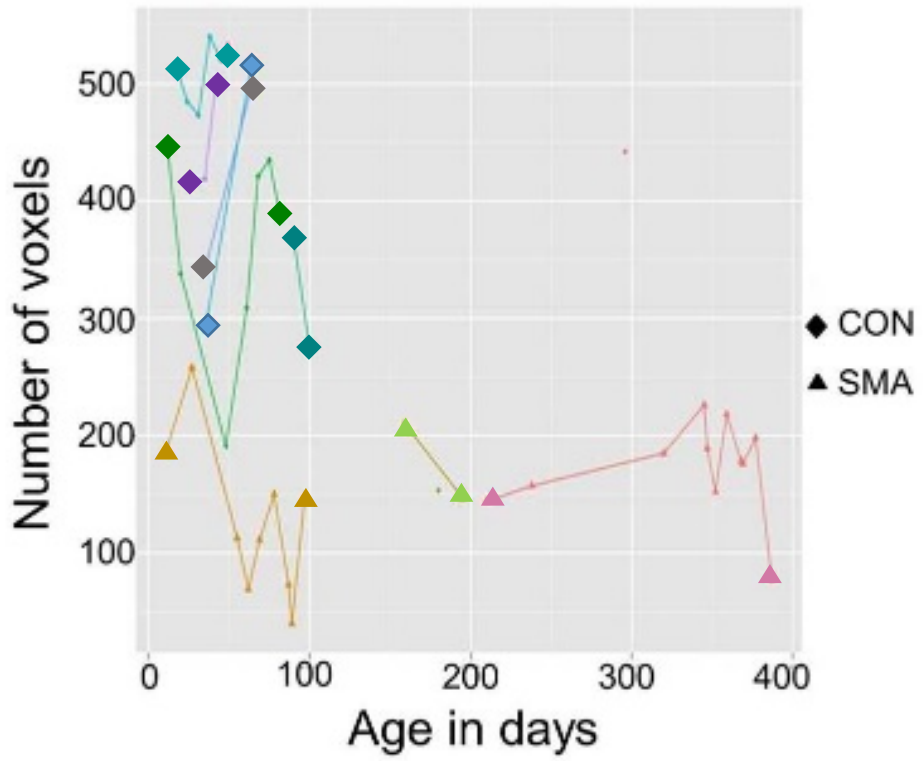

Figure 3. Group average total volume accessed by the upper and lower extremities in infants with SMA I and controls over time as assessed by convex hull analysis.

The researchers concluded that infants with SMA Type I move both their upper and lower extremities through a smaller volume than controls over time (Alfano et al., 2016). This was demonstrated by the total volume accessed decreasing from 30 days of life in the infants with SMA Type I compared to the controls and this discrepancy then increasing over time. In summary, this data demonstrates the feasibility of the tool to measure volume of movement in infants with SMA Type I. To assess movement velocity (m/s), the data was plotted as kernel density plots for variables of movement velocity and jerk (a derivative of acceleration) (see Figure 4). These plots graph each data point collected under the (velocity or jerk) on the x-axis. In both plots, the y-axis indicates frequency of occurrence, with the most frequent value normalized to 1.0. In the first plot, the center of the peak indicates the most frequent velocity. The more diverse the repertoire of available velocities used, the wider the peak. Data collected from three infants with SMA Type I (ages 11, 159, and 210 days at time of first visit) and 32 typically-developing controls (ages: 6 to 296 days at time of first visit) were analyzed. Figure 4 demonstrates the decline of these movement variables of one participant with SMA Type I over time.

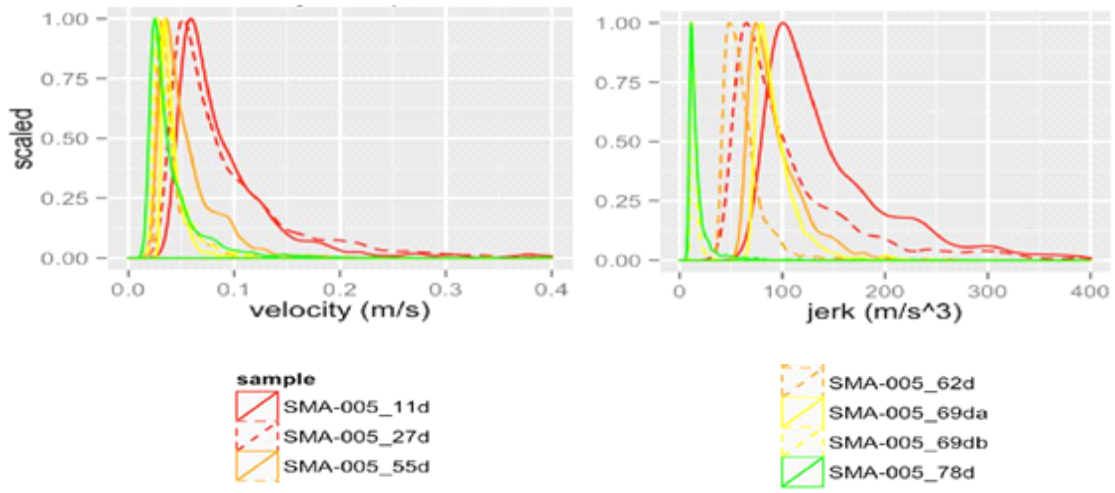

Figure 4. Kernel density plots of movement velocity and jerk (derivative of accerleration) scaled to most frequent value (y-axis) in an infant with SMA I between days 11 to 78 of life.

Based on this data, the developers of the tool concluded that this infant with SMA Type I demonstrates a decline or negative trend over time in the velocity and jerk median. This participant also demonstrated an even more limited repertoire of speeds as demonstrated by the shift of the most frequent velocity and jerk and a diminished peak width over time. Additional research analyzing the correlation of limb movement in infants with SMA compared to unimpaired infants found that the average correlation of limb speeds over time as well as average speed of limb movement were higher in healthy infants as compared to infants with SMA I (Soran, Lowes, Alfano, & Steele, 2016).

Figures 2 and 3 underscore the importance of scaling total volume for infant size when utilizing the ACTIVE-mini. As infants grow, we would expect their total available volume and total volume accessed by limbs to increase simply due to growth of extremities rather than increased strength or function. However, the total number of voxels accessed by infants with SMA Type I, as seen in Figure 2, appears to plateau. We would expect this plot to mimic clinical presentation and illustrate a continual decline in voxel count. However, because the older infant

was much larger in size, the data display an apparent plateau. Utilizing a determinant of growth to accommodate for changes in growth over time, such as an ulnar length measure, is important in obtaining valid data.

Calculation of various aspects of movement per unit time, such as direction change, velocity, and acceleration can be performed individually but may be more meaningful when used together to determine a composite score. A motor score generated from the movement output from the video recording has been developed using the ACTIVE-mini system. In order to evaluate the accuracy of the generated motor score, data comparing infants with SMA as well as healthy controls has been used. Based upon regression analysis, using the data collected with the ACTIVE-mini recording, an ACTIVE-mini score was determined. To determine accuracy of the ACTIVE-mini score, each generated score was compared to a corresponding CHOP INTEND extremity score that had been performed at the same time point. The performance of the proposed scoring system was evaluated by calculating the average error in the ACTIVE-mini scores as compared to actual CHOP INTEND extremity score. The resulting ACTIVE-mini score was equated to the CHOP INTEND extremity score using machine learning so the maximum score is 72.

Rational for Choosing Outcome Measures and Chapter Summary

Because the phenotypic spectrum between the SMA subtypes is continuous and there is overlap in age at onset and functional status, it is a complicated decision to determine the best clinical outcome to use in a research study. This overlap of function within SMA types may also become a complication for researchers and can increase the challenge of completing enrollment depending on the power calculation for a given outcome. To facilitate participation in clinical

trials, outcome measures must assess the entire continuum to avoid a floor and ceiling effect. A combination of the assessments may be necessary, but adds to the cost and length of a trial. Endurance and strength assessments are valuable clinically but may not correlate to function. Standardized motor assessments used in SMA are also important as clinical assessment tools and are clinically meaningful for patients and caregivers. Steps should be taken to strengthen the psychometric properties of these outcomes scales in order to give researchers more precise and valid data relating to function.

As reviewed in this chapter, the importance of clinical research trials evaluating efficacy of intervention in the SMA I population is increasing, as improved medical management of these individuals is allowing them to live longer lives. Efficacy of physical therapy intervention such as bracing, exercise prescription, and functional training, pulmonary and respiratory management, and emerging therapeutics must be assessed with sensitive, reliable and clinically meaningful outcome measures. Current standardized motor function assessments as well as physiologic biomarkers provide valuable clinical information, but may not be sensitive enough to determine the small changes that interventions may achieve. The CHOP INTEND provides a global motor function measure but does have some internal validity-related issues with the extent to which some items adequately measure motor performance. Specifically, the concept of adding together items from related but potentially different constructs such as trunk and extremity function. To help reduce this issue, for purposes of this study, a subset of items looking only at the extremity function components of the CHOP INTEND were used. This CHOP INTEND extremity score was chosen to best represent the extremity function of the participant.

The exploratory outcome of this study, the ACTIVE-mini, provides a possible low cost and portable alternative to standard motion capture systems and functional outcome measures used in the SMA population. An ACTIVE-mini recording can be completed in a variety of settings (e.g., laboratory, clinic, and home, etc.), is quick to administer, and is minimally burdensome to the infant as testing involves collection of spontaneous movements in an uncompromising supine position. Clinical trials in the SMA population could be advanced by the use of an outcome measure reliably quantifies small changes in movement while minimizing stress on the fragile infants with SMA and their families. The ACTIVE-mini may provide the necessary information to capture discrete changes in movement and functional ability in infants with SMA.

CHAPTER III

METHODS

SMA is one of the most common fatal diseases of infancy. Assessing motor function in these infants is difficult due to their profound weakness and fragility. Current standardized motor function outcomes provide valuable clinical information but lack the sensitivity and objectivity that an ideal outcome should have for research trials. The ACTIVE-mini is a newly developed tool that may provide valuable data quantifying movement in these very weak infants, and therefore provide an outcome measure that could be used in clinical research trials to help in determining efficacy of therapeutic intervention in the SMA population.

The purpose of this study was to investigate the reliability and validity of the ACTIVE-mini for quantifying movement in infants with SMA. Specifically, the purpose was to examine both within-day and between-day test-retest reliability of the ACTIVE-mini, convergent construct validity by correlating the ACTIVE-mini scores with the extremity scores obtained using the CHOP INTEND, and construct validity using the known-groups method by comparing the ACTIVE-mini predicted scores between patients with SMA and functional-matched healthy infants. The results of this study have provided researchers with additional knowledge of a possible tool that may be used in clinical research to quantify movement in infants with SMA. This chapter describes the design, participants, examiners, instrumentation, procedures and statistics that were used to analyze the data.

Research Design and Study Overview

This study was a cross-sectional, repeated measure design, investigating the test-retest within- and between-day reliability and the convergent construct validity and the known-groups method construct validity of the ACTIVE-mini. The group variable included two levels (non-rolling infants with SMA and function-matched non-rolling typically developing infants). The dependent variables included a predicted CHOP INTEND extremity score determined by data captured by the ACTIVE-mini and the actual CHOP INTEND extremity score. The dependent variables were collected at two time points over two days at a minimum of 24 hours and no more than 30 days between collections. Variables were collected in a standard order of assessment to minimize fatigue. All participants underwent all assessments as set out in the procedures. Based on results from pilot data, the conclusion was made that the ACTIVE-mini could quantify infant movement parameters well enough to warrant further investigation. These data were important in establishing the feasibility of the specific aims of this research, because they provide initial validation of the ability of ACTIVE-mini to quantify basic infant movement parameters. Further data was needed and data was collected at a later date.

Participants

An a priori power analysis was performed to calculate the sample sizes needed to detect significant correlation using G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2009). Power calculation using an $\alpha = 0.05$ and an effect size of 0.80 determined a sample size of 42 participants, 21 for each group, was needed to achieve a power of 0.80. The large effect size of 0.80 was chosen based upon previous literature and pilot data investigating the feasibility of the ACTIVE-mini (Lowes et al., 2013; Lowes et al., 2015). Both infants without the ability to roll, with

the diagnosis of SMA Type I as well as typically developing function-matched controls were included in the sample population. It is difficult to capture data using the ACTIVE-mini on healthy typically developing infants over the age of approximately 6 months, as the procedures require the child to lie on his/her back for two minutes without rolling or crawling away. Therefore healthy controls were matched based upon function rather than age.

Inclusion criteria for participants in both groups included: (a) non-rolling, (b) age 0 to 5 years, and (c) no concomitant system pathology that would limit clinical evaluation. Exclusion criteria for participants in both groups include: (a) evidence of renal dysfunction, central nervous system damage, neuro-degenerative or neuromuscular disease other than SMA type I or II, and (b) dependency on mechanical ventilation of any type > 16 hours per day.

Participants were recruited from various medical sites in the Dallas-Ft Worth and Columbus, Ohio areas, including but not limited to, neuromuscular specialization clinics at Children's Medical Center in Dallas, Cook's Medical Center in Fort Worth, and Nationwide Children's Hospital in Columbus, Ohio. Typically-developing infants, function-matched with SMA group were recruited from healthy siblings of patients seen in neuromuscular specialization clinics and various pediatric practices and birth to age three child care centers in the Dallas-Ft Worth and Columbus, Ohio areas.

Examiners

Assessments were performed by two physical therapists from Nationwide Children's Hospital and one from the University of Texas Southwestern Medical Center, Children's Health Dallas. All three examiners had prior experience with the pediatric population, and specifically with neuromuscular disease. Experience with patients with neuromuscular disease ranged from

8 to 14 years. The examiners had used the CHOP INTEND as a clinical assessment tool prior to the commencement of the study. All examiners had also undergone trainings for administration of the CHOP INTEND, including several certification sessions for participation as clinical evaluators in industry-sponsored trials. These trainings also included reliability sessions in conjunction with multiple clinical evaluators with experience in the pediatric neuromuscular setting. Specifically for this study, reliability of the three examiners was assessed with scoring video of the CHOP INTEND. Excellent reliability was found between the three examiners with an ICC=0.978 (95% CI 0.950 to 0.991), $p < .001$. Lastly, all therapists also underwent training and education in set-up and administration of the ACTIVE-mini with the developers of the tool.

Instrumentation

CHOP INTEND

The CHOP INTEND was used to assess motor function of the participants in this study. Previous studies have shown both reliable and valid use of the CHOP INTEND as a functional outcome measure in patients with SMA I (Glanzman et al., 2010; Glanzman et al., 2011). Glanzman et al. (2010) reported good intra-rater reliability for the CHOP INTEND in a group of nine infants with SMA I with an interclass correlation coefficient (ICC) of 0.96. Glanzman et al. (2010) also reported good inter rater reliability with an ICC of 0.98 between 4 evaluators scoring 10 infants with a variety of neuromuscular diseases. A preliminary concurrent validation study of the CHOP INTEND demonstrated that it has the ability to measure disease severity, as it was able to differentiate between patients with and without a mechanical ventilation requirement, and also correlated with hours of mechanical ventilation needed (Glanzman et al., 2011). The scale uses both observational and elicited items. The child may be positioned in supine, side-

lying or prone for an item, and the child's function is monitored and graded according to the standardized scale detailed in the user manual (see Appendix D). The maximum total score for the CHOP INTEND is 64 points. The scale takes approximately 20 to 30 minutes to administer and written procedural manuals are available to ensure standardization. Data obtained is a discrete summated score as well as individual sub-set item scores for each scale. Items are scored bilaterally, unless noted otherwise. Data is recorded on the CHOP INTEND score sheet and totaled using the best score from both sides for each item.

The CHOP INTEND total score is comprised of items assessing head, trunk, and extremity movement. The CHOP INTEND may be further evaluated by separating items to determine an extremity score on the CHOP INTEND. This extremity score includes nine items scored for both the right and left extremities on a 0 to 4 scale, resulting in a maximum extremity score on the CHOP INTEND of 72 (see Appendix E).

