Functional outcome measures for type 2 and 3 Spinal Muscular Atrophy

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Physiotherapists

11th November 2016

Disclosures

Jacqueline Montes

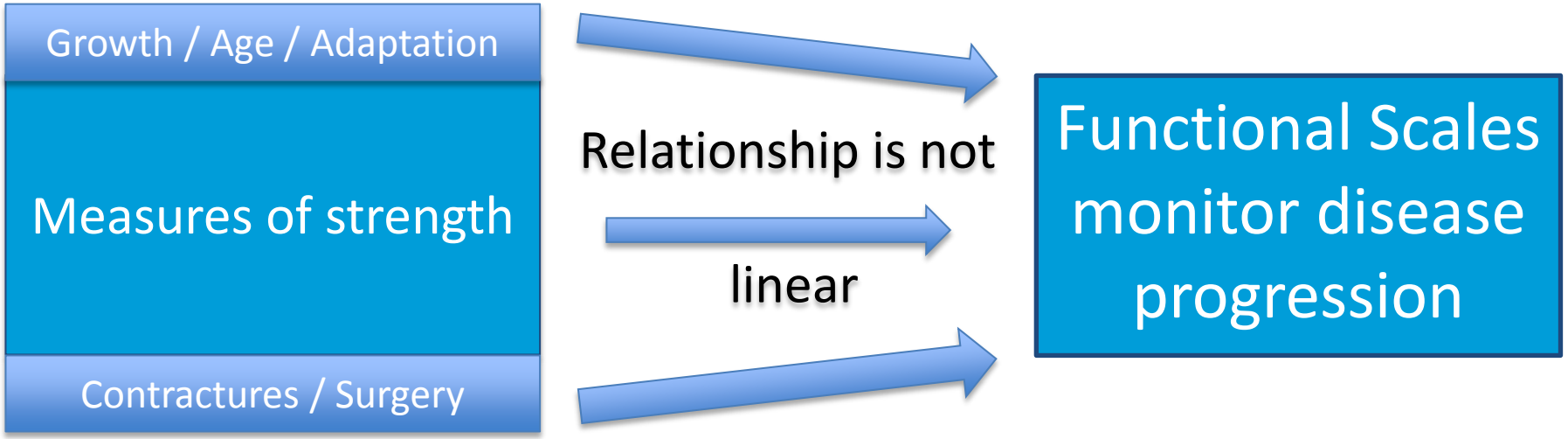
- Receives support from NIH, Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD)

  K01HD084690-01A1
- Consultant for IONIS pharmaceuticals
- Advisory boards for Biogen and Roche Pharmaceuticals

Anna Mayhew

- Consultancy for IONIS, Roche, PTC, Summit, BMS – training clinical evaluators and preparing manuals for functional assessments
- Advisory boards for Summit and Roche Pharmaceuticals

Functional Scales in SMA



A measure of performance that relates to an individuals' function in everyday life carries more meaning and relevance than a measure that quantitates strength.

2008

Functional Scales- Experience

www.elsevier.com/locate/nmd

Workshop report

Towards harmonisation of outcome measures for DMD and SMA within TREAT-NMD; Report of three expert workshops: TREAT-NMD/ENMC Workshop on outcome measures, 12th–13th May 2007, Naarden, The Netherlands; TREAT-NMD Workshop on outcome measures in experimental trials for DMD, 30th June–1st July 2007, Naarden, The Netherlands; Conjoint Institute of Myology TREAT-NMD Meeting on physical activity monitoring in neuromuscular disorders, 11th July 2007, Paris, France

E. Mercuri [a,*], A. Mayhew [b], F. Muntoni [b], S. Messina [a], V. Straub [c], G.J. Van Ommen [d], T. Voit [e], E. Bertini [f], K. Bushby [c], On behalf of the TREAT-NMD Neuromuscular Network

