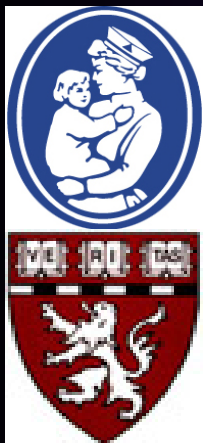


# SMA Type I: Outcome Measures

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**Basil T. Darras, M.D.**  
**Neuromuscular Program**  
**Boston Children's Hospital**  
**Harvard Medical School**  
**Boston, MA**

# Financial disclosures

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## Workshop report

# 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7–9 November 2014, Heemskerk, The Netherlands

Richard Finkel <sup>a,\*</sup>, Enrico Bertini <sup>b</sup>, Francesco Muntoni <sup>c</sup>, Eugenio Mercuri <sup>d</sup> on behalf of the  
ENMC SMA Workshop Study Group <sup>1</sup>

<sup>a</sup> Nemours Children's Hospital, Orlando, USA

<sup>b</sup> UCL Institute of Child Health, Dubowitz Neuromuscular Centre, London, UK

<sup>c</sup> Bambino Gesù Children's Research Hospital, Rome, Italy

<sup>d</sup> Pediatric Neurology Unit, Catholic University, Rome, Italy

Received 2 March 2015

## Suitability of Functional Scales

Table 2A

Outcome measures for clinical trials in SMA: motor function scales, electrophysiological biomarkers and strength testing.

|                                        | HFMSE          | MFME        | 6MWT | ULM         | CHOP INTEND | TIMPSI | CMAP and MUNE      | Myotools |
|----------------------------------------|----------------|-------------|------|-------------|-------------|--------|--------------------|----------|
| Clinical utility:                      | 2 and weaker 3 | 2 and 3     | 3    | 2           | 1           | 1      | ✓                  | ✓        |
| SMA subgroups                          |                |             |      |             |             |        |                    |          |
| Supports mechanisms of action          | ✓              | ✓           | ✓    | ✓           | ✓           | ✓      | ✓                  | ✓        |
| Conceptual framework for SMA           | ✓              | ✓           | ✓    | ✓           | ✓           | ✓      | ✓                  | ✓        |
| Reliability:                           | ✓              | ✓           | ✓    | ✓           | ✓           | ✓      | Protocol dependent | ✓        |
| Inter and intratester                  |                |             |      |             |             |        |                    |          |
| Validation with other outcome measures | ✓              | ✓           | ✓    | ✓           | ✓           | ✓      | ✓                  | ✓        |
| Normative ranges                       | ✓              | ✓           | ✓    | ✓           | ✓           | ✓      | ✓                  | ✓        |
| Published natural history studies      | ✓              | ✓           | ✓    | ✓           | ✓           | ✓      | ✓                  | ✓        |
| Multicentre studies                    | ✓              | ✓           | ✓    | ✓           | ✓           | ×      | Protocol dependent | ✓        |
| Responsiveness to change               | ✓              | ✓           | ✓    | In progress | ✓           | ✓      | ✓                  | ✓        |
| Clinical meaningfulness                | ✓              | ✓           | ✓    | ✓           | ✓           | ✓      | ×                  | ✓        |
| MCID                                   | ×              | ×           | ×    | ×           | ×           | ×      | ×                  | ×        |
| Age-specific changes                   | ✓              | In progress | ✓    | In progress | ×           | ×      | ✓                  | ✓        |
| Ambulant                               | ✓              | ✓           | ✓    | ×           | ×           | ×      | ✓                  | ✓        |
| Non-ambulant                           | ✓              | ✓           | ×    | ✓           | ✓           | ✓      | ✓                  | ✓        |

HFMSE: Hammersmith Functional Motor Scale Expanded, MFME: Motor Function Measure, 6MWT: 6-minute walk test distance, ULM: upper limb module for SMA, CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, TIMPSI: Test of Infant Motor Performance Screening Items, CMAP: compound motor action potential, MUNE: motor unit number estimate, MCID: minimal clinically important difference.

- Longitudinal natural history data
- Reliability
- Validity
- Clinically meaningfulness
- Used in previous clinical trials
- Clinical utility

# CHOP INTEND:

## Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

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- **Source: Jackie Montes, PT, Columbia Univ.**
- Validated, 16 items, 64-point scale
- Shown reliable in SMA Type I subjects
- Derived in part from **TIMP** (Test of Infant Motor Performance)
- Designed to measure motor function in weak infants with neuromuscular disease
- Includes active (spontaneous, goal-directed) and elicited reflex movements

# CHOP INTEND:

## Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

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- Designed to move from easiest to hardest
- Does not include respiratory or feeding assessments
- Grading includes with gravity eliminated (lower scores) to antigravity movements (higher scores)
- Scores range from 0-4 in all items
- Completed in short period of time, well tolerated

# Scoring Sheet

## RESEARCH ARTICLE

## Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

Allan M. Glanzman, PT, DPT, PCS; Michael P. McDermott, PhD; Jacqueline Montes, PT, MA, NCS; William B. Mariens, BA; Jean Flickinger, PT, MPT, PCS; Susan Riley, PT, MS, DPT, PCS; Janet Quigley, PT, DPT; Sally Dunaway, PT, DPT; Jessica O'Hagen, PT, DPT; Liyong Deng, MD; Wendy K. Chung, MD, PhD; Rabi Tawil, MD; Basil T. Darras, MD; Michele Yang, MD; Douglas Sproule, MD; Darryl C. De Vivo, MD; Petra Kaufmann, MD, MS; Richard S. Finkel, MD; The Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy (PNCNCR); The Muscle Study Group (MSG)

The Children's Hospital of Philadelphia (Drs Glanzman and Finkel and Ms. Flickinger), Philadelphia, Pennsylvania; University of Rochester Medical Center (Drs McDermott and Tawil and Mr. Mariens), Rochester, New York; Columbia University (Drs Montes, Dunaway, O'Hagen, Deng, Chung, Sproule, De Vivo, and Kaufmann), New York, New York; Children's Hospital Boston (Drs Riley, Quigley, and Darras), Boston, Massachusetts; Harvard Medical School (Dr Darras), Cambridge, Massachusetts; University of Colorado Denver and The Children's Hospital of Denver (Dr Yang), Denver, Colorado; Perelman School of Medicine at the University of Pennsylvania (Dr Finkel), Philadelphia, Pennsylvania.