ACTIVE-mini

The ACTIVE-mini is a device that provides continuous data sets with information on various movement parameters including, but not limited to, movement volume, movement patterns, and velocity of limb movement. The ACTIVE-mini uses the Microsoft Kinect® camera platform to record movement (see Figure 5). For this assessment, the infant was positioned in supine on a white sheet with the Kinect® camera suspended over top of the infant on a tripod (see Figure 5). A Bescor® LED light was positioned on the tripod to standardize the lighting across settings (e.g., clinic, home). Distinct colored, self-adhering, and latex-free wraps were placed around the hands and feet of the infant to provide discrete markers for tracking. Recordings were initiated when the infant was reactive to external stimulation and content as

determined by a score of four (alert with bright look, minimal activity) or five (eyes open, considerable activity) on the Brazelton Scale to optimize consistency of results (Brazelton, 1995).

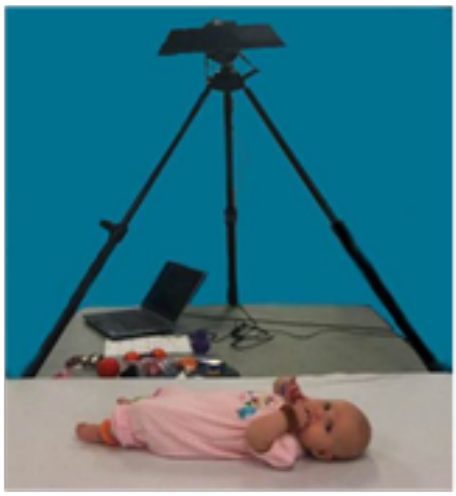

Figure 5. ACTIVE-mini set up with Microsoft Kinect® camera platform

During the recording, efforts were made to motivate the infant to move their extremities in all directions. This motivation was individualized to each infant's developmental maturity (i.e., light tactile contact, sounds, visual stimuli, etc.). Complete set-up of the assessment and preparation of the participant took approximately 10 minutes. The recording time for data capture was two minutes in length, and was chosen based upon clinical expertise and typical tolerance of infants. This two-minute recording allowed sufficient amount of objective data that then were converted into semantic features (see Table 5), such as velocity of movement (m/s) and acceleration. The output of the data captured is the x, y, and z coordinates of each limb within a space (see Table 5 note). Tracking of the coordinates for each limb was completed by comparing frames from recorded video over unit time. Algorithms combine the depth and color data stream at a rate of 30 frames per second to track the endpoint of each marker (i.e., each extremity). Next, software is implemented to process the color data stream and quantify the movement of each extremity based upon differences of coordinates. Features can be calculated per unit time based upon differences in endpoints of each extremity. The features include: (a) difference of coordinates; (b) direction; (c) direction change; (d) velocity and (e) acceleration. Definitions of these concepts as they pertain to the ACTIVE-mini appear in Table 5.

Table 5

Definitions of ACTIVE-mini Features

Feature	Definition
Difference of coordinates	The difference of the x, y, and z coordinate between two time points for each limb, or distance.
Direction	Determined for each of the limbs at each time point for each of the x – y, y – z, and x – z planes.
Directional change	The direction change of each limb between two consecutive time points for each of the x – y, y – z, and x – z planes.
Velocity	The distance taken in unit time per limb.
Acceleration	The velocity change of each limb in unit time.

Note. x = horizontal movement, left and right; y = vertical movement, floor to overhead; and z = movement forward toward the camera planes, representing depth.

A new feature engineering framework was developed to use the features to quantitatively measure extremity movement. Elastic net and Lasso regularized regression models were implemented to obtain a predicted CHOP INTEND Score (henceforth called ACTIVE-mini score) using motion tracking data.

Procedures

IRB approval for this study was obtained from all involved institutions including Nationwide Children's Hospital, the University of Texas Southwestern Medical Center, and Texas Woman's University. (see Appendix F). Potential participants were verbally recruited during clinic visits and with word of mouth marketing. Participants were screened for inclusion and exclusion criteria prior to consent. During the screening process, the parent/caregiver of the

participant was given an overview of the study procedures. Once it was determined that the participant had met the inclusion criteria and the parent/caretaker had agreed to participate, the parent/caretaker of the participant signed the consent form and the participant underwent the day one assessments the same day. The participant returned for day two testing a minimum of 24 hours up to 30 days following day one testing.

The study visits were conducted both in patient homes and at clinical sites including Children's Health™/Children's Medical Center Dallas and Nationwide Children's Hospital, in a private room. All assessments were performed by the trained physical therapists. The assessments were conducted on a firm padded mat with sanitary cover (i.e., fabric or paper sheet). The child was clothed in a lightweight garment (onesie) or in a diaper only. The parent/caregiver was allowed to be present and rest periods were given to the infant as needed, especially to calm the infant if the infant became upset. However, the aim was to complete each test without a pause. Ideally, testing was performed with the infant well-fed, rested, and in a state of four or five on the Brazelton scale to optimize consistency of results. The order of testing proceeded as follows: Two 2-minute ACTIVE-mini recordings followed by the CHOP INTEND. If possible, the family then returned within 24 hours to 30 days for day two of testing with the same procedure and ideally at the same time of day (see Figure 6). The infant's legs and arms were held stable and timing for the ACTIVE-mini recordings began when the extremities were released. Recording continued for two minutes. The 2-minute recording time of the ACTIVE-mini test was chosen to ensure standardization and was based upon empirical experience of an infant's expected tolerance. This was repeated to obtain two recordings. The

CHOP INTEND was then conducted as set out in the assessment manual and all items were performed in the same order (see APPENDIX D).

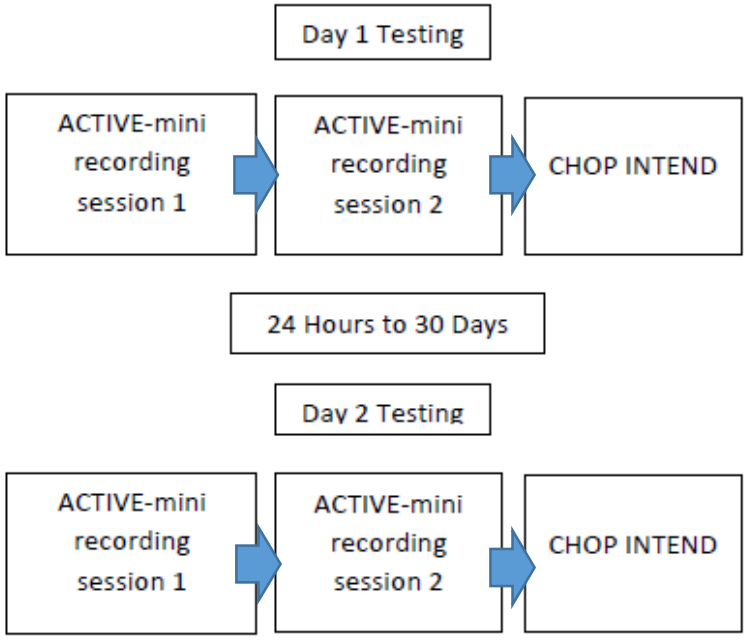

Figure 6. Procedure for Testing

Because the ACTIVE-mini assesses spontaneous natural movement with the infant in a supine position, the two 2-minute recordings should not cause fatigue. Scheduled breaks between ACTIVE-mini recordings were not planned. However, breaks in between each assessment were given as needed to maintain a Brazelton State of four or five. If the infant was unable to achieve an acceptable Brazelton score, a maximum time of 30 minutes was allowed for a break before requiring the infant to return for testing at another date and time. All infants were able to complete the testing at the scheduled visits without need to return due to behavior. The two recordings with the ACTIVE-mini, including set up took approximately 15 to 20 minutes. The CHOP INTEND took approximately 20 to 30 minutes for administration. The entire study time was approximately 60 minutes for each participant each day, including rest times. If possible, the participant returned for day two of testing at a minimum of 24 hours and no more than 30 days from day one to repeat the measures in the same order and process.

Data Analysis

The collected data was analyzed using the Statistical Package for Social Sciences (SPSS 25.0 statistical software package, IBM Corporation, Chicago, IL). A descriptive format was used to present the characteristics of the participants, including gender, age, use of ventilatory support, and incidence of scoliosis surgery. The raw data obtained from the ACTIVE-mini color video recordings was processed using the color tracking software to generate an ACTIVE-mini score. The ACTIVE-mini score of the first recording was compared to the ACTIVE-mini score of the second recording of day one of testing to determine within-day test-retest reliability. The average of the two ACTIVE-mini score recordings from day one of testing were then compared

to the average of the first two ACTIVE-mini score recordings on day two for between-day test-retest reliability. An $ICC_{(3,1)}$ was used to examine the within-day reliability of the ACTIVE-mini predicted score. An $ICC_{(3,k)}$ was used to examine between day reliability of the ACTIVE-mini score. Correlation of the ACTIVE-mini scores and CHOP INTEND extremity scores was examined to determine construct validity of the ACTIVE-mini. The CHOP INTEND extremity score was used for statistical analysis as the total CHOP INTEND score evaluates head, trunk and extremity movement. The CHOP INTEND extremity is a better representation of movement of extremity motor function. Therefore, to obtain a CHOP INTEND extremity score, items pertaining to extremity movement on CHOP INTEND were separated from items evaluating head and trunk motor function. Separation of the items resulted in nine items, scored for both right and left extremities on a 0-4 scale, with a possible score of 0-72. A Pearson correlation coefficient was used to examine the relationship between the ACTIVE-mini score and the CHOP INTEND extremity score in the subjects with SMA. Correlations were interpreted according to Portney and Watkins (2009): .00 to .25 = little or no relationship, .25-.50 = fair relationship, .50-.75 = moderate to good relationship, above .75 = good to excellent relationship. To determine the known-groups method construct validity of ACTIVE-mini, an independent t test was used to compare the ACTIVE-mini scores of the patients with SMA to those of typically developing function-matched controls. Significance was set at $p < 0.05$ for this comparison.

CHAPTER IV

RESULTS

Reliability and validity for the use of the ACTIVE-mini in infants with SMA has not been reported to date. The purpose of this study was to investigate the reliability and validity of the ACTIVE-mini for quantifying movement in infants with SMA. Specifically, the purpose was to examine both within-day and between-day test-retest reliability of the ACTIVE-mini, convergent construct validity by correlating the movement parameters obtained using the ACTIVE-mini with extremity scores obtained using the CHOP INTEND, and construct validity using the known-groups method by comparing the ACTIVE-mini scores between patients with SMA and function-matched healthy infants. This chapter discusses the characteristics of the participants as well as the results of the study.

Participants

Using a sample of convenience, participants were recruited from the Dallas-Fort Worth, Texas and Columbus, Ohio areas via word of mouth marketing. Sixty-four participants, including 29 function-matched non-rolling controls (mean age of 85 days) and 35 participants with SMA (mean age of 401 days), met inclusion criteria and were enrolled in the study. The difference in age is to be expected considering the controls were function-matched to the non-rolling participants with SMA. Forty percent of the 64 participants were male. Of the participants with SMA, 18 reported the intermittent or nighttime use of bimodal positive airway pressure (biPAP) and one had undergone scoliosis surgery. The characteristics of all participants are summarized in Table 6. At least one recording session of the ACTIVE-mini was conducted on day one with all 64 participants (29 function-matched controls and 35 patients with SMA). After data processing,

12 participants (8 function-matched controls and 4 patients with SMA) were found to have incomplete data from day one of testing and were excluded from analysis. Therefore, data from 52 participants (21 function-matched controls and 31 patients with SMA) from day one was analyzed. Sixteen of the 64 participants did not complete day two of testing due to inconvenience or illness. Twenty-one of the 64 participants with SMA returned on an average of 11 days later for day two of testing and completed the same procedures, and the resulting data was used for assessing between-day reliability. The additional 15 participants had missing or incomplete data after data processing and cleaning, and therefore could not be analyzed for Day Two testing. A flow chart illustrating the enrollment and data analysis process is presented in Figure 7.

Table 6

Participant Characteristics

	Function-matched Control *n* = 29	Spinal Muscular Atrophy *n* = 35
Mean Age (days)	85	401
Age Range (days)	17 to 185	12 to 159
Gender (% Male)	41	40
biPAP Use (n)	0	18
Scoliosis Surgery (n)	0	1

Note. Bimodal positive airway pressure (biPAP) less than 16 hours per day.

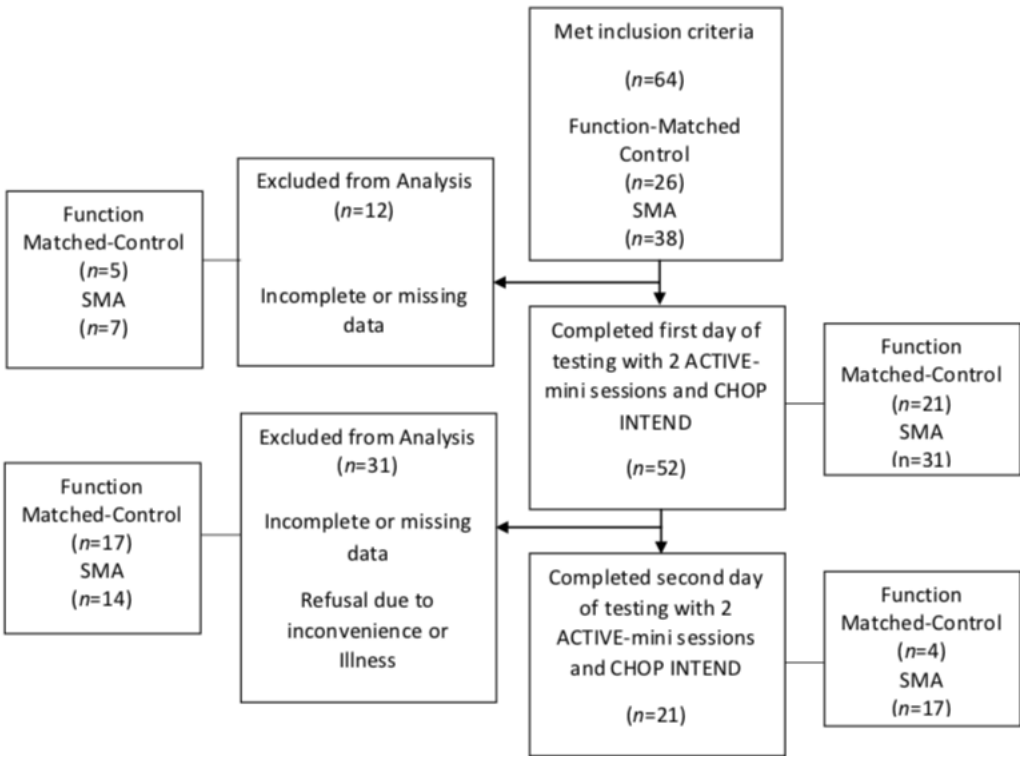

Figure 7. Flow chart for study enrollment and data analysis.

Within-Day Reliability of ACTIVE-mini to Quantify Extremity Movements in Children with SMA I

The tests of normality showed that the variables fell within standard skewness and kurtosis cutoffs (Gravetter & Wallnau, 2014; Trochim & Donnelly, 2006). The histograms, quantile-quantile (Q-Q) plots, and box plots demonstrated adequate normal distributions and no univariate outliers. Within-day test-retest reliability was analyzed with an ICC. Comparison of recording one to recording two on day one of testing were analyzed. Participants with SMA, totaling 31, completed day one of testing with at least two valid recordings. If a participant had

more than two recordings on day one, the first two recordings of day one were used for within-day test-retest reliability analysis. Therefore, a total of 31 sets of data were analyzed using SPSS Version 25.0. The within-day test-retest reliability was found to be good for the first day of testing with an $ICC_{(3,1)}$ = 0.840 (95% CI [0.697, 0.919], $p < 0.001$) and good to excellent for the second day of testing with an $ICC_{(3,1)}$ = 0.910 (95% CI [0.775, 0.966], $p < 0.001$). The means and standard deviations of each recording session are presented in Table 7.

Table 7

Means and Standard Deviation of Recording Session One and Recording Session Two on Day One and Day Two of Testing

Day	Session	Mean	Std. Deviation	N
1	1	47.55	11.59	31
1	2	46.35	12.43	31
2	1	47.12	12.61	17
2	2	48.47	10.57	17

Note. Maximum ACTIVE-mini score = 72.

Between-Day Reliability of ACTIVE-mini to Quantify Extremity Movements in Children with SMA I

The findings of between-day test-retest reliability are summarized in Table 8. Because the within-day reliability was good for both days, the average ACTIVE-mini score from day one was compared to that of day two for between day reliability. Seventeen participants with SMA completed two days of testing with at least two recordings on each day. If a participant had more than two recordings on the same day, the first two recordings of each day were averaged together and used for the between-day test-retest reliability analysis. The collected data was analyzed using SPSS Version 25.0. The results showed good between-day test-retest reliability with $ICC_{(3,2)} = 0.891$ (95% CI [0.691 to 0.961], $p < 0.001$). The means and standard deviations of the average ACTIVE-mini scores of both days are presented in Table 8.