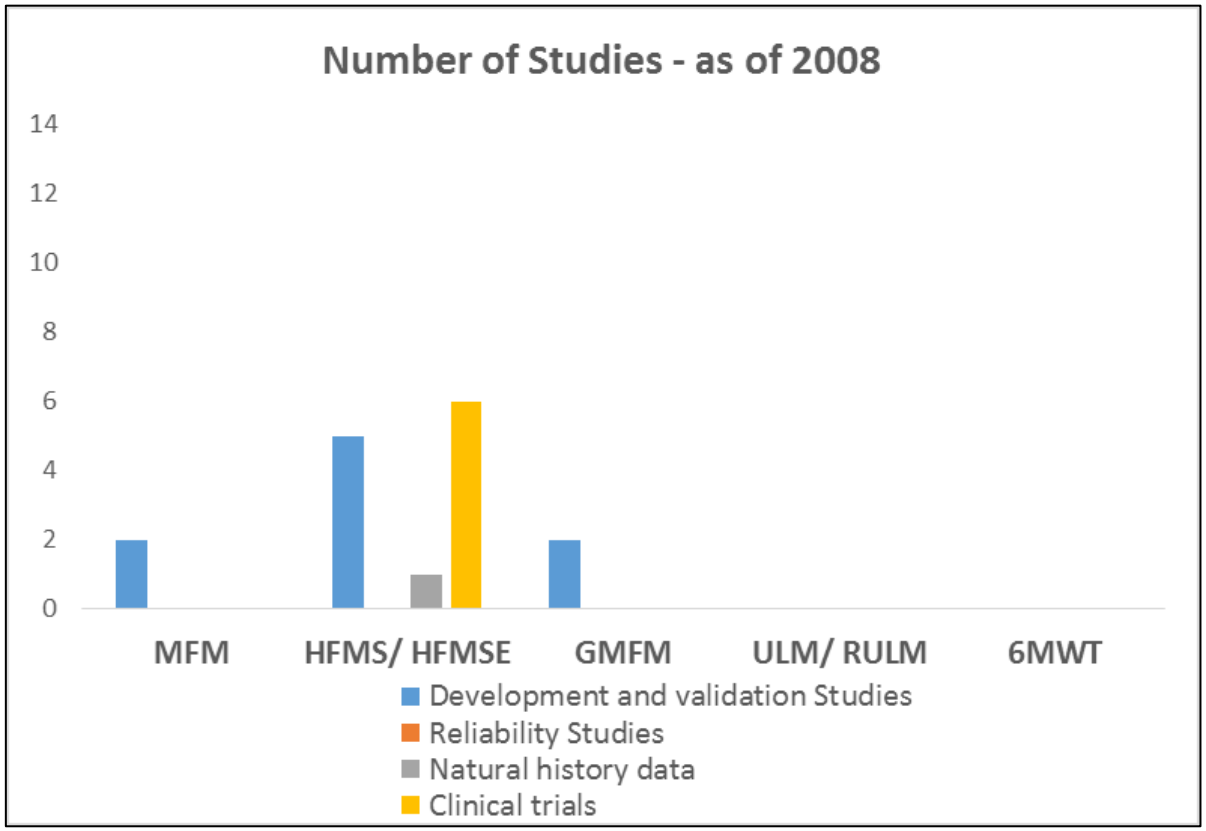


Table 2
Summary of respondents' opinions on advantages and disadvantages for each assessment

Measure	Advantages	Disadvantages
HFMS	Quick/easy Minimal equipment needed tocarry out assessment Already in use in clinical trials	Ceiling effect Lack of manual
M-HFMS	As HFMS	As HFMS
MFM	Generic Relevant to a broad range of ages	Too non-specific Not sensitive for specific diseases
GMFM	Good sensitivity Comprehensive	Too long. Can fatigue neuromuscular patients easily Difficulty measuring those with contractures on prone items
HAMA	Quick Limited equipment needed to carry out assessment	Rolling over-represented within scale Ceiling effect for more able patients
NSAA	Quick Specific Clear instruction and detail	Only relevant to ambulant patients
EK	Quick to perform Functionally relevant to patients	Lack of sensitivity