**CHOP INTEND**  
CHILDREN'S HOSPITAL OF PHILADELPHIA INFANT TEST OF NEUROMUSCULAR DISORDERS

Name: \_\_\_\_\_ Diagnosis: \_\_\_\_\_  
MR: \_\_\_\_\_ Time of evaluation: \_\_\_\_\_  
DOE: \_\_\_\_\_ Time since last feeding: \_\_\_\_\_  
DOB: \_\_\_\_\_

| Item                                                 | Position                                                                    | Test Procedure                                                                                                                                                                                                                                                                     | Graded Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Score                 |              |                      |
|------------------------------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------|----------------------|
| <b>1</b><br>Spontaneous movement (Upper extremity)   | Supine                                                                      | Observe throughout testing<br>May unweight limb or stimulate infant to facilitate response                                                                                                                                                                                         | Antigravity shoulder movement (achieves elbow off surface) 4<br>Antigravity elbow movement (achieves hand and forearm off surface) 3<br>Wrist movement 2<br>Finger movement 1<br>No movement of limbs 0                                                                                                                                                                                                                                                                                     | 4<br>3<br>2<br>1<br>0 | L<br>R       | Best side:<br>State: |
| <b>2</b><br>Spontaneous movement (Lower extremity)   | Supine                                                                      | Observe throughout testing<br>May unweight limb or stimulate infant to facilitate response                                                                                                                                                                                         | Antigravity hip movement (achieves foot and knees off surface) 4<br>Antigravity hip adduction/internal rotation (knees off surface) 3<br>Active gravity eliminated knee movement 2<br>Ankle movement 1<br>No movement of limbs 0                                                                                                                                                                                                                                                            | 4<br>3<br>2<br>1<br>0 | L<br>R       | Best side:<br>State: |
| <b>3</b><br>Hand grip                                | Supine                                                                      | Grip strength: place finger in palm and lift until shoulder comes off surface observe when infant loses grasp<br>May use toy of similar diameter for older children                                                                                                                | Maintains hand grip with shoulder off bed 4<br>Maintains grip with elbow off surface (shoulder on surface) 3<br>Maintains grip with forearm off surface (elbow supported on surface) 2<br>Maintains grip only with no traction 1<br>No attempt to maintain grip 0                                                                                                                                                                                                                           | 4<br>3<br>2<br>1<br>0 | L<br>R       | Best side:<br>State: |
| <b>4</b><br>Head in midline with visual stimulation* | Supine head midline                                                         | Visual stimulation is given with toy.<br>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<br>Turns head part way back to midline 3<br>Maintains midline for 5 or more seconds 2<br>Maintains midline, less than 5 seconds 1<br>Head falls to side, no attempts to regain midline 0                                                                                                                                                                                                                                                         | 4<br>3<br>2<br>1<br>0 | L>R<br>R>L   | Best side:<br>State: |
| <b>5</b><br>Hip adductors                            | Supine, no diaper                                                           | Hips flexed and adducted<br>Feet hip width apart and thighs parallel, knees slightly apart                                                                                                                                                                                         | Keeps knee off surface of bed > 5 sec or lifts foot off surface 4<br>Keeps knees off surface of bed 1-5 sec 2<br>No attempt to maintain knees off surface 0                                                                                                                                                                                                                                                                                                                                 | 4<br>2<br>0           | L<br>R       | Best side:<br>State: |
| <b>6</b><br>Rolling: elicited from legs*             | Supine (arms at side)<br>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.<br>2. If infant rolls to side apply traction at a 45° diagonal to body and pause to allow infant to attempt to decelerate body | When traction is applied at the end of the maneuver, rolls to prone with lateral head righting 4<br>Rolls through side lying into prone without lateral head righting, clears weight-bearing arm to complete roll 3<br>Pelvis, trunk and arm lift from support surface, head turns and rolls onto side, arm comes thru to front of body 2<br>Pelvis and trunk lift from support surface and head turns to side. Arm remains behind trunk 1<br>Pelvis lifted passively off support surface 0 | 4<br>3<br>2<br>1<br>0 | To R<br>To L | Best side:<br>State: |
| <b>7</b><br>Rolling: elicited from arms*             | Supine (arms at side)<br>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 decelerate 2. If the pelvis achieves vertical continue to provide traction                                                               | Rolls to prone with lateral head righting 4<br>Rolls into prone without lateral head righting, must clear weight-bearing arm completely to finish roll 3<br>Rolls onto side, leg comes thru and adducts, bringing the pelvis vertical 2<br>Head turns to side and shoulder and trunk lift from surface 1<br>Head turns to side; body remains limp or shoulder lifts passively 0                                                                                                             | 4<br>3<br>2<br>1<br>0 | To R<br>To L | Best side:<br>State: |

|                                                                 |                                                                                                                                    |                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |                      |
|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|----------------------|
| <b>8</b><br>Shoulder and elbow flexion And horizontal abduction | Side-lying with upper arm at 30° shoulder extension and elbow flexion and supported on body (swim lower arm if needed)             |                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |                      |
| <b>9</b><br>Shoulder flexion & Elbow flexion                    | Sitting in lap or on mat with head and trunk support (20° recline)                                                                 |                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |                      |
| <b>10</b><br>Knee extension                                     | Sitting in lap or over edge of mat with head and trunk support (20° recline thigh horizontal & ground)                             |                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |                      |
| <b>11</b><br>Hip flexion and foot dorsiflexion                  | Hold infant against body with legs free, but outward. Support at abdomen with the child's head resting between your arm and thorax |                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |        |                      |
| <b>12</b><br>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).<br>(may delay scoring a grade of 1 and 4 until end of test)   | Ankle dorsiflexion only 2<br>No active hip, knee or ankle motion 0<br>Attains head upright from flexion and turns head side to side 4<br>Maintains head upright for >15 sec (for bobbing head control score a 2) 3<br>Maintains head in midline for >5 sec. with the head tipped in up to 30° of forward flexion or extension 2<br>Actively lifts or rotates head twice from flexion within 15 seconds (do not credit if movement is in time with breathing) 1<br>No response, head hangs 0 | L<br>R | Score:<br>State:     |
| <b>13</b><br>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<br>Visible biceps contraction without elbow flexion 2<br>No visible contraction 0                                                                                                                                                                                                                                                                                                                                                                                            | L<br>R | Best side:<br>State: |
| <b>14</b><br>Neck Flexion Score with item 13                    | Supine                                                                                                                             | Traction response: hold in neutral proximal to wrist and shoulder at 45°, to point of nearly lifting head off surface                                              | Lifts head off bed 4<br>Visible muscle contraction of SCM 2<br>No muscle contraction 0                                                                                                                                                                                                                                                                                                                                                                                                      |        | Score:<br>State:     |
| <b>15</b><br>Head/Neck Extension (Landon)                       | Ventral suspension: Prone, held in one hand upper abdomen                                                                          | Stroke 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<br>Extends head partially, but not to horizontal 2<br>No head extension 0                                                                                                                                                                                                                                                                                                                                                                       |        | Score:<br>State:     |
| <b>16</b><br>Spinal Incubation (Galant)                         | Ventral suspension: Prone, held in one hand upper abdomen                                                                          | Stroke Right then Left thoracolumbar paraspinal 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<br>Visible paraspinal muscle contraction 2<br>No response 0                                                                                                                                                                                                                                                                                                                                                                                       | L<br>R | Best side:<br>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.