Table 8
Means and Standard Deviations of the Average ACTIVE-mini scores of Both Days of Testing

Day of Recording Session	Mean	Std. Deviation	*N*
1	44.74	11.78	17
2	47.88	11.42	17

Note. Maximum ACTIVE-mini score = 72

Convergent Construct Validity

A Pearson's product-moment correlation was conducted to determine the relationship between the average ACTIVE-mini scores from day one and CHOP INTEND Extremity Scores (see Figure 8). The correlation analysis showed a statistically significant moderate to good positive correlation between the two scores,(r = 0.54, p = 0.002). The results were confirmed with a Spearman's correlation (r_s = .50, p = .004). However, observation of the distribution of the data identifies two potential outliers. Analysis for multivariate outliers using the Mahalanobis distance test did not identify outliers through the limitations of this statistical analysis. Collaborative discussion with a biostatistician suggested excluding the observed outliers to compare analysis with the projection of a minor increase in the correlation coefficient. After elimination of the two potential outliers, the Pearson's correlation coefficient improved from to 0.79, p < 0.001 indicating a good correlation (see Figure 9).

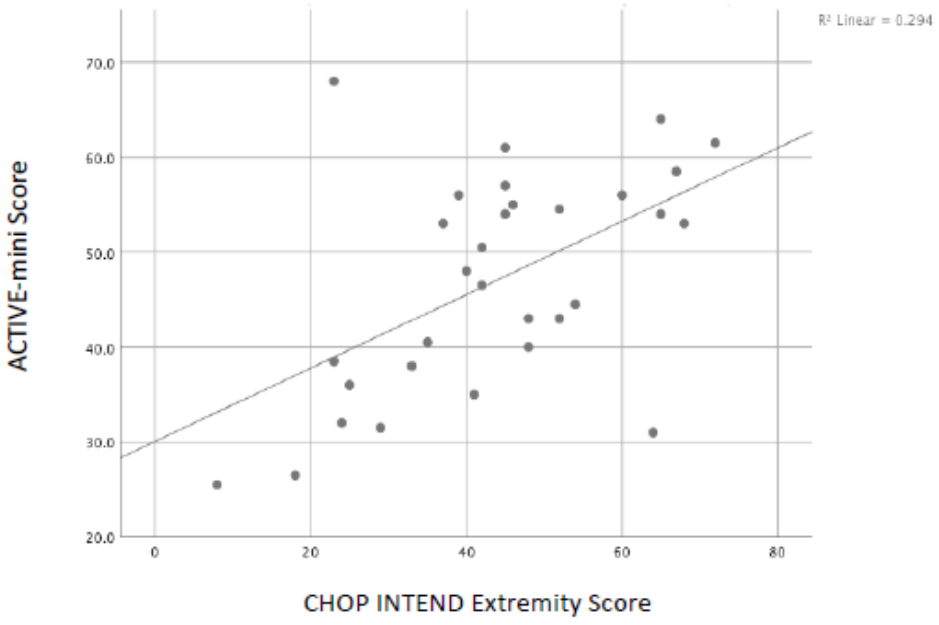

Figure 8. Scatterplot with Line of Fit of ACTIVE-mini score by CHOP INTEND extremity score.

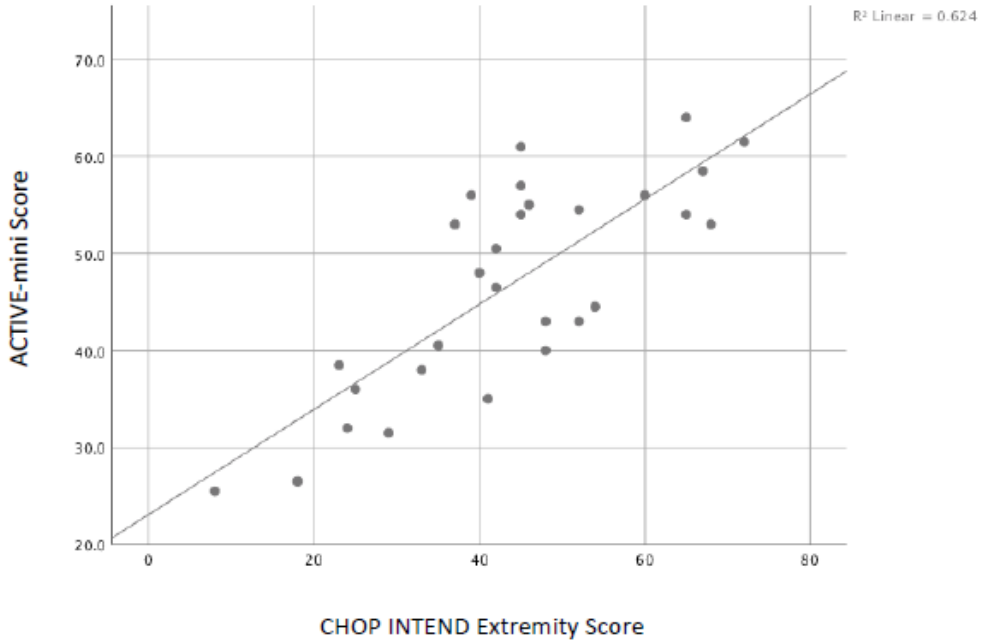

Figure 9. Scatterplot with Line of Fit of ACTIVE-mini score by CHOP INTEND extremity score with extreme subjects removed.

To further examine the convergent construct validity, a Bland-Altman plot was created to assess the level of agreement between the CHOP INTEND extremity score and the ACTIVE-mini score. The difference between the two scores was plotted on the x-axis against the mean of the two scores plotted on the y-axis. A confidence interval, or range of agreement, was defined as ± 2 standard deviations from the mean difference. Figure 10 demonstrate the level of agreement, noting that only two out of 31 data points were found to lie outside the 95% confidence interval, suggesting that the error was minimal. In addition, the results for agreement between the two measures demonstrate a roughly equal distribution above and below the 0 line. The presence of slightly more data points above the line suggested that the

differences between means were slightly higher for the stronger participants. The mean difference between scores was -3.24 (*SD* = 13.86), with a 95% CI [-8.32, 1.84]. Lastly, the inclusion of 0 in the confidence interval suggests minimal bias.

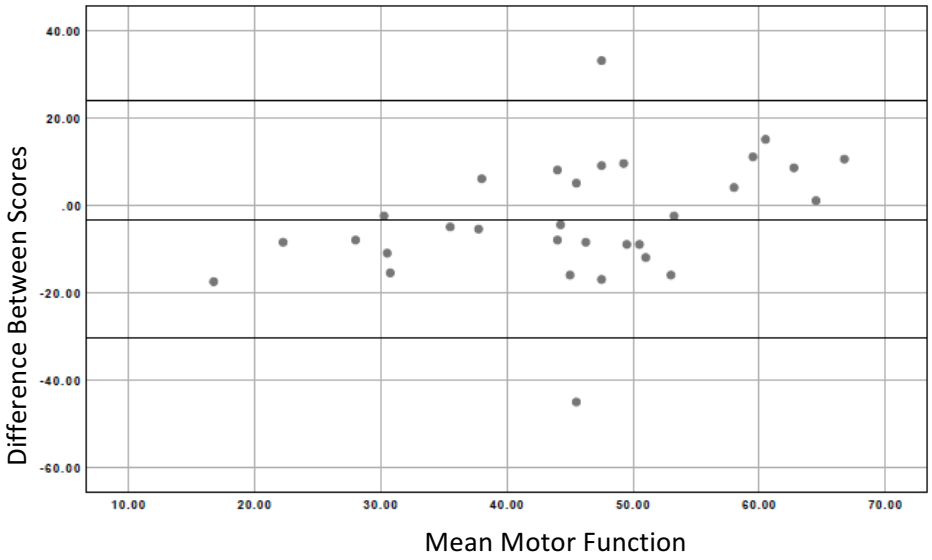

Figure 10. Bland-Altman plot with limits of agreement demonstrating agreement between mean ACTIVE-mini and CHOP INTEND extremity scores. The difference between the two scales is plotted on the Y-axis, and mean ACTIVE-mini and CHOP INTEND extremity score on the X-axis.

Construct Validity

An independent samples *t*-test was conducted to examine construct validity with the known-groups method. The known groups were defined those with SMA 1 and function-matched controls. As seen in Figure 11, children with SMA had significantly lower (t_{50}=-6.64, p < 0.001) ACTIVE-mini scores (mean = 46.95, *SD* = 11.53) as compared to the function-matched controls (mean = 64.50, *SD* = 4.40).

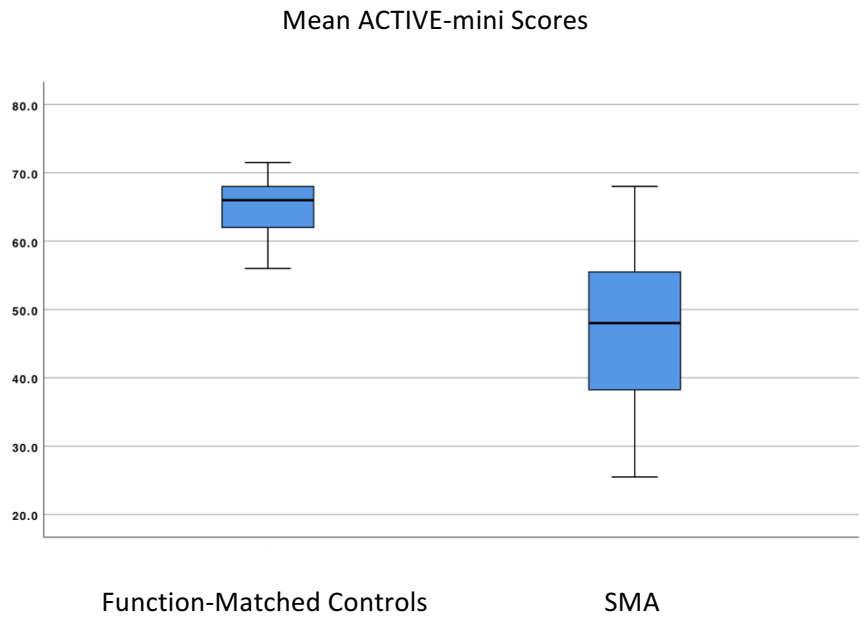

Figure 11. ACTIVE-mini score means by group

Summary

The results showed that the ACTIVE-mini has good within-day and between-day reliability. Analysis of the relationship of the ACTIVE-mini with the CHOP INTEND extremity score showed a moderate-to-good positive correlation, indicating some convergent construct validity and good agreement in the 31 patients with SMA type I. Using the known-groups method to determine construct validity, the ACTIVE-mini score was able to discriminate between patients with SMA and function-matched controls.

CHAPTER V

DISCUSSION

Outcome measures that can objectively distinguish small changes over time without adding significant stress on the infant with SMA Type I are needed to determine the effectiveness of intervention and change over time. The purpose of this study was to evaluate the ability of the recently developed ACTIVE-mini to quantify spontaneous extremity movement in infants with SMA I. Specifically, the aims were to determine the within-day test-retest reliability, between-day test-retest reliability, convergent validity, and construct validity of the ACTIVE-mini. This chapter presents a summary and discussion of the findings, conclusion, study limitations, and recommendations for future research.

Summary of Findings

Hypothesis 1

There will be good within-day test-retest reliability of the ACTIVE-mini for quantifying movement with intraclass correlation coefficients (ICC) ≥ 75% (Portney & Watkins, 2009).

Results showed good within-day test-retest reliability of the ACTIVE-mini in participants with SMA I. Therefore, the null hypothesis was rejected.

Hypothesis 2

There will be good between-day test-retest reliability of the ACTIVE-mini for quantifying movement with ICC ≥ 75% (Portney & Watkins, 2009).

There was good between-day test-retest reliability of the ACTIVE-mini in participants with SMA I. Therefore, the null hypothesis was rejected.

Hypothesis 3

There will be good convergent construct validity of the ACTIVE-mini for assessing motor function level of infants with SMA I, with a good-to-excellent positive correlation ($r \geq .75$) (Portney & Watkins, 2009) *between the movement score obtained with the ACTIVE-mini and the extremity score of the CHOP INTEND.*

Results showed a significant moderate-to-good positive correlation of the ACTIVE-mini score with the observed CHOP INTEND extremity score. Although the results did not reveal a good-to-excellent relationship as hypothesized this significant moderate correlation suggests that the two tests produce similar results. To interpret findings further, level of agreement was also examined using a Bland Altman plot. A high level of agreement between the two measures was found. Together, the moderate correlation and high level of agreement suggests that there is convergent validity of the ACTIVE-mini as a measure of motor function in infants with SMA. Nevertheless, the results did not meet the standards of the hypothesis; and therefore, the null hypothesis was accepted.

Hypothesis 4

There will be good construct validity of the ACTIVE-mini using the known-groups method for assessing motor function level, with a significant difference in the movement score obtained with the ACTIVE-mini ($p < 0.05$) between infants with SMA and functional-matched healthy infants (Portney & Watkins, 2009).

Based on the ACTIVE-mini score, the investigator was able to detect a statistically significant difference between function-matched control group and the participants with SMA I. This significant difference between known groups implies that the instrument is able to discriminate between the individuals known to have SMA Type I and those that do not have SMA I. Therefore, the null hypothesis was rejected. A summary of the research questions, analysis methods and the findings is reported in Table 9.

Table 9

Summary of Research Questions, Analysis Methods, and Results

Question	Analysis Method	Results	Assessment
Is the within-day test-retest reliability of the ACTIVE-mini good for quantifying movement in infants with SMA?	$ICC_{(3,1)}$	$ICC_{(3,1)}$ = 0.84, 95% CI [0.70 to 0.92], p < 0.001	Good reliability found, Criteria ICC ≥ 0.75
Is the between-day test-retest reliability of the ACTIVE-mini good for quantifying movement in infants with SMA?	$ICC_{(3,2)}$	$ICC_{(3,k)}$ = 0.89, 95% CI [0.69 to 0.96], p < 0.001	Good reliability found, Criteria ICC ≥ 0.75
Does the ACTIVE-mini have good convergent validity for quantifying movement of infants with SMA?	Pearson Correlation Bland-Altman Plot	r = 0.54, p = 0.002	Moderate positive correlation found, Criteria r ≥ 0.75
Does ACTIVE-mini have good construct validity using the known-groups method for quantifying movement of infants with SMA?	Independent t-test ROC Curve	t_{50} = -6.64, p < 0.001	Significant differences between groups Criteria p < 0.05

Note. Criteria defined by Portney and Watkins, 2009.

Discussion of Findings

A recently developed ACTIVE-mini system appears to be an alternative motor outcome measure for infants with SMA Type I. ACTIVE-mini testing can be completed in various settings (e.g., laboratory, clinic, home), is quick to administer, and is minimally burdensome to the infant as it involves collection of natural spontaneous movements in an uncompromising supine position. Clinical trials in the SMA I population could be advanced by the use of a functional outcome measure, such as the ACTIVE-mini, which reliably quantifies small changes in movement while minimizing stress on the fragile infants with SMA and their families.

Reliability

In order for outcome measures to be useful, the first step is to establish its reliability, which is defined as the overall consistency of a measure, or its reproducibility. A measure is said to have good reliability if it produces similar results under set conditions (Portney & Watkins, 2009). To establish that the ACTIVE-mini is capable of measuring extremity motor function with consistency, test-retest reliability was determined. A measurement tool that has good test-retest reliability will find the same or similar test results with repeated administration of that tool (Portney & Watkins, 2009).

In the case of this study, both within-day and between-day test-retest reliability were examined. The investigator chose a time interval between days in which she did not expect the participants with SMA Type I to change and thus expected both types of reliability to yield similar results. The rationale for doing so was to test this assumption given that in early studies on the reliability of three-dimensional motion analysis systems, authors found that between-day variability was greater than within-day variability (Carson, Harrington, Thompson, O'Connor, &

Theologis, 2001) among healthy adults. Authors attributed within-day variability to measurement error, skin marker movement, and inherent physiological variability during human movement (Carson et al., 2001; Kadaba et al., 1989; Liu, Siegler, HIllstrom, & Whitney, 1997). Between-day variability could be attributed to these same factors varying by day as well as slight differences in equipment set-up between the two occasions, and differences in time of day or any other environmental conditions that were not controlled. In research trials, perfect reliability (ICC = 1) of an instrument is difficult to obtain due to error of the instrument or inconsistency in human behavior. Since not all possible extraneous variables can be controlled in clinical situations, it is important to assess both within- and between-day reliability.