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

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

Testing environment:

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

Test on a firm padded mat

Diaper on only unless the infant is cold

Test with red ball on ring to encourage participation

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

# CHOP INTEND:

## Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

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- SMA Type I infant average baseline score: 20–22 out of 64 points
- Infants with 2 copies of *SMN2*: no baseline value over 40 points
- Score above 50 may correlate with sitting milestone
- Used successfully in ASO (Ionis/Biogen) and gene therapy (Avexis) Type I clinical trials

# NeuroNEXT Baseline Results

**ANNALS**  
of Clinical and Translational Neurology

Open Access



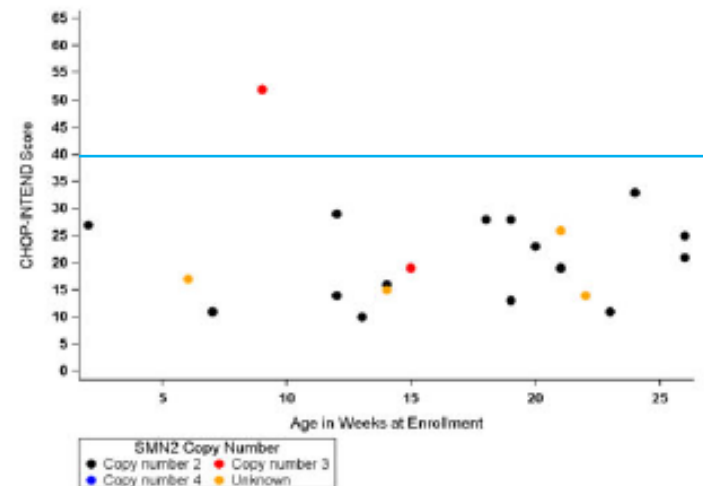
## RESEARCH ARTICLE

### Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study

Stephen J. Kolb<sup>1,2</sup>, Christopher S. Coffey<sup>3</sup>, Jon W. Yankey<sup>3</sup>, Kristin Krosschell<sup>4</sup>, W. David Arnold<sup>1,5</sup>, Seward B. Rutkove<sup>6</sup>, Kathryn J. Swoboda<sup>7,8</sup>, Sandra P. Reyna<sup>7,8</sup>, Ai Sakonju<sup>7</sup>, Basil T. Darras<sup>9</sup>, Richard Shell<sup>10</sup>, Nancy Kuntz<sup>11</sup>, Diana Castro<sup>12</sup>, Susan T. Iannaccone<sup>12</sup>, Julie Parsons<sup>13</sup>, Anne M. Connolly<sup>14</sup>, Claudia A. Chiriboga<sup>15</sup>, Craig McDonald<sup>16</sup>, W. Bryan Burnette<sup>17</sup>, Klaus Werner<sup>18</sup>, Mathula Thangarajh<sup>19</sup>, Perry B. Shieh<sup>20</sup>, Erika Finanger<sup>21</sup>, Merit E. Cudkovic<sup>8</sup>, Michelle M. McGovern<sup>8</sup>, D. Elizabeth McNeil<sup>22</sup>, Richard Finkel<sup>23</sup>, Edward Kaye<sup>24</sup>, Allison Kingsley<sup>1</sup>, Samantha R. Renusch<sup>2</sup>, Vicki L. McGovern<sup>2</sup>, Xueqian Wang<sup>2</sup>, Phillip G. Zaworski<sup>25</sup>, Thomas W. Prior<sup>26</sup>, Arthur H.M. Burghes<sup>2</sup>, Amy Bartlett<sup>1</sup> & John T. Kissel<sup>1</sup> the NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators

*Annals of Clinical and Translational Neurology* 2016; 3(2): 132–145

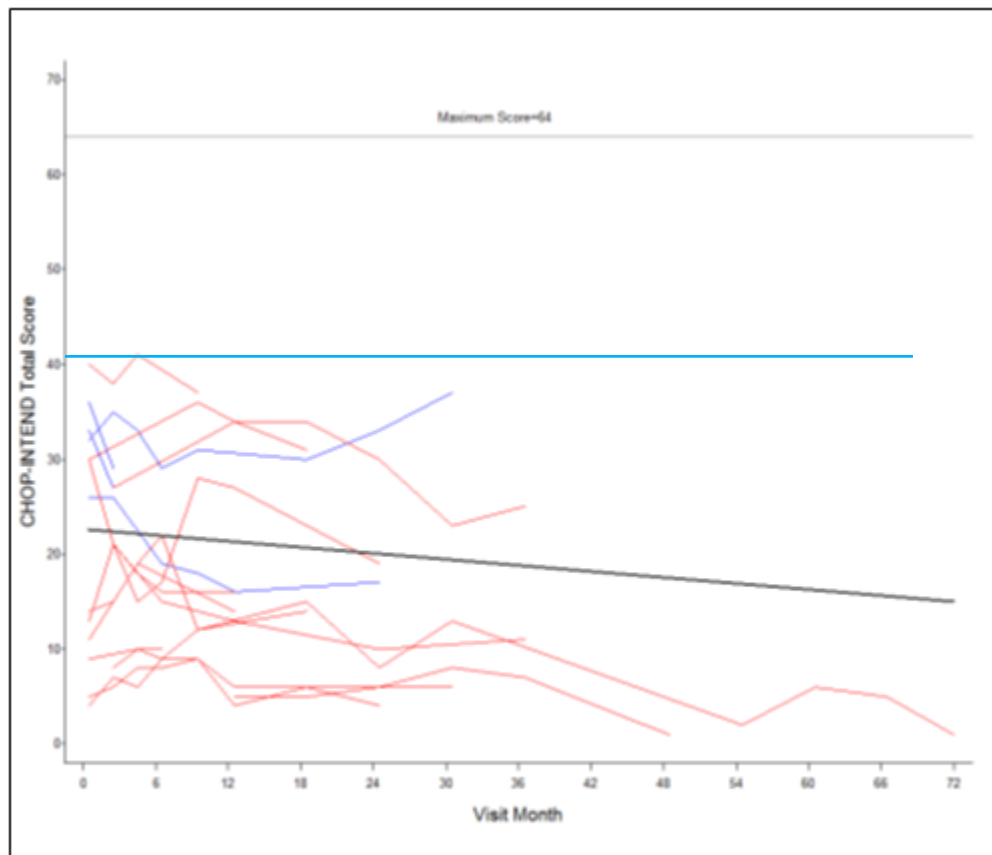
CHOP-INTEND



# PNCR NH Study: CHOP INTEND

## Longitudinal Data

- Subjects enrolled within 3 months of symptom onset (“recent”)
- Subjects enrolled more than 3 months after symptom onset (“chronic”)