The results of the study showed good within-day reliability of the ACTIVE-mini when measuring movement of extremities in infants with SMA. Differences between session one and session two on the first day of testing may be due to inconsistencies of the participants' behavior. Infant behavior was controlled for by using the Brazelton state as a guideline for acceptable state during testing. The infant was tested when in a Brazelton state four or five, meaning that the child was awake and minimally to considerably active. These two states were used for previous reliability and validity studies for the CHOP INTEND (Glanzman et al., 2010; Glanzman et al., 2011). However, there is a wide variation in acceptable behaviors within the "minimal" to "considerable activity" states and the infant may change from one state to another during the testing session. To help control for the state of the infant, breaks were taken as needed to maintain the infant in an acceptable state similar to clinical practice. In addition, there was a standard order of procedures with the more stressful CHOP INTEND carried out after the ACTIVE-mini. Also, some within-day variability could be due to accommodation. An

infant, who was more awake and alert in the first session of the ACTIVE-mini (Brazelton state of five) may accommodate or habituate to the testing environment and/or examiner and thus become much more content and less active (Brazelton state of four) during the second within-day session. Both states are within acceptable testing conditions as defined by this protocol, but the differences could be a reason why the two measures are not more perfectly related.

Clinical practice and interventional research requires that outcome measures are stable from day to day (Bland & Altman, 1986). Therefore, between-day reliability needs to be established even though the within-day reliability has been shown to be good. The results of the study showed good between-day reliability of the ACTIVE-mini when measuring movement of extremities in infants with SMA Type I 1 to 30 days apart. Differences between days could be due to extraneous variables such as time of day, time since feeding, or time since sleeping. For instance, a baby that is well rested and tested in the morning on the first day of testing may yield higher scores than when they return for the second day of testing at a later time and closer to their nap or feeding time. Between-day reliability may have been stronger if these variables had been controlled for in this study. Nevertheless, the results are good, and more clinically relevant as clinicians will not always be able to control for these variables when testing infants in the clinical setting.

Both within-day and between-day reliability was found to be good for the ACTIVE-mini when testing infants with SMA. This study found that the ACTIVE-mini is a reliable tool for non-rolling infants who were tested when they were awake and active, as defined by a Brazelton state four or five. More importantly, between-day reliability was slightly stronger than within-day reliability suggesting that tighter control of extraneous variables such as time of day or time

since last feeding is not necessary to produce reliable findings. The reliability of the tool is essential, because without it we cannot be sure the data being collected is accurate and if the data is not accurate, we cannot draw conclusions from the data to assist with decision making in the care of an infant with SMA Type I.

Validity

Once a measurement tool has been found to be reliable, the second requirement for determining the tool's usefulness in a given situation is establishing its validity. Validity is defined as the ability of a tool to measure what it is intended to measure (Portney & Watkins, 2009). In addition to reliability, validity is needed in order to draw conclusions from the data collected. Validity may be established in several ways depending on how the tool is intended to be used and the type of data that is generated. Evidence of convergent and known-group validity supports the construct validity of a test or measure.

Construct validity is the concept that a measurement tool is able to measure an abstract concept or construct that typically cannot be measured directly (Vogt, 2005). Convergent validity is one method for confirming construct validity. Evidence of convergent validity is found when two measurement tools that are believed to measure similar concepts will produce similar results or will correlate well (Portney & Watkins, 2009). The medium correlation (.54) between ACTIVE-mini and CHOP INTEND extremity scores is inconclusive. While the two measures do not indicate convergence, the correlation is too high to indicate discriminant validity. While a plot of the relationship of the ACTIVE-mini with the CHOP INTEND extremity score does illustrate a linear relationship (see Figure 8), without removal of 2 discordant participants (scored high on one test and low on the other), this correlation was weaker than expected and could be due to a

variety of reasons. These reasons include (a) issues relating to the established technique used to compare the new ACTIVE-mini test, (b) the nature of the underlying concept, (c) age as a confounding variable, and (d) two participants scoring very high on one test and very low on the other.

First, the established technique, CHOP INTEND, was used in a way that is not intended by using only a subset of items. The test was administered as set out in the CHOP INTEND manual, but only the items directly related to extremity function were used for analysis. The CHOP INTEND extremity score has not been validated and therefore may not be the best indicator of functional extremity mobility in an infant with SMA Type I. Further investigation into the psychometric properties of the CHOP INTEND extremity score is warranted. It may be a useful tool that gives good information regarding the gross motor function of an infant without the issues of fit that the CHOP INTEND has been shown to have (Cano et al., 2014).

Another issue relating to the established technique used to compare the new ACTIVE-mini test is that the CHOP INTEND extremity items are indirect measures of extremity movement just as the ACTIVE-mini; the true value of an infant's ability to move its extremities is unknown. When these two methods are compared, neither provides an unequivocally correct measurement, and thus could explain the moderate, inconclusive relationship. In such cases, assessing the degree of agreement between two indirect measures may be a more appropriate approach. As stated earlier, the correlation between the two measures indicates the strength of a relation (moderate), and does not mean that the two methods agree. Given that different methods are unlikely to agree exactly (Bland & Altman, 1986), it may be helpful when considering validity to know by how much the ACTIVE-mine score is likely to differ from the

CHOP INTEND extremity score. Small differences would not affect clinical decisions and in general, the ACTIVE-mine scores are 3 points lower that CHOP INTEND extremity scores (Figure 10). Therefore, the Bland-Altman plot indicates good agreement between the two measures. Here the mean difference is -3.24 points with 95% confidence interval of -8.32 to 1.84. Thus, ACTIVE-mini tends to give a lower reading on average of a little over three points. Despite this, the limits of agreement (-30 and 24) are small enough for us to be confident that the two methods are interchangeable for clinical purposes.

The second reason that the correlation between the ACTIVE-mini and the CHOP INTEND extremity scores was weaker than expected could be that the ACTIVE-mini and the CHOP INTEND extremity score are not measuring the same concept. The ACTIVE-mini assesses spontaneous movements only, whereas the CHOP INTEND extremity score is comprised of both spontaneous and elicited movement. It could be that the underlying constructs are slightly different.

The third reason that only a moderate correlation was found between the ACTIVE-mini and the CHOP INTEND extremity scores is that age and subsequent behavior due to age also may play a part in the strength of the correlation. Just as changes behavior state may explain some variability in the data between the administration of the two tests within the same session, age may also be a factor in the differences between scores. A young infant is expected to have fidgety movement and will theoretically respond well with spontaneous observation. An older child will theoretically perform better with elicited and facilitated purposeful movement. Perhaps the ACTIVE-mini is a better tool for young infants and the CHOP INTEND extremity score may be more appropriate for an older, non-rolling child who wants to interact with an examiner.

The forth reason that results of the Pearson correlation analysis indicate that the ACTIVE-mini scores were only moderately related to the CHOP INTEND extremity scores is that there were two data points representing two participants with extreme variability. The participants scored extremely high on one test and extremely low on the other test. Clinically, this did not make sense when compared to the other 29 participants. Further statistical analysis and visual assessment were performed to investigate these two extreme participants. Theoretically, a minor increase in the correlation coefficient was expected with the two extreme participants set as missing. After eliminating these two participants, the strength of the relationship between the two tests increased (r = .54 increased to .79). By re-watching the video recordings, further insight was gained by visualizing what the participants were doing during the ACTIVE-mini recordings on these particular sessions. It was confirmed that the participant who scored poorly on the ACTIVE-mini was indeed lying motionless for most of the recording time. This particular participant was a two-year-old female with SMA Type I. During the ACTIVE-mini recording sessions, she was very content to lie still and quietly. With performance of the CHOP INTEND, she then became much more active as she was facilitated and enticed to perform purposeful movement. This participant's scores reflect these changes in behavior as she had an ACTIVE-mini score of 31 out of 72 and 64 out of 72 on the CHOP INTEND extremity score. This finding supports the idea suggested earlier in this chapter that age may be an extraneous variable that should be controlled by limiting the ACTIVE-mini to young infants.

Conversely, the other participant with extreme variability between the tests scored 68 out of 72 with the ACTIVE-mini and 23 out of 72 on the CHOP INTEND extremity score. This participant also had SMA Type I and was approximately six weeks old at time of testing. Upon

watching the recording, it was apparent that the child had little to no movement with the exception of some slight movement in the right arm. When reviewing the tracking data, it became obvious that this was a file that should have been eliminated at the beginning of the study due to tracking issues and error and should have not been analyzed. This file, similar to other files that were not analyzed had tracking errors due to the presence of an inanimate object (i.e., a red toy) with similar hues to the colored tape on the participant's extremity in the view of the camera. This caused the data processor to create inaccurate data points by tracking the toy rather than the red color-coded extremity. In addition to the requirements of hardware, understanding the preparation of the environment was an important lesson learned. It will be important for future use of the system to ensure that there are no items with color, such as clothing or toys, in the frame of the camera so as not to interfere with the tracking of hues when processing the data. In addition to preparing the environment free of color, it may be useful to use a green screen backdrop to potentially reduce error in the hue tracking software. Hardware speed and environment set up are two areas that can be controlled for any future use of the ACTIVE-mini. Having these set requirements will help to ensure accurate data will be captured.

Convergent validity is a form of validity used to judge the construct validity of an outcome measure, but does not address construct validity directly (Carlson & Herdman, 2012). Therefore, the known-groups method was used to provide a general indication of the ACTIVE-mini's construct validity. The known-groups method provides evidence of a measurement tool's construct validity by discriminating between individuals who are known to have a trait (in this case, SMA Type I) and those that do not (Portney & Watkins, 2009). In this study, the participants with SMA Type I scored lower on the ACTIVE-mini indicating less extremity

movement compared to the function-matched controls. This significant difference between the two groups indicates that the tool is able to discriminate between infants with and without SMA I, and thus providing evidence of construct validity.

Because the ACTIVE-mini can discriminate against known groups, a receiver operating characteristic (ROC) curve was calculated to determine the degree to which the ACTIVE-mini may be able to identify participants who have SMA (i.e., test accuracy). The ROC curve is derived from sensitivity (true-positive) and specificity (true-negative) data and is widely accepted as a method for comparing the accuracy of diagnostic tests and outcome measures. The area under the curve (AUC) indicates the ability of the outcome measure to correctly classify true positives and true negatives (Park, Goo, & Jo, 2004; Portney & Watkins, 2009). An AUC of 0.50 would indicate that the ACTIVE-mini was unable to identify the difference between the two groups any better than due to random chance, while a measurement tool with perfect predictive value would produce an AUC of 1.0. Both assessments revealed a desirable AUC with the CHOP INTEND extremity score of 0.959 and the ACTIVE-mini score only slightly lower at 0.941.

The ROC curve also is widely accepted as a method for selecting an optimal cutoff point for an outcome measure. Figures 12 and 13 depict the ROC curve generated by plotting sensitivity of all possible cutoff points for the ACTIVE-mini or the CHOP INTEND extremity score on the *y*-axis as a function of 1-specificity on the *x*-axis. The decision on detecting a particular cutoff score is based on the sensitivity and specificity of the outcome measure. It is desirable for a screening test to be both sensitive and specific. The cutoff was determined by finding the area on the curve with the best balance between sensitivity and specificity for this test. The results of the ROC curve analysis are shown in Table 10.

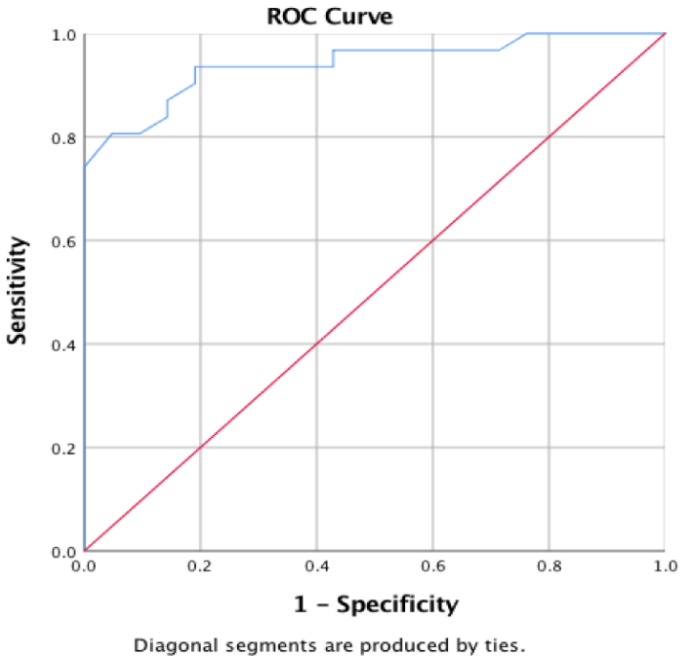

Figure 12. Receiver Operating Characteristic Curve for ACTIVE-mini Score

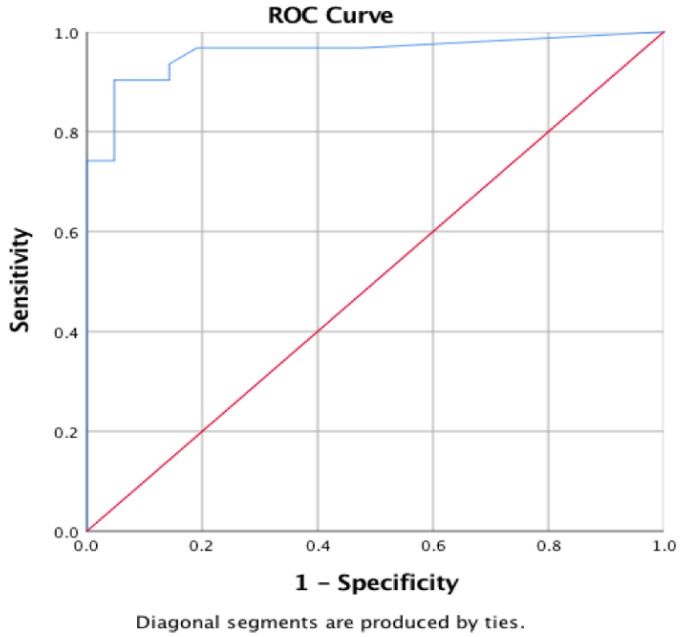

Figure 13. Receiver Operating Characteristic Curve for CHOP INTEND Extremity Score

Table 10

Results of Receiver Operating Curve Analysis for the ACTIVE-mini score and CHOP INTEND extremity score

	Sensitivity	Specificity	Cutoff Score	Area Under Curve (AUC)	*p*-value
CHOP INTEND Extremity Score	0.90	0.86	65	0.96	< 0.001
ACTIVE-mini Score	0.90	0.81	61	0.94	< 0.001

When closely examining Figure 12 and 13, the curve for CHOP INTEND extremity score is closer to the upper left-hand corner suggesting that it was a slightly better test for predicting SMA Type I than the ACTIVE-mini. Both outcome measures were equally able to identify true positives (i.e., test sensitivity); participants who had SMA Type I and scored below the cutoff score. The CHOP INTEND extremity score was slightly better than the ACTIVE-mini to identify true negatives (i.e., test specificity) participants without SMA Type I and scored above the cutoff score.

The 4-point difference in cutoff scores is somewhat unexpected since the ACTIVE-mini score is derived from machine learning and equated to the CHOP INTEND extremity score, so that both scales have a maximum score of 72. This cutoff score variation may be explained by the possibility that the two outcomes may have slightly different constructs. The ACTIVE-mini measures spontaneous movement only whereas the CHOP INTEND extremity score measures both spontaneous and elicited movement. Both cutoff scores fall in the upper range of the corresponding scale, but are not at the top end of the score, suggesting that neither has a ceiling

effect. Although the cutoff scores should be considered with caution for the fact that this is a small sample size and many more subjects would be needed to confirm the sensitivity and specificity found in this study.

Limitations

The results of this study should be interpreted with the consideration of several limitations related to the participants and the hardware used. The participants in this study were a sample of convenience and a small sample size. This is mainly due to the rarity of the disease, which makes a large sample size difficult to obtain. In addition, some participants were lost to inadequate hardware speed of the computer processing the data that created gaps of missing data points. Future studies should insure that all hardware has similar processing speed.

In addition to a sample of convenience, the Microsoft Kinect® system was set up on a tripod over the infant, thus limiting the sample to non-rolling infants, which limits the utility of the tool to a lower range of function comparable to non-rolling, typically developing infants. Nevertheless, the results suggest that the ACTIVE-mini is a reliable tool that may be useful in quantifying movement of infants with SMA Type I given their limited mobility.

Furthermore, the ACTIVE-mini has two problems that limit its clinical utility: (a) ACTIVE-mini is based on the Microsoft Kinect® system and (b) the score was calculated using machine learning. In the fourth quarter of 2017, Microsoft confirmed that it was no longer manufacturing Kinect®, the motion-sensing device for the Xbox 360® and Xbox One®, and none will be sold once retailers run out (Good, 2017). While there are still Kinect® systems in circulation and prices may decline as users move to newer systems, Microsoft is no longer manufacturing this product and this limits the clinical utility of the ACTIVE-mini. In addition, there is not a

commercially available download or application to obtain the ACTIVE-mini algorithm for calculation. Clinicians cannot calculate an ACTIVE-mini score without assistance from Nationwide Department of Research Information Solutions and Innovation, Nationwide Children's Hospital. For the ACTIVE-mini to be clinically useful, a smart device application or online calculator would need to be developed that could analyze a standard length video clip using the appropriate markers to yield a score.

As mentioned earlier in this dissertation, there are some noted limitations of the CHOP INTEND, and therefore the CHOP INTEND extremity score. Cano et al. (2004), using Rasch measurement methods, provided a detailed description of the measurement performance of the items on the CHOP INTEND. The scale demonstrated adequate reliability, but did show some internal validity-related problems regarding the extent to which some items adequately measure motor performance. There is also a noted subjective nature of CHOP INTEND. While reliability has been established and there is a standardized manual and scoresheet for the CHOP INTEND, scoring of the items requires the evaluator's interpretation and clinical judgement. These limitations of the full CHOP INTEND also apply to the CHOP INTEND extremity score. In this dissertation study, these limitations were addressed examiner training and by confirming their excellent inter-rater reliability when scoring video of the CHOP INTEND prior to the start of the study.

Lastly, the CHOP INTEND extremity score itself is not a validated measure in SMA. It was used so that items corresponding to head and trunk movement would not affect the comparison to extremities movement only captured by the ACTIVE-mini. Comparison to the full CHOP INTEND may be more clinically meaningful and should be considered for future research.

Recommendations for Future Research

This study was the first to investigate a novel assessment system for infants in SMA. The results of this study are promising, and encourage further examination of the ACTIVE-mini. The CHOP INTEND extremity score was used to determine usefulness of the ACTIVE-mini, which cannot be compared to the full CHOP INTEND score, a measure that may be more meaningful clinically at this time. However, the CHOP INTEND extremity score may be useful and meaningful when examining very weak infants with SMA Type I compared to the full CHOP INTEND. Eliminating the head and trunk items may mitigate testing fatigue associated with the full CHOP INTEND. Therefore, examining the measurement properties of the CHOP INTEND extremity score may be useful for clinicians. The psychometric properties of the CHOP INTEND extremity score should be assessed to determine the utility of the subset of scores.

Important to those clinicians currently assessing children with SMA is the CHOP INTEND. Future studies should explore the relationship of the ACTIVE-mini to the full score of the CHOP INTEND. This will allow clinicians to understand the practicality of both tools better. In addition, the psychometric properties of the CHOP INTEND have not been fully explored. A cutoff score for the CHOP INTEND may be devised with future research and could potentially be beneficial to clinical decision making.

In addition to understanding the relationship of the CHOP INTEND with the ACTIVE-mini, it may be useful to have age-based normative values for both outcome measures for persons with and without SMA. Such age-based values would allow the comparison of treated infants with SMA to the natural history of SMA and to typically developing infants. Clinicians currently determine effectiveness of an intervention by comparison the natural history of the disease,

which is a decline in function over time. Understanding the magnitude of the effectiveness of promising interventions may require comparison to typically developing children.

Finally, given Microsoft's decision to discontinue the Kinect® system, research using alternative technologies for video capture need to be explored along with the development of a smart device application or online calculator to score standard video clips. If these utility issues can be solved, the resulting procedures could be clinically useful to quantify the spontaneous extremity movements of very weak or frail infants with other diagnosis to monitor progress or decline over time and assess various interventions.

Conclusion

To the author's knowledge, this is the first study investigating the reliability and validity of the ACTIVE-mini in infants with SMA I. The results of this study support the use of the ACTIVE-mini for quantifying extremity movement in infants with SMA Type I. The study established the reliability of the ACTIVE-mini tool and partially established its validity. Therefore, the ACTIVE-mini can be used in conjunction with physiologic biomarkers and clinical assessments to offer a more complete report of overall status of the child with SMA I. It may also offer information regarding function over a period of time or at multiple time points, which cannot be completed with clinical assessment. ACTIVE-mini can be completed in various settings, is quick to administer, and is minimally burdensome to the infant. Although the CHOP INTEND will continue to be the established outcome for the measurement of function in infants with SMA, the ACTIVE-mini has strong potential for future application and may be a useful tool that can resolve the issues of the CHOP INTEND such as fatigue with testing and subjectivity of scoring. Use of

the ACTIVE-mini system may aid in understanding disease progression and response to therapeutic agents and interventions in multisite clinical trials and for clinical assessment.

REFERENCES

Alfano, L., Soran, B., Berry, K., Miller, N., Steele, K., & Lowes, L. (2016). Pilot data evaluating the utility of ACTIVE-mini as a biomarker in spinal muscular atrophy type 1. [Abstract]. *Neuromuscular Disorders*, *26*(Suppl. 2), S102. http://doi.org/10.1016/j.nmd.2016.06.064

Arnold, W. D., Kassar, D., & Kissel, J. T. (2015). Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle & Nerve*, *51*(2), 157-167. http://doi.org/10.1002/mus.24497

Berard, C., Payan, C., Hodgkinson, I., & Fermanian, J. (2005). A motor function measure for neuromuscular diseases. Construction and validation study. *Neuromuscular Disorders, 15*(7), 463-470.

Bertini, E., Burghes, A., Bushby, K., Estournet-Mathiaud, B., Finkel, R. S., & Hughes, R. A. (2005). 134th ENMC International Workshop: Outcome Measures and Treatment of Spinal Muscular Atrophy, 11-13 February 2005, Naarden, The Netherlands. *Neuromuscular Disorders*, *15*(11), 802-816. http://doi.org/10.1016/j.nmd.2005.07.005

Bhat, N., Lee, H. M., & Galloway, J. C. (2007). Toy-oriented changes in early arm movements II-joint kinematics. *Infant Behavior & Development*, *30*(2), 307-324. http://doi.org/10.1016/j.infbeh.2006.10.007

Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical agreement. *Lancet*, *19*(5), 307-310. https://doi.org/10.1016/j.ijnurstu.2009.10.001

Boitano, L. (2009). Equipment options for cough augmentation, ventilation, and noninvasive interfaces in neuromuscular respiratory management. *Pediatrics*, *123*(Suppl. 4), S2226-30. http://doi.org/10.1542/peds.2008-2952F

Brazelton, T. B. (1995). Working with families. Opportunities for early intervention. *Pediatric Clinics of North America*, *42*(1), 1-9. https://doi.org/10.1016/S0031-3955(16)38903-9

Brazelton, T.B. & Cramer, B.G. (1990). The earliest relationship: Parents, infants, and the drama of early attachment. Reading, MA: Addison-Wesley/Addison Wesley Longman.

Butchbach, M. E. (2016). Copy number variations in the survival motor neuron genes: implications for spinal muscular atrophy and other neurodegenerative diseases. *Frontiers in Molecular Biosciences*, *3*(7), 1-10. http://doi.org/10.3389/fmolb.2016.00007

Cano, S., Mayhew, A., Glanzman, A., Krosschell, K., Swoboda, K., & Main, M. (2014). Rasch analysis of clinical outcome measures in spinal muscular atrophy. *Muscle & Nerve*, *49*(3), 422-430. http://doi.org/10.1002/mus.23937

Carlson, K.D., & Herdman, A.O. (2012). Understanding the Impact of convergent validity on research results. *Ogranizational Research Methods*. *15*(1), 17-32. http://doi.org/10.1177/1094428110392383

Carson MC, Harrington ME, Thompson N, O'Connor JJ, Theologis TN. (2001) Kinematic analysis of a multi-segment foot model for research and clinical applications: a repeatability analysis. *Journal of Biomechanics, 34*(10), 1299-1307. http://doi.org/10.1016/S0021-9290(01)00101-4

Catteruccia, M., Vuillerot, C., Vaugier, I., Leclair, D., Azzi, V.,Viollet, L., . . Quijano-Roy, S. (2015). Orthopedic management of scoliosis by Garches brace and spinal fusion in SMA Type 2.

Childrens Journal of Neuromuscular Diseases, *2*(4), 463-470. http://doi.org/10.3233/JND-150084

Chang, Y. L., Chen, S. F., & Huang, J. D. (2011). A Kinect-based system for physical rehabilitation: a pilot study for yound adults with motor disabilities. *Research in Developmental Disabilties*, *32*(6), 2566-2570. http://doi.org/10.1016/j.ridd.2011.07.002

Chen, T.H., Chang, J.G., Yang, Y.H., Mai, H.H., Liang, W.C., Wu, Y.C.., . .Jong.Y.J., (2010). Randomized, double blind, placebo-controlled trial of hydroxyurea in spinal muscular atrophy. *Neurology*, *75*(24), 2190-2197. http://doi.org/10.1212/WNL.0b013e3182020332

Chester, V. L., & Calhoun, M. (2012). Gait symmetry in children with autism. *Autism Research and Treatment, 2012,* 1-5. http://doi.org/10.1155/2012/576478

Chiriboga, C. A., Swoboda, K. J., Darras, B. T., Iannaccone , S. T., Montes, J., & DeVivo, D. C. (2016). Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. *Neurology, 86*(10), 890-897. http://doi.org/10.1212/WNL.0000000000002445

Chiriboga, C., Swoboda, K., Darras, B.,Iannaccone, S., Montes, J., Allen, H., . . . Bishop, K. (2013). Results of an open-label, escalating dose study to assess the safety, tolerabiltiy, and dose range finding of a single intrathecal dose of ISIS-SMNRx in patients with spinal muscular atrophy [Abstract]. *Neurology*, *80*(7), S36.002.

Cobben, J. M., Lemmink, H. H., Snoeck, I., Barth, P. A., van der Lee, J. H., & de Visser, M. (2008). Survival in SMA type I: a prospective analysis of 34 consecutive cases. *Neuromuscular Disorders*, *18*(7), 541–44. http://doi.org/10.1016/j.nmd.2008.05.008

Cobben, J., de Visser, M., & Scheffer, H. (2001). From gene to disease; 'survival' motor neuron protein and hereditary proximal spinal muscular atrophy. *Nederlands Tijdschrift voor Geneeskunde, 145*(52), 2525–2527.

Crawford, T. O. (2004). Concerns about the design of clinical trials for spinal muscular atrophy. *Neuromuscular Disorders*, *14*(8-9), 456-460. http://doi.org/10.1016/j.nmd.2004.04.004

Cuhna, M. C., Oliveria, A. S., Labronici, R., & Gabbai, A. A. (1996). Spinal muscular atrophy type II (intermediatry) and III (Kugelberg-Welander). Evolution of 50 patients with physiotherapy and hydrotherapy in a swimming pool. *Arquivos de Neuro-Psiquiatria*, *54*, 402-406. http://dx.doi.org/10.1590/S0004-282X1996000300007

Cusco, I., Barcelo, M. J., Baiget, M., & Tizzano, E. F. (2002). Implementation of SMA carrier testing in genetic laboratories: comparison of two methods for quantifying the SMN1 gene. *Human Mutation*, *20*(6), 452-459. http://doi.org/10.1002/humu.10144

D'Amico, A., Mercuri, E., Tiziano, F., & Bertini, E. (2011). Spinal muscular atrophy. *Orphanet Journal of Rare Disease*, *6*, 71. http://doi.org/10.1186/1750-1172-6-71

Darras, B., Chinboga, C., Swoboda, K., Iannaccone, S., Montes, J., Castro, D.,…Bishop., K. (2014). Results of a Phase 2 Study of ISIS-SNMRX in Children with Spinal Muscular Atrophy. *Neuromuscular Disorders,* 24(9-10), 920. http://doi.org/10.1016/j.nmd.2014.06.417

Dubowitz, V. (1995). *Disorders of the lower motor neurone: the spinal muscular atrophies.* London: WB Saunders Company.

Dunaway, S., Montes, J., McDermott, M. P., Martens, W., Neisen, A., Glanzman, A. M., . . . Pandya, S. (2016). Physical therapy services received by individuals with spinal muscular

atrophy (SMA). *Journal of Pediatric Rehabilitation Medicine, 9*(1), 35-44. http://doi.org/10.3233/PRM-160360

Dunaway, S., Montes, J., O'Hagen, J., Sproule, D. M., De Vivo, D. C., & Kaufmann, P. (2013). Independent mobility after early introduction of a power wheelchair in spinal muscular atrophy. *Journal of Child Neurology*, *28*(5), 576-582. http://doi.org/10.1177/0883073812449383

Farrar, M. A., Vucic, S., Johnston, H. M., du Sart, D., & Kiernan, M. C. (2013). Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. *The Journal of Pediatrics*, *162*(1), 155-159. http://doi.org/10.1016/j.jpeds.2012.05.067

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G., (2009). Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behavior Research Methods*. *41*(4), 1149-1160. http://doi.org/10.3758/BRM.41.4.1149

Finkel, R. S., Chriboga, C. A., Vajsar, J., Day, J. W., Montes, J., & DeVivo, D. C. (2017). Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet of Neurology, 388*(10633), 3017–3026. https://doi.org/10.1016/S0140-6736(16)31408-8

Finkel, R. S., Hynan, L. S., Glanzman, A. M., Owens, H., Nelson, L., Cone, S. R., . . . AmSMART Group. (2008). The Test of Infant Motor Performance: reliability in spinal muscular atrophy type I. *Pediatric Physical Therapy*, *20*(3), 242-246. http://doi.org/10.1097/PEP.0b013e318181ae96

Finkel, R. S., McDermott, M. P., Kaufmann, P., Darras, B. T., Chung, W. K., Sproule, D., . . . De Vivo, D. C. (2014). Observational study of spinal muscular atrophy type I and

implications for clinical trials. *Neurology, 83*(9), 810-817. http://doi.org/10.1212/WNL.0000000000000741

Finkel, R. S., Mercuri, E., Meyer, O. H., Simonds, A. K., Schroth, M. K., Graham, R. J., . . . Sejersen, T. (2018). Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscular Disorders*, *28*(3), 197-207. http://doi.org/10.1016/j.nmd.2017.11.004

Finkel, R. S., Sejersen, T., & Mercuri, E. (2017). Workshop report 218th ENMC International Workshop: Revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19–21 February 2016. *Neuromuscular Disorders, 27*(6), 596-605. http://doi.org/10.1016/j.nmd.2017.02.014

Foust, K., Wang, X., McGovern, V., Braun, L., Bevan, A., Haidet, A., . . . Kaspar, B. K. (2010). Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. *Nature Biotechnology*, *28*(3), 271-274. http://doi.org/10.1038/nbt.1610

Fujak, A., Raab, W., Schuh, A., Richter, S., Forst, R., & Forst, J. (2013). Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. *BMC Musculoskeletal Disorders*, *14*, 283. http://doi.org/10.1186/1471-2474-14-283

Glanzman, A. M., Mazzone, E., Main, M., Pelliccioni, M., Wood, J., Swoboda, K. J., . . . Finkel, R. S. (2010). The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

(CHOP INTEND): test development and reliability. *Neuromuscular Disorders*, *20*(3), 155-161. http://doi.org/10.1016/j.nmd.2009.11.014

Glanzman, A. M., McDermott, M. P., Montes, J., Martens, W. B., Flickinger, J., Riley, S., . . . MSG. (2011). Validation of the Children's Hospital of Philadelphis Infant Test of Neuromuscular Disorders (CHOP INTEND). *Pediatric Physical Therapy*, *23*(4), 322-326. http://doi.org/10.1097/PEP.0b013e3182351f04

Good, O. S. (2017, October 25). *Kinect is officially dead. Really. Officially. It's dead.* Retrieved from Polygon: https://www.polygon.com/2017/10/25/16543192/kinect-discontinued-microsoft-announcement.