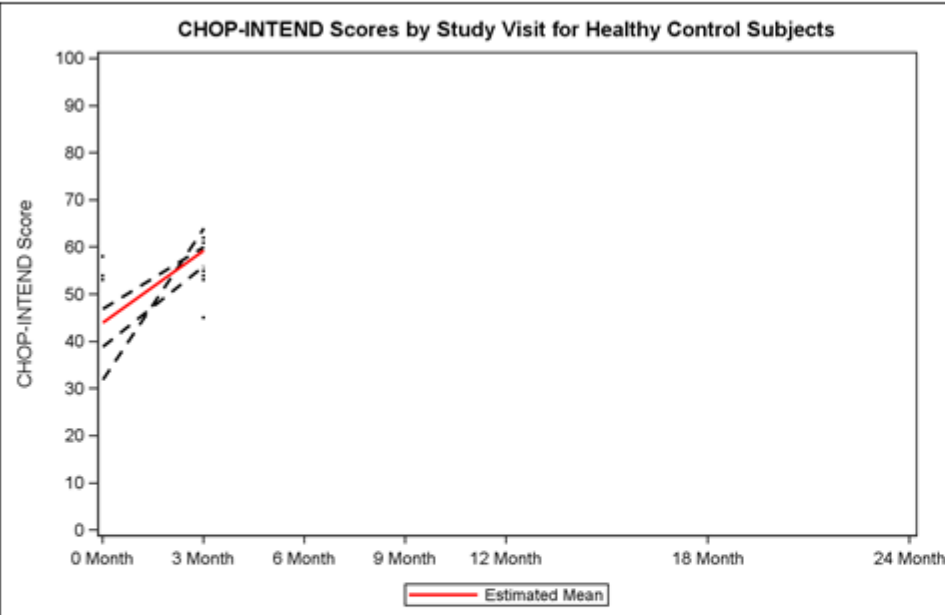
N = 17  
(4 recent, 13 chronic)

mean change over 1 year  
= -1.27

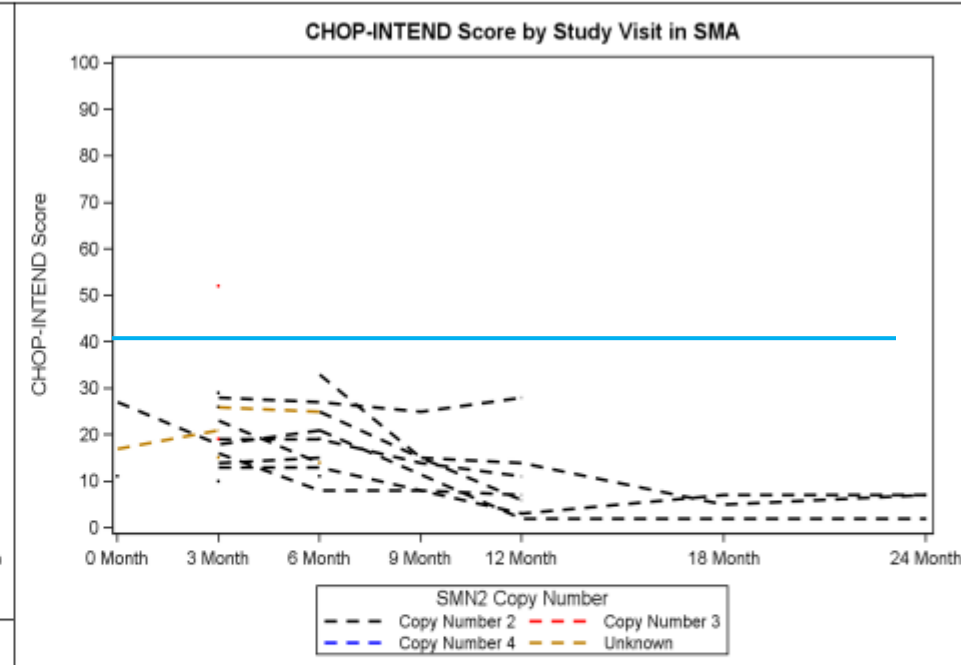
*Finkel R et al. Neurology 2014*

# NeuroNEXT: Longitudinal CHOP-INTEND Data

## Healthy



## SMA



Repeated Measures model with Heterogeneous AR(1) Covariance Structure

For SMN2 = 2 cohort vs healthy cohort

Visit-Group Interaction F-test:  $p = < 0.001$

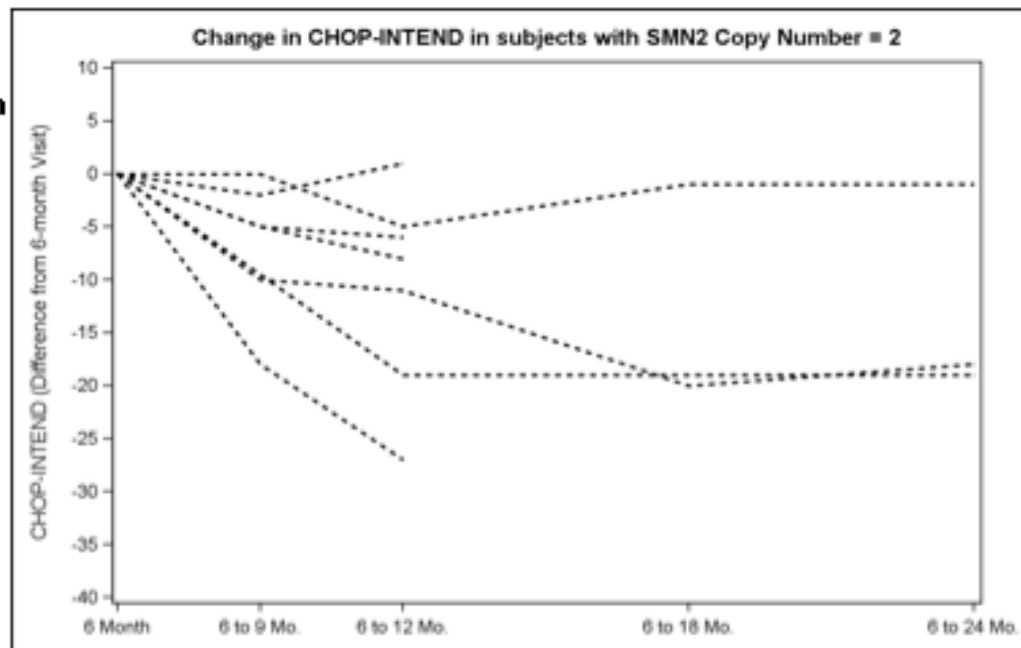
Group F-test  $p = < 0.001$



# Change of CHOP-INTEND from 6 month visit

**Descriptive statistics for change in CHOP-INTEND scores from 6 month visit**

| Time period    | Observed       |             |
|----------------|----------------|-------------|
|                | Mean (sd)      | Min. – max. |
| 6 to 9 months  | -6.67 (6.50)   | -18 – 0     |
| 6 to 12 months | -10.71 (9.43)  | -27 – 1     |
| 6 to 18 months | -10.50 (13.44) | -20 – -1    |
| 6 to 24 months | -12.67 (10.12) | -19 – -1    |



All differences in CHOP-INTEND from 6 months were statistically significant.

The observed trend in differences is not linear ( $p = 0.1161$ ).

# TIMPSI:

## Test of Infant Motor Performance Screening Items

---

- 29 items, 99-point scale
- Valid and reproducible in SMA Type I infants
- Tests rolling, crawling, not sitting, and **includes many items in prone position**
- Not well tolerated by Type I infants
- Overlaps with CHOP INTEND
- Has been used in Biomarker NNext SMA 101 study but not in clinical trials

# AIMS:

## Alberta Infant Motor Scale

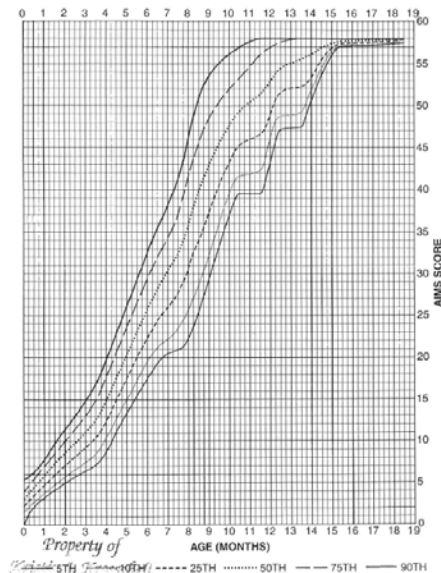
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- 58-item observational scale
- Developed to assess motor development in children from birth to independent walking
- Includes many items in prone position
- Used in Pompe's disease clinical trial
- **Used in NeuroNEXT infant biomarkers study to evaluate infants scoring high on TIMPSI**
- No infants with 2 copies of *SMN2* received AIMS in NeuroNEXT study (too weak)