Gravetter, F., & Wallnau, L. (2014). *Essentials of statistics for the behavioral sciences.* Belmont, CA: Wadsworth.

Griggs, R. C., Batshaw, M., Dunkle, M., Gopal-Srivastava, R., Kaye, E., Krischer, J., . . . Merkel, P. A. (2009). Clinical research for rare disease: opportunities, challenges, and solutions. *Molecular Genetics and Metabolism 96*(1), 20-26. http://doi.org/10.1016/j.ymgme.2008.10.003

Haaker, G., & Fujak, A. (2013). Proximal spinal muscular atrophy: current orthopedic perspective. *The Application of Clinical Genetics*, *6*, 113-120. http://doi.org/10.2147/TACG.S53615

Hartley, S., & Stockley, R. (2013). It's more than just physical therapy: reported utilization of physiotherapy services for adults with neuromuscular disorders attending a specialist centre. *Disability and Rehabiliation*, *35*(4), 282-290. http://doi.org/10.3109/09638288.2012.691940

Iannaccone, S. T., & AmSMART Group. (2002). Outcome measures for pediatric spinal muscular atrophy. *Archives of Neurology*, *59*(9), 1445-50. http://doi.org/10.1001/archneur.59.9.1445

Iannaccone, S. T., Browne, R. H., Samaha, F. J., & Buncher, C. R. (1993). Prospective study of spinal muscular atrophy before age 6 years. DCN/SMA Group. *Pediatric Neurology*, *9*(3), 187-193. http://doi.org/10.1016/0887-8994(93)90082-N

Iannaccone, S. T., Hynan, L. S., & AMSMART Group. (2003). Reliability of 4 outcome measures in pediatric spinal muscular atrophy. *Archives of Neurology*, *60*(8), 1130-1136. http://doi.org/10.1001/archneur.60.8.1130

Jones, M. A., McEwen, I. R., & Hansen, L. (2003). Use of power mobility for a young child with spinal muscular atrophy. *Physical Therapy*, *83*(3), 253-262. http://doi.org/10.1093/ptj/83.3.253

Kadaba M. P., Ramakrishnan H. K., Wootten M. E., Gainey J., Gorton G., Cochrdn G. V. (1989). Repeatability of kinematic, kinetic, and electroniyographic data in normal adult gait. *Journal of Orthopaedic Research, 7*(6), 849-860. http://doi.org/10.1002/jor.1100070611

Kaufmann, P., & Finkel, R. (2007). Learning to walk: challenges for spinal muscular atrophy clinical trials. *Neurology*, *68*(1), 11-2. http://doi.org/10.1212/01.wnl.0000251192.70723.80

Kissel, J. T., Elsheikh, B., King, W. M., Freimer, M., Scott, C.B., Kolb, S.J., . . Swoboda, K.J., (2013). SMA VALIANT Trial: A prospective, double-blind, placebo controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy. *Muscle & Nerve*, *49*(2), 187-192. http://doi.org/10.1002/mus.23904

Kissel, J. T., Scott, C. B., Reyna, S. B., Crawford, T.O., Simard, L.R., Krosschell, K.J. ., . . Swoboda, K.J., (2011). SMA CARNIVAL Trial Part II: A prospective, single-armed trial of L-carnitine and valproic acid in ambulatory children with spinal muscular atrophy. *PloS One*, *6*(7):e21296. http://doi.org/ 10.1371/journal.pone.0021296

Klotz, M., van Drongelen, S., Rettig, O., Wenger, P., Gantz, S., Dreher, T., & Wolf, S. I. (2014). Motion analysis of the upper extremity in children with unilateral cerebal palsy-An assessment of six daily tasks. *Research in Developmental Disabilities*, *35*(11), 2950-2957. http://doi.org/10.1016/j.ridd.2014.07.021

Kolb, S. J. (2013). NeuroNEXT SMA Biomarkers Study. *Annals of Neurology*, *74*(2), A8. http://doi.org/10.1002/ana.23984

Kolb, S. J., Coffey, C. S., Yankey, J. W., Krosschell, K., Arnold, W. D., Rutkove, S. B., . . . Kissel, J. T. (2016). Baseline results of the NeuroNEXT spinal muscular atrophyinfant biomarker study. *Annals of Clinical and TranslationalNeurology*, *3*(2), 132-145. http://doi.org/10.1002/acn3.283

Kroksmark, A. K., Beckung, E., & Tulinius, M. (2001). Muscle strength and motor function in children and adolescents with spinal muscular atrophy II and III. *European Journal of Pediatric Neurology*, *5*(5), 191-198. http://doi.org/10.1053/ejpn.2001.0510

Krosschell, K. J., Maczulski, J., Scott, C., King, W., Hartman, J. T., Case, L. E., . . . Swoboda, K. J. (2013). Reliability and Validity of the TIMPSI for Infants with Spinal Muscular Atrophy Type I. *Pediatric Physical Therapy*, *25*(2), 140-149. http://doi.org/10.1097/PEP.0b013e31828a205f

Kurillo, G., Chen, A., Bajcsy, R., & Han, J. J. (2013). Evaluation of upper extremity reachable workspace using Kinect camera. *Technology and Health Care*, *21*(6), 641-656. http://doi.org/10.3233/THC-130764

Lally, C., Jones, C., Farwell, W., Reyna, S. P., Cook, S. F., & Flanders, W. D. (2017). Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. *Orphanet Journal of Rare Diseases*. *12*(1), 1-6. http://doi.org/10.1186/s13023-017-0724-z

Larkindale, J., Yan, W., Hogan, P. F., Simon, C. J., Zhang, Y., Jain, A., . . . Cwik, V. A. (2014). Cost of illness for neuromuscular diseases in the United States. *Muscle & Nerve*, *49*(3), 431-438. http://doi.org/10.1002/mus.23942

Lefebvre, S., Burglen, L., Reboullet, S., Clermont, O., Burlet, P., & Viollet, L. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. *Cell, 80(1)*, 155-165. http://doi.org/10.1016/0092-8674(95)90460-3

Lemke, D., Rothwell, E., Newcomb, T. M., & Swoboda, K. J. (2014). Perceptions of equine-assisted activities and therpies by parents and children with spinal muscular atrophpy. *Pediatric Physical Therapy*, *26*(2), 237-244. http://doi.org/10.1097/PEP.0000000000000027

Lewelt, A., Krosschell, K. J., & Stoddard, G. (2015). Resistance strength training exercise in children with spinal muscular atrophy. *Muscle & Nerve*, *52*(4), 240-244. http://doi.org/10.1002/mus.24568

Liang, W. C., Yuo, C. Y., Chang, J. G., Chen, Y.C., Chang, Y.F., Wang, H.Y., . . Jong, Y.J., (2008). The effect of hydroxyurea in spinal muscular atrophy cells and patients. *Journal of the Neurological Sciences*, *268*(1-2), 87-94. http://doi.org/10.1016/j.jns.2007.11.012

Liu W., Siegler S., Hillstrom H., Whitney K. (1997). Three-dimensional, six degrees-of-freedom kinematics of the human hindfoot during the stance phase of level walking. *Human Movement Science, 16*, 283-298. http://doi.org/10.1016/S0167-9457(96)00057-7

Llorens, R., Alcaniz, M., Colomer, C., & Navarro, M. D. (2012). Balance Recovery through virtual stepping exercises using Kinect skeleton tracking: a follow-up study with chronic stroke patients. *Studies in Health Technology and Informatics*, *181*, 108-112. http://doi.org/10.3233/978-1-61499-121-2-108

Lowes, L. P., Alfano, L. N., Crawfis, R., Berry, K., Yin, H., Dvorchik, I., . . . Medell, J. R. (2015). Reliability and validity of ACTIVE-seated: An outcome in dystrophinopathy. *Muscle & Nerve*, *52*(3), 356-362. http://doi.org/10.1002/mus.24557

Lowes, L. P., Alfano, L. N., Yetter, B. A., Worthen-Chaudhari, L., Hinchman, W., Savage, J., . . . Medell, J. R. (2013). Proof of Concept of the Ability of the Kinect to Quantify Upper Extremity Function in Dysrophinopathy. *PLoS Currents Muscular Dystophy*. Mar 14, 5. http://doi.org/10.1371/currents.md.9ab5d872bbb944c6035c9f9bfd314ee2.

Main, M., Kairon, H., Mercuri, E., & Muntoni, F. (2003). The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. *European Journal of Paediatric Neurology*, *7*(4), 155-159. http://doi.org/10.1016/S1090-3798(03)00060-6

Mentiplay, B. F., Parraton, L. G., Bower, K. J., Pua, Y.-H., McGaw, R., Heywood, S., & Clark, R. A. (2015). Gait assessment using the Microsoft Xbox One Kinect: Concurrent validity and interday-reliability of spatiotemporal and kinematic variables. *Journal of Biomechanics*, *48*(10), 2166-2170. http://doi.org/10.1016/j.jbiomech.2015.05.021

Mercuri, E., Bertini, E., & Iannaccone, S. T. (2012). Childhood spinal muscular atrophy: controversies and challenges. *The Lancet Neurology, 11*(5), 443-452. http://doi.org/10.1016/S1474-4422(12)70061-3

Mercuri, E., Bertini, E., Messina, S.,Solari, A., D'Amico, A., Angelozzi, C., . . Brahe, C., (2007). Randomized, double-blind, placebo-controlled trial of phyenylbutyrate in spinal muscular atrophy. *Neurology*, *68*(1), 51-55. http://doi.org/10.1212/01.wnl.0000249142.82285.d6

Mercuri, E., Finkel, R. S., Muntoni, F., Brunhilde, W., Montes, J., Main, M., . . . Sejersen, T. (2018). Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular Disorders*, *28*(2), 103-115. https://doi.org/10.1016/j.nmd.2017.11.005

Merlini, L., Mazzone, E. S., Solari, A., & Morandi, L. (2002). Reliability of hand-held dynamometry in spinal muscular atrophy. *Muscle & Nerve*, *26*(1), 64-70. http://doi.org/10.1002/mus.10166

Merlini, L., Solari, A., & Vita, G. (2003). Role of gabapentin in spinal muscular atrophy: results of a multicenter, randomized Italian study. *Journal of Child Neurology, 18*(8), 537-541. http://doi.org/10.1177/08830738030180080501

Miller, R.G., Moore, D.H., Dronsky, V., Bradley, W., Barohn, R., Bryan, W., . . . Smith, S., (2001). A

placebo-controlled trial of gabapentin in spinal muscular atrophy. *Journal of the Neurological Sciences*. *191*(1-2), 127-131. http://doi.org/10.1016/S0022-510X(01)00632-3

Montes, J., Garber, C. E., Kramer, S. S., Montgomery, M. J., Dunaway, S., Kamil-Rosenberg, S., . . . De Vivo, D. C. (2015). Single-Blind Randomized controlled clinical trial of exercise in ambulatory spinal muscular atrophy: why are the results negative? *Journal of Neuromuscular Diseases*, *2*(4), 463-470. http://doi.org/10.3233/JND-150101

Montes, J., Gordon, A., Pandya, S., DeVivo, D., & and Kaufmann, P. (2009). Clinical outcome measures in spinal muscular atrophy. *Journal of Child Neurology, 24*(8), 968-978. https://doi.org/10.1177/0883073809332702

Montes, J., McDermott, M. P., Martens, W. B., Dunaway, S., Glanzman, A. M., Riley, S., . . . Muscle Study Group and PNCR Network. (2010). Six-minute walk test demonstrates motor fatigue in spinal muscular atrophy. *Neurology*, *74*(10), 833-838. http://doi.org/10.1212/WNL.0b013e3181d3e308

Nelson, L. L., Owens, H., Hynan, L. S., & Iannaccone, S. T. (2006). The gross motor function mesasure is a valid and sensitive outcome measure for spinal muscular atrophy. *Neuromuscular Disorders*, *16*(6), 374-380. http://doi.org/10.1016/j.nmd.2006.03.005

Nicole, S., Diaz, C. C., Frugier, T., & Melki, J. (2002). Spinal muscular atrophy: recent advances and future prospects. *Muscle & Nerve, 26*(1), 4-13. http://doi.org/10.1002/mus.10110

Oskoui, M., Levy, G., Garland, C. J., Gray, J. M., O'Hagen, J., De Vivo, D. C., & Kaufmann, P. (2007). The changing natural history of spinal muscular atrohpy type 1. *Neurology*, *69*(20). 1931-1936. http://doi.org/10.1212/01.wnl.0000290830.40544.b9

Ottesen, E. W. (2017). ISS-N1 makes the first FDA-approved drug for spinal muscular atrophy. *Translational Neuroscience, 26*(8), 1-6. http://doi.org/10.1515/tnsci-2017-0001

Ottonello, G., Mastella, C., Franceschi, A., Bosticco, D., Wolfler, A., & Pedemonte, M. (2011). Spinal Muscular Atrophy Type I. Avoidance of Hospitalization by Respiratory Muscle Support. *American Journal of Physical Medicine and Rehabilitation*, *90*(11), 895-900. http://doi.org/10.1097/PHM.0b013e318232883a

Park, S. H., Goo, J. M., & Jo, C. H. (2004). Receiver operating characteristic (ROC) curve: practical review for radiologists. *Korean Journal of Radiology*, *5*(1), 11-18. http://doi.org/10.3348/kjr.2004.5.1.11

Porensky, P. N., & Burghes, A. H. (2013). Antisense oligonucleaotides for the treatment of spinal muscular atrophy. *Human Gene Therapy*, *24*(5), 489-498. http://doi.org/10.1089/hum.2012.225

Portney, L. G., & Watkins, M. P. (2009). *Foundations of clinical research: Applications to practice.* Upper Saddle River, New Jersey: Prentice-Hall, Inc.

Prior, T. W., & Russman, B. S. (2000). *Spinal Muscular Atrophy*. Seattle, WA:Gene Reviews. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1352/?report=printable

Qian, Y., McGraw, S., Henne, J., Jarecki, J., Hobby, K., & Yeh, W. S. (2015). Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: a qualitative study. *BMC Neurology*, *15*, 217. https://doi.org/10.1186/s12883-015-0473-3

Rocha, N., Silva, F., & Tudella, E. (2006). The impact of object size and rigidity on infant reaching. *Infant Behavior & Development*, *29*(2), 251-261. http://doi.org/10.1016/j.infbeh.2005.12.007

Rodillo, E., Marini, M. L., Heckmatt, J. Z., & Dubowitz, V. (1989). Scoliosis in spinal muscular atrophy: review of 63 cases. *Journal of Child Neurology*, *4*(2), 118-123. http://doi.org/10.1177/088307388900400208

Rudnik-Schoneborn, S., Berg, C., Zerres, K., Betzler, C., Grimm, T., Eggermann, T., . . . Heller, R. (2009). Genotype-phenotype studies in infantile spinal muscular atrophy (SMA) type I in Germany: implications for clinical trials and genetic counselling. *Clinical Genetics*, *76*(2), 168-178. http://doi.org/10.1111/j.1399-0004.2009.01200.x

Russman, B. S., Buncher, C. R., White, M., Samaha, F. J., & Iannaccone, S. T. (1996). Function changes in spinal muscular atrophy II and III. The DCN/SMA Group. *Neurology*, *47*(4), 973–976.

Russman, B. S., Iannaccone, S. T., Buncher, C. R., Samaha, F. J., White, M., & Perkins, B. (1992). Spinal muscular atrophy: new thoughts on the pathogenesis and classification schema. *Journal of Child Neurology*, *7*(4), 347-353. http://doi.org/10.1177/088307389200700403

Russman, B., Iannaccone, S., & Samaha, F. (2003). A phase 1 trial of riluzole in spinal muscular atrophy. *Archives of Neurology, 60*(11), 1601-1603. http://doi.org/10.1001/archneur.60.11.1601

Salem, Y., & Gropak, S. J. (2010). Aquatic therapy for a child with type III spinal muscular atrophy: a case report. *Physical and Occupational Therapy in Pediatrics*, *30*(4), 313-324. http://doi.org/10.3109/01942638.2010.493097

Soran, B., Lowes, L., Alfano, L., & Steele, K. M. (2016). Correlation of limb movements in infants with spinal muscular atrophy. *38th Annual International Conference of the IEEE. Engineering in Medicine and Biology Society*. Orlando, FL.