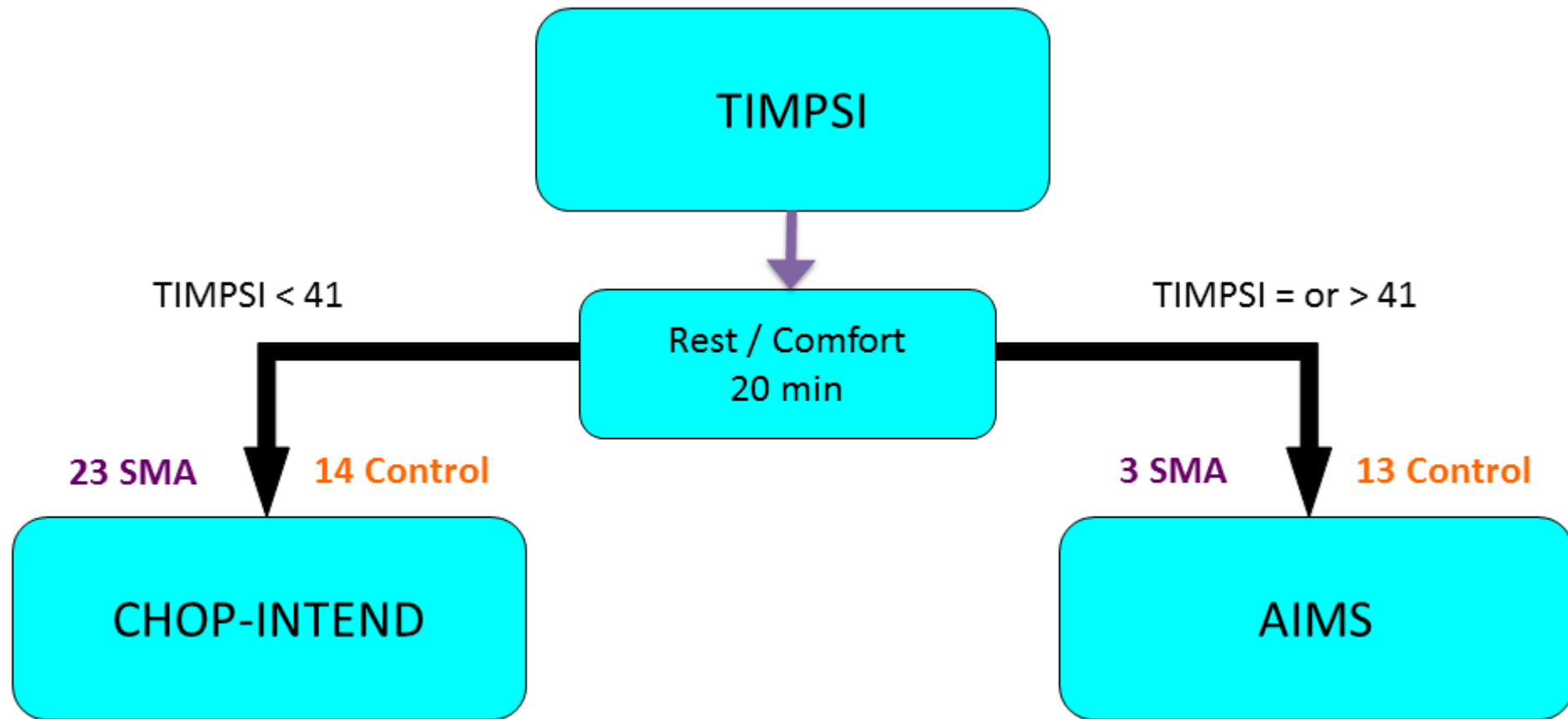
# AIMS: Alberta Infant Motor Scale

| STUDY #  | Prone Lying (1)                                                                            | Prone Lying (2)                                                              | Prone Prop                                                                           | Forearm Support (1)                                                                        | Forearm Support (2)                                                                      | Extended Arm Support                                                     | Rolling Prone to Supine Without Rotation                                              | Reaching from Forearm Support                                                         | Pivoting                                                        | Four-Point Kneeling (1)                                                                   |
|----------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| PRONE    | Physiological flexion<br>Turns head to clear<br>nose from surface                          | Lifts head symmetrically<br>to 45°<br>Cervical maintain head<br>in midline   | Elbows behind shoulders<br>Unassisted head raising<br>to 45°                         | Lifts and maintains<br>head past 45°<br>Elbows in line with<br>shoulders<br>Chest centered | Elbows in front of shoulders<br>Active chin tuck with neck<br>elongation                 | Arms extended<br>Chin tuck and chest<br>elevated<br>Lateral weight shift | Movement initiated by<br>head<br>Trunk moves as one unit                              | Active weight shift from<br>one side<br>Controlled reach with<br>free arm             | Pivots<br>Movement in arms<br>and legs<br>Lateral trunk flexion | Legs flexed, abducted,<br>and externally rotated<br>Lumbar lordosis<br>Maintains position |
| SUPINE   | Supine Lying (1)                                                                           | Supine Lying (3)                                                             | Supine Lying (2)                                                                     | Supine Lying (4)                                                                           | Hands to Knees                                                                           | Hands to Feet                                                            | Rolling Supine to Prone Without Rotation                                              |                                                                                       |                                                                 | Rolling Supine to Prone with Rotation                                                     |
|          | Physiological flexion<br>Head rotation mouth<br>to hand<br>Random arm and leg<br>movements | Head in midline<br>Moves arms but unable to<br>bring hands to midline        | Head rotation toward midline<br>Nonobligatory ATNR                                   | Neck flexion active—chin tuck<br>Brings hands to midline                                   | Chin tuck<br>Reaches hands to knees<br>Abdominals active                                 | Can maintain legs in<br>mid-range<br>Pelvic mobility present             | Lateral head lifting<br>Trunk moves as one unit                                       |                                                                                       |                                                                 | Trunk rotation                                                                            |
| SITTING  | Sitting With Support                                                                       | Sitting With Propped Arms                                                    | Pull to Sit                                                                          | Unassisted Sitting                                                                         | Sitting With Arm Support                                                                 | Unassisted Sitting Without Arm Support                                   | Weight Shift in Unassisted Sitting                                                    | Sitting Without Arm Support (1)                                                       | Reach With Rotation in Sitting                                  |                                                                                           |
|          | Lifts and maintains head<br>in midline briefly                                             | Maintains head in midline<br>Supports weight on<br>arms briefly              | Chin tuck: head in line<br>or in front of body                                       | Scapular adduction<br>and humeral<br>extension<br>Cannot maintain position                 | Thoracic spine extended<br>Head movements free<br>from trunk propped<br>on extended arms | Cannot be left alone<br>in sitting indefinitely                          | Weight shift forward,<br>backward, or sideways<br>Cannot sit left alone<br>in sitting | Arms move away<br>from body<br>Can play with a toy<br>Can be left alone<br>in sitting | Sits independently<br>Reaches for toy with<br>trunk rotation    |                                                                                           |
| STANDING | Supported Standing (1)                                                                     | Supported Standing (2)                                                       | Supported Standing (3)                                                               |                                                                                            |                                                                                          |                                                                          |                                                                                       |                                                                                       |                                                                 |                                                                                           |
|          | May have intermittent<br>hip and knee flexion                                              | Head in line with body<br>Hips behind shoulders<br>Variable movement of legs | Hips in line with shoulders<br>Active control of trunk<br>Variable movements of legs |                                                                                            |                                                                                          |                                                                          |                                                                                       |                                                                                       |                                                                 |                                                                                           |

Percentile Ranks



# Motor Function Testing Algorithm



# Bayley Scales of Infant Development

---

- Includes assessment of fine and gross motor function, cognition, language
- Bayley-III language assessment includes receptive and expressive language
- Bayley-III motor assessment includes scale scores for fine and gross motor development
- Normative data available
- Advantage: can also assess fine motor, cognition, and language (receptive and expressive)

# HINE:

## Hammersmith Infant Neurological Examination

---

- Neurological exam for infants 2–24 mo
- 37 items in 3 sections
  - Section I: Neurological examination
  - **Section II: Developmental milestones**
  - Section III: Behavioral scale, state of consciousness
- Pure motor milestone test
- Not developed specifically for SMA, not validated in SMA

# HINE: Hammersmith Infant Neurological Examination

Optimality score for the neurologic examination of the infant at 12 and 18 months of age

*Leena Haataja, MD, PhD, Eugenio Mercuri, MD, PhD, Rivka Regev, MD, Frances Cowan, MBBS, MRCP, PhD, Mary Rutherford, MD, MRCP, Victor Dubowitz, MD, FRCPCH, PhD, and Lilly Dubowitz, MD, FRCPCH*

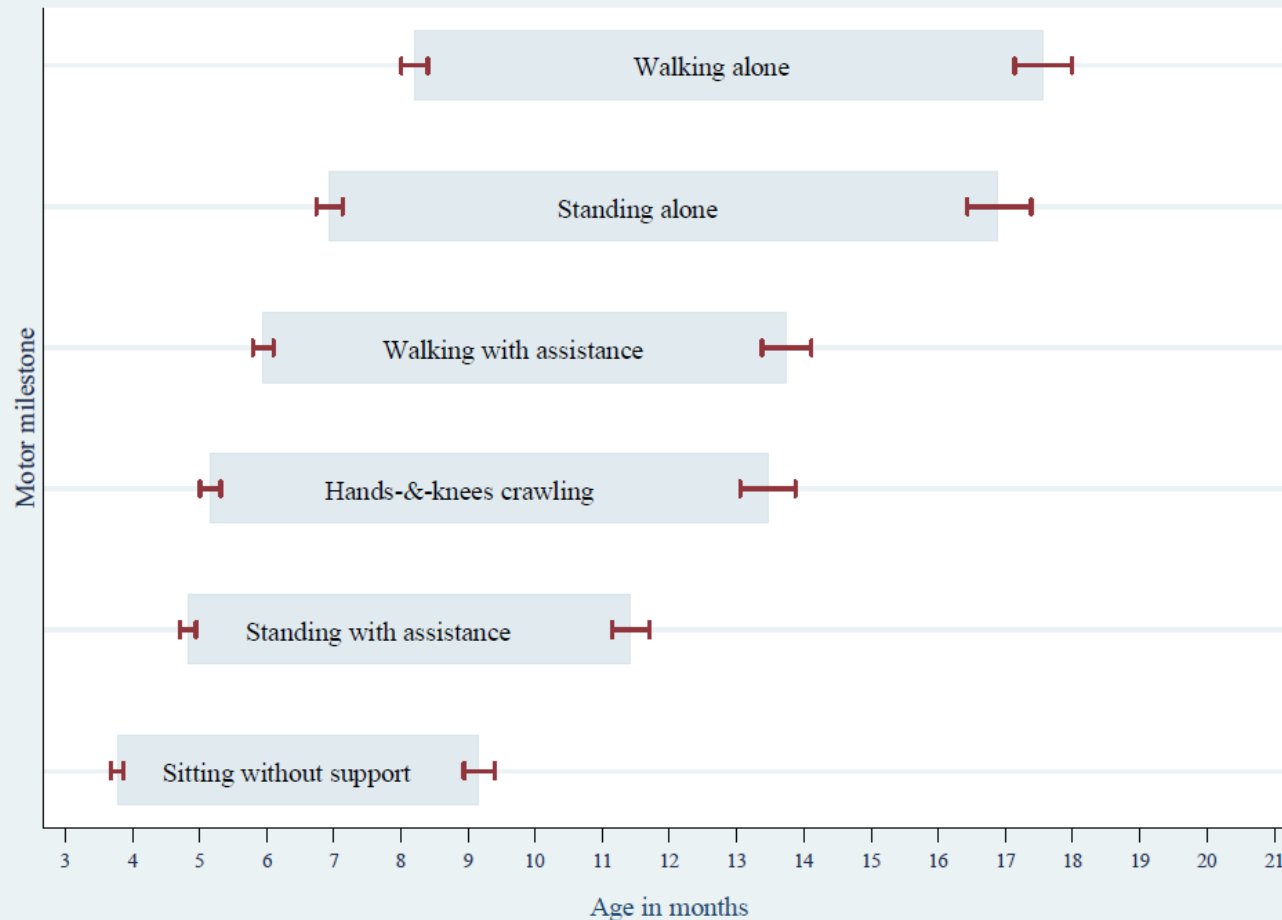
- Used as exploratory outcome measure in Ionis **CS3A** open label Type I study
- Used as primary outcome measure in **ENDEAR** Ionis **CS3B** study of Nusinersen