Steffensen, B., Lyager, S., Werge, B., Rahbek, J., & Mattsson, E. (2002). Physical capicity in non-ambulatory people with Duchenne muscular dystrophy or spinal muscular atrophy: a longitudinal study. *Developmental Medicine & Child Neurology*, *44*(9), 623-632. http://doi.org/10.1111/j.1469-8749.2002.tb00847.x

Swoboda, K. J., Kissel, J. T., Crawford, T. O., Bromberg, M. B., Acsadi, G., D'Anjou, G., . . . Simard, L. R. (2007). Perspectives on clinical trials in spinal muscular atrophy. *Journal of Child Neurology, 22*(8), 957-966. http://doi.org/10.1177/0883073807305665

Swoboda, K. J., Prior, T. W., Scott, C. B., McNaught, T. P., Write, M. C., Reyna, S. P., & Bromberg, M. B. (2005). Natural History of denervation in SMA:relation to age, SMN2 copy number and function. *Annals of Neurology*, *57*(5), 704-712. http://doi.org/10.1002/ana.20473

Swoboda, K. J., Scott, C. B., Crawford, T. O., Simard, L., Reyna, S. P., Krosschell, K., . . . Kissel, J. (2010). SMA CARNIVAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One*, 5:e12140. http://doi.org/10.1371/journal.pone.0012140

Swoboda, K. J., Scott, C. B., Reyna, S. P., Prior, T. W., LaSalle, B., Sorenson, S. L., . . . Simard, L. R. (2009). Phase II open label study of valproic acid in spinal muscular atrophy. *PloS One*, 4:e5268. http://doi.org/10.1371/journal.pone.0005268

Tangsrud, S. E., Carlsen, K. C., Lund-Petersen, I., & Carlsen, K. H. (2001). Lung function measurements in young children with spinal muscular atrophy; a cross sectional survey on the effect of position and bracing. *Archives of Disease in Childhood*, *84*(6), 521-524. http://doi.org/10.1136/adc.84.6.521

Taylor, M. J., McCormick, D., Shawis, T., Impson, R., & Griffin, M. (2011). Activity promoting gaming systems in exercise and rehabilitation. *Journal of Rehabilitation Research and Development*, *48*(10), 1171-1186. http://doi.org/10.1682/JRRD.2010.09.0171

Thomas, N. H., & Dubowitz, V. (1994). The natural history of type I (severe) spinal muscular atrophy. *Neuromuscular Disorders, 4*(5-6), 497-502. http://doi.org/10.1016/0960-8966(94)90090-6

Trochim, W. M., & Donnelly, J. P. (2006). *The research methods knowledge base.* Cincinnati, OH: Atomic Dog.

Tzeng, A.C., Cheng, J., Fryczynski, H., Niranjan, V., Stitik, T., Sial, A., . .Bach, J.R. (2000). A study of thyrotropin-releasing hormone for the treatment of spinal muscular atrophy: a preliminary report. *American Journal of Physical Medicine and Rehabilitation*. *79*(5), 435-440.

Vogt WP. (2005) *Dictionary of Statistics & Methodology: A Nontechnical Guide for the Social Sciences*. 3rd ed. Thousand Oaks, CA: Sage Publications.

Wadman, R. I., Bosboom, W. M., van der Pol, W. L., van den Berg, L. H., Wokke, J. H., Iannaccone, S. T., & Vrancken, A. F. (2012). Drug treatment for spinal muscular atrophy type I (Review). *The Cochrane Database of Systematic Reviews,* (4), CD006281. http://doi.org/10.1002/14651858.CD006281.pub4

Wang, C., Finkel, R., & Bertini, E. (2007). Consensus statement for standard of care in spinal muscular atrophy. *Journal of Child Neurology*, *22*(8), 1027-1049. http://doi.org/10.1177/0883073807305788

Wong, B., Hynan, L., Iannaccone, S., & AmSMART group. (2007). A randomized, placebo-

controlled trial of creatine in children with spinal muscular atrophy. *Journal of Clinical Neuromuscular Dis*orders. *8*(3), 101-110. http://doi.org/10.1097/CND.0b013e3180315c99

Young, S. D., Montes, J., Kramer, S., Marra, J., Salazar, R., Cruz, R., . . . DeVivo, D. C. (2016). Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle & Nerve*. *54*(5), 836-842. http://doi.org/doi:10.1002/mus.25120

Yuan, P., & Jiang, L. (2015). Clinical characteristics of three subtypes of spinal muscular atrophy in children. *Brain & Development*, *37*(5), 537-541. http://doi.org/10.1016/j.braindev.2014.08.007

Zerres, K., & Rudnik-Schoneborn, S. (1995). Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Archives of Neurology*, *52*(5), 518–523. http://doi.org/10.1001/archneur.1995.00540290108025

Zerres, K., Rudnik-Schoneborn, S., Forrest, E., Lusakowska, A., Borkowska, J., & Hausmanowa-Petrusewicz, I. (1997). A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. *Journal of the Neurological Sciences*, *146*(1), 67-72. http://doi.org/10.1016/S0022-510X(96)00284-5

APPENDIX A

Studies Investigating the use of Physical Therapy Services in Patients with SMA

Topic / Category	Article	Study Type & Population	Summary of Findings	Level of Evidence
Intervention (TES)	Fehlings et al 2002	Randomized control trial SMA 2 and 3, average age 9.9 years	Therapeutic Electrical Stimulation (TES) was not effective in improving strength or self-care function (by parent report) within 6 months of treatment. Muscle strength remained stable by both quantitative and manual methods in the control arm over 1 year.	B
Intervention (Power WC Mobility)	Jones et al 2003	Case Report 20 month old female child with SMA 2	Child provided with custom fit power chair, and practiced daily over 6 weeks. Both BDI and PEDI showed changes, not likely caused by just maturation. There was particular improvement in communication, personal-social and cognitive skills, suggesting they were likely due in part to the power mobility intervention.	D
Intervention (Equine-Assisted Activities and Therapy)	Lemke et al 2014	Qualitative Study SMA Type 2 & 3, ages 4-15 years	Perceived benefits include muscle function, core strength, balance, and flexibility. Psychological benefits included increased self-confidence, efficacy, esteem and sportsmanship. Also provided a rich social outlet, enjoyable and fun therapy. Barriers included cost of therapy and finding appropriate facilities familiar with SMA	X
Intervention (Aerobic Training)	Lindhardt et al. 2015	Prospective, controlled SMA 3 adults and age/gender match controls	12 weeks of aerobic training improved VO2max in SMAIII but also induces fatigue and has no beneficial effects on physical function	B
Intervention (Strengthening exercise)	Lewelt et al 2015	Observational Study SMA 2 and 3	A 12-week supervised, home-based, 3-day/week progressive resistance training exercise program is feasible, safe, and well tolerated in children with SMA types II and III. These findings can inform future studies of exercise in SMA.	C
Intervention (Aerobic and Strengthening Exercise)	Montes et al 2015	Randomized controlled trial/ Ambulatory	Before the study, patients were identified as insufficiently active as they spent on average 83.5% of waking hours in sedentary activity. No significant group	A

		patients with SMA IIIb and IIIa,ages 8-50	change after 6 months regarding primary outcome. Moderate but significant increase in VO2 max on a 6 month period, providing evidence of exercise tolerance in SMA patients with time. Exercise capacity measured by VO2 max appeared to be lower in ambulatory SMA patients compared to other myopathic and denervating disorders. Researchers speculated this blunted response reflected an SMA specific mitochondrial dysfunction.	
Intervention (Whole Body Vibration Training)	Vry et al 2014	Prospective Observational Clinical Study Duchene MD and SMA	In boys with DMD, creatine kinase increased by 56% after the first day of training and returned to baseline after 8 weeks of continuous whole-body vibration training. No changes in laboratory parameters were observed in children with SMA. No significant increase noted in muscle strength. Secondary outcomes showed mild improvements with the exception of the distance walked in the 6-min walking test in children with SMA, which rose from 371.3 m to 402.8 m. ($p < 0.01$).	C
Intervention (Aquatic PT)	Salem et al 2010	Case Study SMA III	Overall, there was consistent improvement in MMT grades in the lower limb muscles with exceptions of right hamstring and bilateral dorsiflexor strength, which stayed the same. GMFM 11% increase (standard dimension 28%,walk run jump 18%, gross motor quotient 66 to74) GaitRite improvement in velocity stride single limb support.	D
Intervention (Aquatic PT/ Physiotherapy)	Cunha et al. 1996	Prospective SMA 2 and 3 (uncontrolled) (2- 40 years)	Aquatic Physiotherapy and Physiotherapy over 2 years. Deformities in LE increased in all subjects SMA 3 MMT – strength stabilized or improved Improved daily activities (Barthel) in 93% SMA 2 and 100% SMA 3	C
Intervention (Physiotherapy)	Hartley et al 2013	Prospective – Survey 104 adults with various NMD (11	Over 79% of respondents were satisfied with the frequency and duration of their treatment 88% attended PT at least once a fortnight	C

		with SMA). Mean age 46 years	Identified psychosocial as well as physical benefits from attending physiotherapy. Barriers to attendance included work commitments, economic factors and time, and lack of Centre resources.	

APPENDIX B

CHOP INTEND Scoresheet

PNCR Network for SMA

CHOP INTEND

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

Name: Diagnosis:
MR: Gestational age:
DOE: Time of evaluation: Time since last feeding:
DOB: Current health: URI☐ Gtube ☐ BIPAP☐ HRS/Day HRSoff BIPAP at testing___

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 looses 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		
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		State:
			No attempt to maintain knees off surface	0	R	
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 45^0 diagonal to body and pause to allow infant to attempt to derotate 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	
			Pelvis and trunk lift from support surface and head turns to side. Arm remains behind trunk	1		State:
			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 derotate **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	To L	
			Head turns to side and shoulder and trunk lift from surface	1		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 30^0 of shoulder extension and elbow flexion and supported on body (restrain lower arm if needed)	Prompt reach for a toy presented at arms 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 (20^0 recline)	Present stimulus at midline and at shoulder level at arms 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		State:
			No attempt to lift arm	0	R	
10 Knee extension	Sitting in lap or over edge of mat with head and trunk support (20^0 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 > 30^0	4	L	Best side:
			Any hip flexion or knee flexion	3		
			Ankle dorsiflexion only	2		State:
			No active hip, knee or ankle motion	0	R	
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		Score:
			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 30^0 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		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		
			No visible contraction	0	R	State:
14 Neck Flexion Score with item 13	Supine	**Traction response:** hold in neutral proximal to wrist and shoulder at 45^0, ***to point of nearly lifting head off surface***	Lifts head off bed	4		Score:
			Visible muscle contraction of SCM	2		
			No muscle contraction	0		State:
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		
			No head extension	0		State:
16 Spinal Incurvation (Galant)	Ventral suspension: Prone, held in one hand upper abdomen	Stroke Right then Left thoracolumbar paraspinals or tickle abdomen or foot or tilt in infants with integrated Galant 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		
			No response	0	R	State:
Total score, best score on each side for each item (maximum 64 points):						

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

Contractures :
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 red wool ball on ring to encourage participation
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

APPENDIX C

TIMPSI Item List

Item Number	Description	Possible Score
Screening Set		
14	Head rotation side to side	0,1,2,3,4
15	Head control – supported sitting	0,1,2,3,4,5
27	Hip and Knee Flexion	0,1,2,3,4
28	R Rolling: Elicited from legs	0,1,2,3,4,5
29	L Rolling: Elicited from legs	0,1,2,3,4,5
32	Pull to sit	0,1,2,3,4,5
35	Prone Suspension	0,1,2,3,4
36	Head lift in prone	0,1,2,3,4,5
37	Crawling	0,1,2,3,4
38	R Head turn to sound in prone	0,1,2,3,4,5, 6
41	R Lateral head righting	0,1,2,3,4
Easy Set		
2	Individual R finger movement	0,1
5	Fingers objects/surfaces L side	0,1
7	Isolated ankle movement R	0,1
9	Reciprocal kicking	0,1
20	Inhibition of neonatal neck righting	0,1,2,3,4,5

22	Head held in midline – visual stimulation	0,1,2,3,4
23	Supine neck rotation to R	0,1,2,3,4
24	Supine neck rotation to L	0,1,2,3,4
30	Rolling to R: Elicited from arms	0,1,2,3,4,5
31	Rolling to L: Elicited from arms	0,1,2,3,4,5
Hard Set		
4	Fingers objects surfaces R side	0,1
10	Fidgety movements	0,1
11	Ballistic movements arms or legs	0,1
12	Oscillation of arm or leg during movement	0,1
13	Reaches for person or object	0,1
33	Lateral straightening of head and body	0,1,2,3,4
34	Lateral hip abduction reaction	0,1,2,3,4
40	Standing	0,1,2,3,4

APPENDIX D

CHOP INTEND Manual of Procedures

CHOP INTEND
Manual of Procedures
Testing environment:
• Ideally test first thing in the AM or same time of day, about 1 hour after feeding, when sated and alert but not fussy.
• Test on a firm padded mat
• Clothing: in a diaper only, unless the infant is cold where you can use a sleeveless "onesie" garment.
• Test with red wool ball on ring to encourage participation
• May use pacifier only if needed to maintain state 4 or 5 (see definition, below).
• Allow parent to be present and give rest period especially to calm the infant if upset. Aim to complete the entire test without a pause.
Behavioral State:
Include a rating of Brazelton behavioral state for each test item. The optimal state for testing is state 4 and 5. If a subject cannot be tested for an item due to an adverse behavioral state, score as "CNT" (cannot test) and not a zero. Directly quoted descriptions for each state from the Brazelton text (T. Berry Brazelton, Neonatal Behavioral Assessment Scale, 2nd ed. Clinics in Developmental Medicine No 88, Spastics International Medical Publications, London 1984):
State 1 = deep sleep
State 2 = light sleep
State 3 = "drowsy or semi-dozing"
• eyes may be open but dull and heavy–lidded or closed, eyelids fluttering. Dazed look when infant not processing information and is not "available".
• activity level variable, with interspersed, mild startles from time to time
reactive to sensory stimuli, but response often delayed. State change after stimulation frequently noted. Movements are usually smooth.
State 4 = "alert, with bright look"
• seems to focus invested attention on source of stimulation, such as an object to be sucked or a visual or auditory stimulus impinging stimuli may break through, but with some delay in response.
• Motor activity is at a minimum.
• There is a kind of glazed look, which can be easily broken though in this state.
State 5 = eyes open
• **considerable motor activity, with thrusting movements of the extremities, and even a few spontaneous startles**
• reactive to external stimulation with increase in startles or motor activity, but discrete reactions difficult to distinguish because of general activity level.
• Brief fussy vocalizations occur in this state.
State 6 = Crying

• Characterized by intense crying which is difficult to break through with stimulation
• Motor activity is high.

Testing and Scoring:

• All items can be scored either with spontaneous movement or active movement depending on the cognitive level and age of the subject.
• An attempt should be made to elicit the maximum performance with either verbal encouragement or use of toys.
• Perform each test item in the order listed unless otherwise noted.
• Make a note in the margin of any comments about performing or scoring an item
• If in doubt in scoring between two responses, "score down".
• Videotape your testing and review the tape to learn how to improve your administration of the test item and see if you score it the same.

Item 1: Spontaneous movement (upper extremity)

Start Position: This item can be observed throughout the test and can be observed in any position. An initial period of observation in supine should be completed with the child in an alert awake state.
Stimulus: The examiner may support the arm or leg and observe the hand or foot without the friction of the surface. The examiner may stroke the hand or foot to elicit a response if none is observed.
Scoring Criteria:
Score 4 Antigravity shoulder movement (elbows off surface in supine)
Score 3 For active antigravity movement (hand and forearm off surface in supine)
Score 2 For active wrist movement
Score 1 For isolated finger movement
Score 0 For no movement of limbs
Score both sides and select the maximum score for a final score.

Item 2: Spontaneous movement (lower extremity)

Start Position: This item can be observed throughout the test and can be observed in any position. An initial period of observation in supine should be completed with the child in an alert awake state.
Stimulus: The examiner may support the arm or leg and observe the hand or foot without the friction of the surface. The examiner may stroke the hand or foot to elicit a response if none is observed.
Scoring Criteria:
Score 4 Antigravity hip movement (feet and knees off surface in supine)
Score 3 Active antigravity hip adduction/internal rotation (knees off surface in supine do not give credit if maintained only due to range of motion loss)
Score 2 Active gravity eliminated knee/hip movement (extension and flexion in abduction and external rotation)
Score 1 Isolated ankle movement

Score 0 No movement of limbs

Score both sides and select the maximum score for a final score.

Item 3: Hand Grip

Start Position: Supine with arm and forearm on the surface of testing mat and in pronation with the wrist extended.

Stimulus: Place your "pinkie" (or a toy of the same diameter for infants without a grasp reflex) in the infant's hand until a grip response is secure, then slowly lift the arm and hand, creating traction on the arm at 90^0 to the support surface, then continue to draw shoulder off the mat. Record score when the child loses grip. May repeat 3 times to make sure the child's best effort is obtained. Repeat for the other arm. Provide verbal encouragement for older infants.

Scoring Criteria:

Score 4 Maintains handgrip with shoulder off bed

Score 3 Maintains grip with elbow just off bed but shoulder on surface

Score 2 Maintains grip with forearm off surface but elbow still supported

Score 1 Maintains grip only with no traction

Score 0 No grip or pinkie slips out

Score both sides and select the maximum score for a final score

Item 4: Head in midline

Start Position: Supine head midline

Stimulus: Visual stimulation with a bright object at midline. If the infant maintains midline for 15 seconds then turn the infant's head 90 degrees to the right and provide visual stimulation to encourage return to midline, then repeat to the left. Note: If the infant's head cannot be turned passively at least 60 degrees off midline, due to a neck contracture, then this second part (scores of 3 and 4) cannot be tested and a score of no more than 2 can be given for that side.

Scoring Criteria:

Score 4 Rotates from 90^0 back fully to midline

Score 3 Actively turns head part way towards midline

Score 2: Maintains head within 15^0 of midline for 5 or more sec.

Score 1: Maintains within 15^0 of midline for less than 5 sec.

Score 0 Head falls to side and no attempt to regain midline is noted

Score both sides and select the maximum score for a final score.

Item 5: Hip adductors

Start Position: Supine, with hips at 45^0, knees at 90^0, feet hip width apart, remove diaper.

Stimulus: Position legs in neutral with thighs parallel and release; observe response of legs

Scoring Criteria:

Score 4 Maintains knee off surface of bed more than 5 sec. or lifts feet off surface

Score 2 Keeps knee off surface of bed 1 to 5 seconds

Score 0 No attempt to maintain knees off surface

Score both sides and select the maximum score for a final score.

Note: may score item based on regaining adducted position and maintaining for prescribed time after a fall to the surface or maintaining adduction.

Item 6: Rolling: elicited from the legs
Start Position: Supine arms at sides
Stimulus: Holding infant's lower thigh, flex hip and knee and adduct across midline of the body to stimulate rolling. If the infant rolls to side continue to apply traction at diagonal to body to maintain tension on the leg, pause with hips at 90^0 to surface to allow infant to attempt to derotate body against the fixed distal leg, continue to maintain tension on the leg as the infant derotates the upper body against it. Do not passively pull the child across to prone the goal is to observe the active derotation of the trunk against the stabilized lower extremity with the hips vertical and then the head control and ability to clear the weight bearing shoulder as the child rolls to prone and frees the arm and brings the head across the arm.
Scoring Criteria:
Score 4 When traction is applied at the end of the maneuver, rolls to prone with lateral head righting
Score 3 Rolls through side lying into prone without lateral head righting (clears weight bearing arm completely to finish roll)
Score 2 Pelvis, trunk and arm lift from support surface, head turns and rolls onto side (arm comes through to front of body)
Score 1 Pelvis and trunk lift from support surface and head turns to side. Arm remains behind trunk
Score 0 Pelvis lifted passively off support surface with no active participation
Score both sides and select the maximum score for a final score.

Item 7: Rolling: elicited from the arms
Start Position: Supine arms at side
Stimulus: Hold infant at the elbow and move across midline toward opposite shoulder to elicit rolling pause with shoulders 90^0 to surface and maintain traction on limb and allow infant to derotate. Pause with shoulders vertical and wait for trunk to derotate and lower extremity and hips to come to sideling do not passively pull the infant to prone. Continue to apply traction to arm and observe head control and ability to free arm and complete roll to prone.
Scoring Criteria:
Score 4 Rolls onto side with lateral head righting (infant lifts head laterally off the support surface to complete the roll to prone)
Score 3 Rolls into prone without lateral head righting (Clears weight bearing arm completely to finish roll)
Score 2 Rolls onto side (leg comes through and adducts bringing the pelvis vertical)
Score 1 Head turns to side and shoulder and trunk lift from surface
Score 0 Head turns to side; body remains limp or shoulder lifts passively without active participation
Score both sides and select the maximum score for a final score.

Item 8: Shoulder flexion and elbow flexion and horizontal abduction
Start Position: Side-lying with upper arm supported on body in 30 degrees of elbow flexion and shoulder extension. The dependent arm should be restrained along the trunk.
Stimulus: Prompt reaching for a toy presented at arm's length at shoulder level (hold the lower arm to prevent the child from reaching with that arm). You may touch the infant's hand with the toy to encourage reaching. Any spontaneous upper extremity movements should be scored; intent is not required.
Scoring Criteria:
Score 4 Clears hand from the surface while reaching (the infant demonstrates any antigravity horizontal abduction)
Score 3 Able to flex shoulder to 45 degrees (the infant demonstrates gravity eliminated shoulder flexion)
Score 2 Flexes elbow after arm comes off body
Score 1 Able to get arm off body
Score 0 No attempt (the arm remains on the infants trunk)
Intent is not necessary and spontaneous movement may be scored
Score both sides and select the maximum score for a final score.

Item 9: Shoulder flexion & elbow flexion

Start Position: Sitting (slightly reclined about 20) on mat or on therapist or parents lap straddled over examiners leg, with support for trunk and posterior head, child's arm dangling at side.
Stimulus: Present toy at midline and at shoulder level (May touch the infant's hand with toy to stimulate movement).
Scoring Criteria:
Score 4 If the infant makes contact with the toy
Score 3 If the infant flexes the shoulder to 60 degrees
Score 2 If the infant demonstrates any flexion or abduction of the shoulder
Score 1 If the infant flexes the elbow only
Score 0 If the infant does not lift the arm
Intent is not necessary and spontaneous movement may be scored
Score both sides and select the maximum score for a final score.

Item 10: Knee extension
Start Position: sitting on mat or parent's or examiner's lap in straddle position on one leg, with approximately 20 degree recline of the subject's torso and thigh horizontal to the ground. Support with hand under knee to maintain knee position as needed.
Stimulus: Tickle planter surface of the foot or gently pinch the toe with the thigh horizontal to the ground.
Scoring Criteria:
Score 4 If the infant extends the knee greater than 45 degrees. Make sure this is not due to passive swinging of the leg from examiner's repositioning.
Score 2 If the infant extends knee 15 to 45 degrees
Score 1 If any visible knee extension is noted
Score 0 If no visible knee extension is noted
Score both sides and select the maximum score for a final score.

Item 11: Hip flexion and foot dorsiflexion
Start Position: To attain this test position start in supine, hold the infant with your non dominant hand under the chin and roll the infant to prone over your hand then place your dominant hand across the infants abdomen lean forward and lift the child against your chest. Support the infant's back against the examiner's chest and with the support provided by the examiner across the subject's abdomen with their dominant arm, with the legs dangling unsupported. Tickle, or have the parent tickle, the child's foot and observe the child's response (a mirror may aid in evaluating the score).
Stimulus: Stroke plantar surface of foot.
Scoring Criteria:
Score 4 If hip flexion or knee flexion > than 30^0
Score 3 If any hip flexion or knee flexion is noted
Score 2 If only dorsiflexion is observed
Score 0 If no active hip, knee, or ankle motion is noted
Score both sides and select the maximum score for a final score.
Item 12: Head Control
Start Position: Sitting facing the examiner in ring sit, with the examiner supporting with both hands at the shoulders on the anterior and posterior surface. Position the infant's trunk in an erect position with shoulders and trunk neutral. Try to get the infant positioned with the head erect. This may take some repositioning as many infants only have tenuous head control and have a very limited cone of stability.
Stimulus: If the infant cannot be positioned with head erect allow the head to fall forward and support the chin with your thumbs at end range to keep the chin off the chest.
Scoring Criteria:
Score 4 Attains upright head position at least once from flexion and moves the head freely with control
Score 3 Maintains head upright for greater than 15 seconds
Score 2 Maintains head in midline for >5 sec. with the head tipped in up to 30^0 of forward flexion or extension
Score 1 Actively lifts or rotates the head twice within 15 seconds (This may not be scored only on head movement with breathing effort)
Score 0 No response, head hangs
Evaluation of scores of 1 and 4 can be delayed till the end of the test to maintain calm
Item 13: (Elbow Flexion, Score with item 14)
Start Position: Supine
Stimulus: Traction response: initiate "pull to sit" with arms extended at 45 degree angle until shoulders are lifted off the surface, to point of nearly lifting head off the surface.
Scoring Criteria:
Score 4: Active elbow flexion
Score 2: Visible biceps contraction without elbow flexion
Score 0: No visible biceps contraction

Score both sides and select the maximum score for a final score.

Item 14: (Neck Flexion, Score with item 13)

Start Position: Supine

Stimulus: **Traction response:** Initiate "pull to sit" with arms extended at 45 degree angle to trunk until shoulders are lifted off the surface, to point of nearly lifting head off the surface.

Scoring Criteria:

Score 4 Lifts head off bed

Score 2 Visible muscle contraction of SCM

Score 0 No visible contraction

Item 15: Head/Neck extension (Landau)

Start Position: Ventral suspension: prone, held in one hand over upper abdomen/lower rib cage. For larger infants, if necessary, the head and knees are allowed to rest on the mat.

Stimulus: Stroke the paraspinal muscles bilaterally along spine from neck to sacrum.

Scoring Criteria:

The coronal axis of the head when parallel to the bed surface = 0 degrees (horizontal)

Score 4 If the head is extended to or above the horizontal plane.

Score 2 If the head is extended partially, but not to the horizontal plane.

Score 0 If no active head extension is noted.

Item 16: Spinal incurvation (Galant)

Start Position: Prone over examiners hand supported at the upper abdomen or lower thorax. For larger infants, if necessary, the head and knees are allowed to rest on the mat.

Stimulus: Stroke right then left throacolumbar paraspinal muscles with thumbnail, from sacrum to mid-thoracic level (**Galant's reflex**). For older children tilt them to facilitate righting reaction, tickle them at the side or foot or ask them to wiggle their buttock.

Scoring Criteria:

Score 4 Twists pelvis toward stimulus off axis

Score 2 Visible paraspinal muscle contraction

Score 0 No Response

Score both sides and select the maximum score for a final score.

APPENDIX E

CHOP INTEND Extremity Score

Items included in CHOP extremity score

Item Number	Description	Position	Test procedure	Graded response	Right	Left
1	spontaneous movement of upper extremity	supine	Observe throughout testing	Antigravity shoulder movement (elbow off surface)	4	4
				Antigravity shoulder movement hand and forearm off surface)	3	3
				Wrist movement	2	2
				Finger movement	1	1
				No movement of upper limbs	0	0
2	spontaneous movement of lower extremity	supine	Observe throughout testing	antigravity hip movement (feet and knees off surface)	4	4
				antigravity hip adduction/internal rotation (knees off surface)	3	3
				active gravity eliminated knee movement	2	2
				ankle movement	1	1
				no movement of lower limbs	0	0
3	Hand grip	supine	place finger in palm and lift until shoulder comes off surface. Observe when infant looses grasp	maintains hand grip with shoulder off bed	4	4
				maintains hand grip with elbow off bed	3	3
				maintains hand grip with forearm off surface	2	2
				maintains grip with no traction	1	1
				no attempt to maintain grip	0	0
5	Hip Adductors	supine, no diaper	hips flexed and adducted. Feet hip width apart and thighs parallel, knees slightly apart	keeps knee off surface > 5 sec or lifts foot off surface	4	4
				keeps knees off surface 1-5 sec	2	2
				no attempt to maintain knee off surface	0	0
8	shoulder and elbow flexion and horizontal abduction	sidelying	prompt reach for a toy presented at arms length at shoulder level	clears hand from surface with antigravity arm movement	4	4
				able to flex shoulder to 45 degrees, without antigravity arm movement	3	3
				flexes elbow after arm comes off body	2	2
				able to get arm off body	1	1
				no attempt to move arm	0	0
9	shoulder flexion and elbow flexion	sitting with head and trunk support	present stimulus at midline and shoulder level at arms length	abducts or flexes shoulder 60 deg	4	4
				abducts or flexes shoulder 30 deg	3	3
				any shoulder flexion or abduction	2	2
				flexes elbow only	1	1
				no attempt to lift arm	0	0
10	knee extension	sitting with head and trunk support	tickle plantar surface of foot	extends knee to >45 deg	4	4
				extends knee 15 to 45 deg	2	2
				any visible knee extension	1	1
				no visible knee extension	0	0
11	hip flexion and foot dorsiflexion	hold infant against body with legs free facing outward, support at abdomen	stroke foot or pinch toe	hip flexion or knee flexion >30 deg	4	4
				any hip flexion or knee flexion	3	3
				ankle dorsiflexion only	2	2
				no active hip, knee, or ankle motion	0	0
13	elbow flexion	supine	traction response: pull to sit	flexes elbow	4	4
				visible biceps contraction without elbow flexion	2	2
				no visible contraction	1	1

APPENDIX F

IRB APPROVAL LETTERS

UT Southwestern Medical Center — eIRB System

From:	Scott Roberts Institutional Review Board Chairperson IRB - 8843
To:	Leslie Nelson , Leslie Nelson ,
Date:	Friday, November 04, 2016
Re:	Study Approval
IRB Number:	STU 052016-109
Title:	Reliability and Validity of the ACTIVE-mini for Quantifying Movement in Infants with Spinal Muscular Atrophy
Documents:	Protocol, Consent Forms, HIPAA Authorization Forms, and All Smart Form Attachments

The UT Southwestern Institutional Review Board (IRB) reviewed the above-referenced research study via an expedited review procedure on Wednesday, November 02, 2016 in accordance with 45 CFR 46.110(a)-(b)(1). Having met all applicable requirements, the research study is approved for a period of 12 months. The approval period for this research study begins on Wednesday, November 02, 2016 and lasts until Wednesday, November 01, 2017 .

Having met all regulatory criteria outlined in 45 CFR 164.512, the IRB also approved a waiver of authorization for the release of protected health information for this study.

The research study cannot continue beyond the approval period without continuing review and approval by the IRB. In order to avoid a lapse in IRB approval, the Principal Investigator must apply for continuing review of the protocol and related documents before the expiration date. A reminder will be sent to you approximately 90 days prior to expiration of research study approval.

The approved number of subjects to be enrolled is 30 . The IRB considers a subject to be enrolled once s/he signs a Consent Form. If additional subjects are needed, you must first obtain permission from the IRB to increase the sample size.

If you have any questions related to this approval letter or about IRB policies and procedures, please telephone the IRB Office at 214-648-3060.

Institutional Review Board (IRB) Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution/Organization A):
University of Texas Southwestern Medical Center

IRB Registration #: IORG0000638 Federalwide Assurance (FWA) #, if any: FWA00005087

Name of Institution Relying on the Designated IRB (Institution B):

Texas Woman's University (FWA #: 00000178)

The Officials signing below agree that **Texas Woman's University** may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (*check one*)

(___) This agreement applies to all human subjects research covered by Institution B's FWA.

(_X_) This agreement is limited to the following specific protocol(s):

Name of Research Project:	Reliability and Validity of the ACTIVE-mini for Quantifying Movement in Infants with Spinal Muscular Atrophy (protocol # STU 052016-109)
Name of Principal Investigator:	UTSW: Leslie Nelson, TWU: Mary Thompson
Sponsor or Funding Agency:	N/A Award Number, if any: _____

(___) Other (*describe*):_____

The review performed by the designated IRB will meet the human subject protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

Signature of Signatory Official (Institution/Organization A):

DocuSigned by:
Angela Wishon
[illegible]

Angela Wishon, Vice President for Research Administration

Date: 1/27/2017 | 10:16 AM CST

Signature of Signatory Official (Institution B):

Jennifer Martin

Jennifer Martin, PhD, Interim Provost and Vice President for Academic Affairs

Date: 1/30/17

DS
KO