# Developmental Milestones

## Windows of achievement for six gross motor milestones



World Health Organization

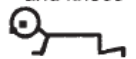


Reference: WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Paediatrica Supplement 2006;450:86-95.

# HINE

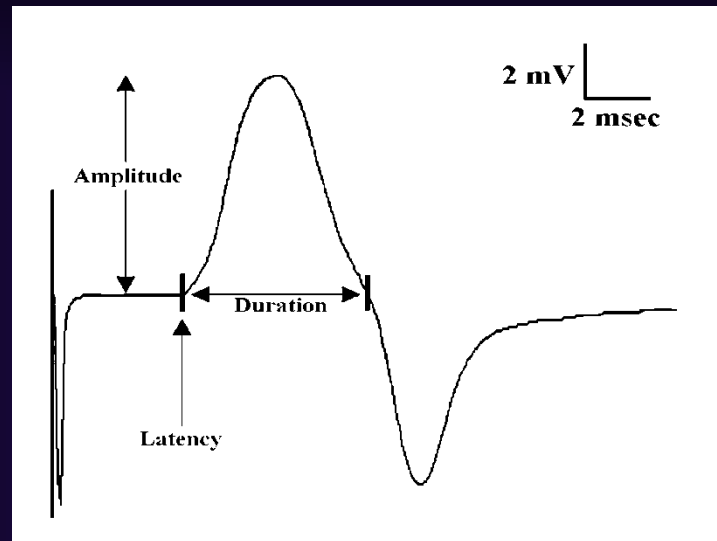
## Section II: Developmental milestones

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| Column                              | 1                                                  | 2                                                                                                                       | 3                                                                                                                                  | 4                                                                                                                                    | 5                                                                                                                                        | 6                                |
|-------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Head control</b>                 | unable to maintain head upright<br>(normal < 3 mo) | wobbles<br>(normal at 4 mo)                                                                                             | all the time maintained upright<br>(normal at 5 mo)                                                                                |                                                                                                                                      |                                                                                                                                          | Observed:<br><br>Reported (age): |
| 12 m (%)                            |                                                    |                                                                                                                         | 100                                                                                                                                |                                                                                                                                      |                                                                                                                                          |                                  |
| 18 m (%)                            |                                                    |                                                                                                                         | 100                                                                                                                                |                                                                                                                                      |                                                                                                                                          |                                  |
| <b>Sitting</b>                      | Cannot sit                                         | With support<br><br>(normal at 4 mo) | Props<br><br>(normal at 6 mo)                   | Stable sit<br><br>(normal at 7 mo)                | Pivots<br><br>(normal at 10 mo)                       | Observed:<br><br>Reported (age): |
| 12 m (%)                            |                                                    |                                                                                                                         |                                                                                                                                    | 1                                                                                                                                    | 99                                                                                                                                       |                                  |
| 18 m (%)                            |                                                    |                                                                                                                         |                                                                                                                                    |                                                                                                                                      | 100                                                                                                                                      |                                  |
| <b>Voluntary grasp</b>              | no grasp                                           | uses whole hand                                                                                                         | index finger and thumb but immature grasp                                                                                          | pincer grasp                                                                                                                         |                                                                                                                                          | Observed:<br><br>Reported (age): |
| 12 m (%)                            |                                                    |                                                                                                                         | 3                                                                                                                                  | 97                                                                                                                                   |                                                                                                                                          |                                  |
| 18 m (%)                            |                                                    |                                                                                                                         | 2                                                                                                                                  | 98                                                                                                                                   |                                                                                                                                          |                                  |
| <b>Ability to kick: (in supine)</b> | no kicking                                         | horizontally legs do not lift                                                                                           | upward (vertically)<br><br>(normal at 3 mo)     | touches leg<br><br>(normal at 4-5 mo)             | touches toes<br><br>(normal at 5-6 mo)                | Observed:<br><br>Reported (age): |
| 12 m (%)                            |                                                    |                                                                                                                         |                                                                                                                                    |                                                                                                                                      | 100                                                                                                                                      |                                  |
| 18 m (%)                            |                                                    |                                                                                                                         |                                                                                                                                    |                                                                                                                                      | 100                                                                                                                                      |                                  |
| <b>Rolling</b>                      | no rolling                                         | rolling to side<br>(normal at 4 mo)                                                                                     | prone to supine or supine to prone<br>(normal at 6 mo)                                                                             | supine to prone and prone to supine<br>(normal at 7 mo)                                                                              |                                                                                                                                          | Observed:<br><br>Reported (age): |
| 12 m (%)                            |                                                    | 1                                                                                                                       | 1                                                                                                                                  | 98                                                                                                                                   |                                                                                                                                          |                                  |
| 18 m (%)                            |                                                    |                                                                                                                         |                                                                                                                                    | 100                                                                                                                                  |                                                                                                                                          |                                  |
| <b>Crawling</b>                     | Does not lift head                                 | On elbow<br><br>(normal at 3 mo)    | On outstretched hand<br><br>(normal at 4-5 mo) | Crawling flat on abdomen<br><br>(normal at 8 mo) | Crawling on hands and knees<br><br>(normal at 10 mo) | Observed:<br><br>Reported (age): |
|                                     |                                                    |                                                                                                                         | 2                                                                                                                                  | 4                                                                                                                                    | 94                                                                                                                                       |                                  |
|                                     |                                                    |                                                                                                                         |                                                                                                                                    |                                                                                                                                      | 100                                                                                                                                      |                                  |
| <b>Standing</b>                     | Does not support weight                            | Supports weight<br>(normal at 4-5 mo)                                                                                   | Stands with support<br>(normal at 8 mo)                                                                                            | Stands unaided<br>(normal at 12 mo)                                                                                                  |                                                                                                                                          | Observed:<br><br>Reported (age): |
| 12 m (%)                            |                                                    | 3                                                                                                                       | 18                                                                                                                                 | 79                                                                                                                                   |                                                                                                                                          |                                  |
| 18 m (%)                            |                                                    |                                                                                                                         | 2                                                                                                                                  | 98                                                                                                                                   |                                                                                                                                          |                                  |
| <b>Walking</b>                      |                                                    | Bouncing<br>(normal at 6 mo)                                                                                            | Cruising (walks holding on)<br>(normal at 11 mo)                                                                                   | Walking<br>(normal at 15 mo)                                                                                                         |                                                                                                                                          | Observed:<br><br>Reported (age): |
| 12 m (%)                            |                                                    | 4                                                                                                                       | 45                                                                                                                                 | 51                                                                                                                                   |                                                                                                                                          |                                  |
| 18 m (%)                            |                                                    |                                                                                                                         | 2                                                                                                                                  | 98                                                                                                                                   |                                                                                                                                          |                                  |

# CMAP:

## Compound Muscle Action Potential



- **Summation of all motor unit potentials** with supramaximal stimulation of the nerve innervating a particular muscle
- Used in recent SMA Type I clinical trials as electrophysiological biomarker

# CMAP

## Compound Muscle Action Potential

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- Correlates with age, motor function, and *SMN2* copy number (Swoboda et al., Ann Neurol 2005)
- **Symptomatic Type I patients:** reduced CMAP amplitudes remain low over time
- **Presymptomatic infants:** CMAP amplitudes normal with subsequent precipitous decline

# CMAP

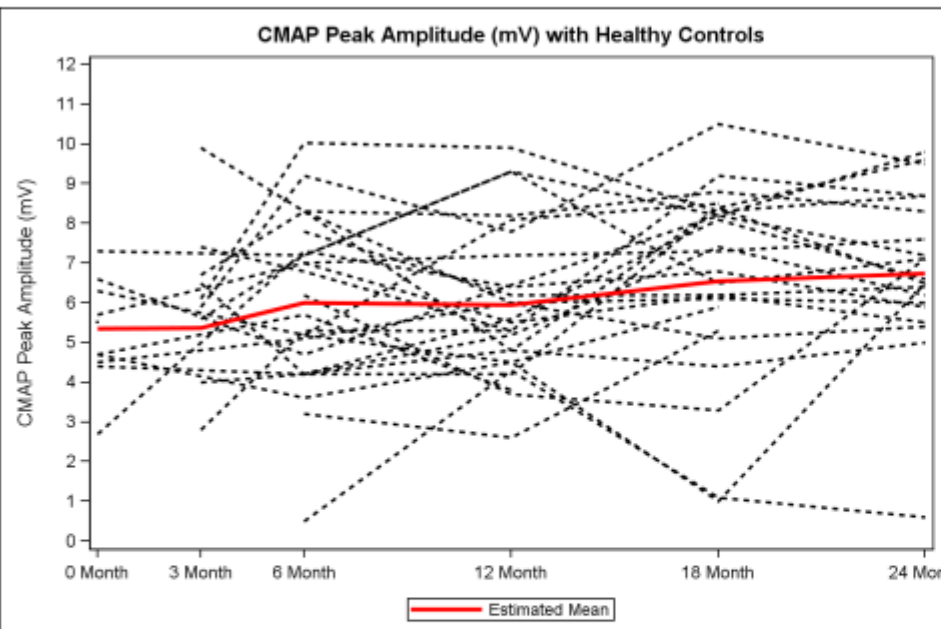
## Compound Muscle Action Potential

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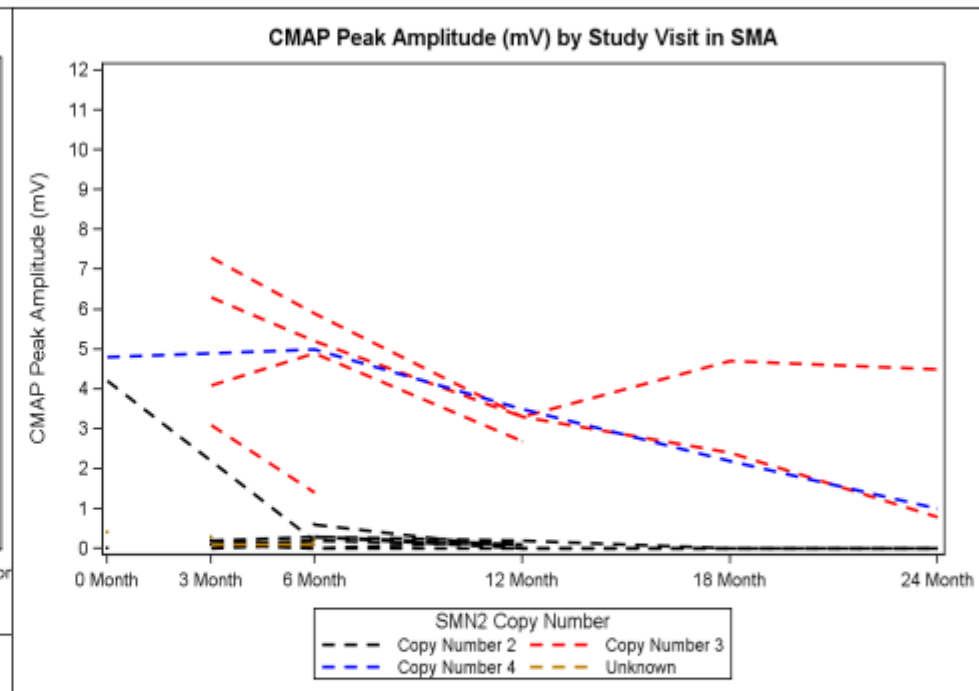
- Used in NeuroNEXT SMA infant biomarker study
  - Average CMAP peak amplitudes:
    - entire SMA cohort: 1.4 mV
    - SMA patients with 2 copies SMN2: 0.5 mV
    - control cohort: 5.5 mV
  - Entire SMA cohort had positive correlation between CMAP amplitude values and motor functional ability

# CMAP Peak Amplitude (mV)

## Healthy



## SMA



Repeated Measures model with Heterogeneous AR(1) Covariance Structure

For SMN2 = 2 cohort vs healthy cohort

Visit-Group Interaction F-test:  $p = 0.271$

Group F-test  $p = <0.001$



Courtesy of Dr. Steven J. Kolb, OSU



Wexner  
Medical  
Center