EMA SMA workshop

2008

13 Oct 2008

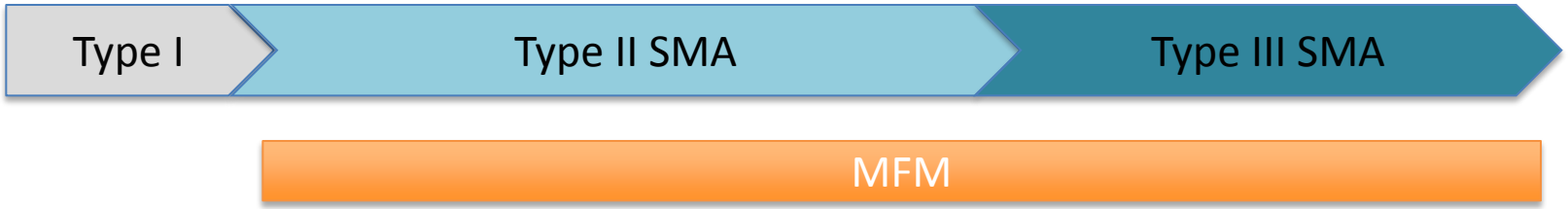
EMA SMA Workshop
London, UK

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Complimented on proactive approach, organisation and teamwork
- Type II – non-ambulant: Important to demonstrate internal consistency, clinical meaning and responder profiles for the functional scales. Secondary measures trending in the same direction will be important
- Type III (ambulant): 6MWT seems reasonable but the clinical meaning of improvement needs to be carefully described. Secondary measures need to be further refined.

Moving in the right direction– work to be done

Motor Function Measure – Generic scale



- Ambulatory and non-ambulatory children and adults aged 6 - 62 years, and for all levels of severity of the disease (Vuillerot 2010, 2012, 2013)
- MFM32 is suitable for children older than 6 years
- Modified version (MFM20) has been validated for children under 6 years of age (de Lattre 2013)
- Longitudinal data is available in a small sample of SMA type 2 and 3 patients demonstrating slow deterioration over follow-up greater than 6 months (Vuillerot 2013)
- Used in a recent clinical trial to detect change (Clinicaltrials.gov NCT02628743)
- Issues - Administration time, potential gaps in items between the non-ambulant and ambulant phenotypes with a possible ceiling effect for stronger non-ambulant patients (Cano 2014)

Disease specific scales

- Majority of the available natural history studies have been using disease specific assessments
- Designed to target the functionally relevant problems common to SMA patients and are less likely to include items not appropriate to the disease phenotype
- Reduces the burden to individuals where fatigue is a major issue (Piepers 2008, Iannaccone 1997, Montes 2010, 2013).

Hammersmith Function Motor Scale (HFMS)

Type I | Type II SMA | Type III SMA

HFMS

ORIGINAL ARTICLE

The Hammersmith Functional Motor Scale for Children with Spinal Muscular Atrophy: a Scale to Test Ability and Monitor Progress in Children with Limited Ambulation

Marion Main[a], Harvey Kairon[a], Eugenio Mercuri[b,c], Francesco Muntoni[b,*]

[a]*Department of Physiotherapy, Hammersmith Hospital, Du Cane Road, London W12 OHS, UK*
[b]*Department of Paediatrics, Dubowitz Neuromuscular centre, Hammersmith Hospital, Imperial College Du Cane Road, London W12 OHS, UK*
[c]*Department of Paediatric Neurology, Catholic University, 02100 Rome, Italy*

Received 17 April 2002; received in revised form 6 August 2002; accepted 16 April 2003

- 20 items ordered according to frequency distribution and the number of patients being able to achieve them.
- Hierarchical organization of items permits characterization of patients across the spectrum of type 2 patients from those who are just able to sit to those who are able to stand with and without support.

The aims of the scale were to:

(i) Evaluate and illustrate the motor ability of children with SMA with limited ambulation;
(ii) monitor the progression of function;
(iii) provide a tool for an accurate classification of SMA and in particular to allow a graded scale that takes into account the significant clinical variability of children with this disorder.

Hammersmith Functional Motor Scale Expanded (HFMSE)

ELSEVIER

Neuromuscular Disorders 17 (2007) 693–697

www.elsevier.com/locate/nmd

An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients

Jessica M. O'Hagen [a,*,1], Allan M. Glanzman [b,1], Michael P. McDermott [d], Patricia A. Ryan [a], Jean Flickinger [b], Janet Quigley [d], Susan Riley [d], Erica Sanborn [d], Carrie Irvine [f], William B. Martens [f], Christine Annis [f], Rabi Tawil [f], Maryam Oskoui [a], Basil T. Darras [d,e], Richard S. Finkel [b,c], Darryl C. De Vivo [a]

[a] *Columbia University, New York, NY, USA*
[b] *Children's Hospital of Philadelphia (Pediatrics [RSF] and Physical Therapy [AMG, JF])*
[c] *The University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[d] *Children's Hospital Boston, Boston, MA, USA*
[e] *Harvard Medical School, Boston, MA, USA*
[f] *University of Rochester Medical Center, Rochester, NY, USA*

Received 4 January 2007; received in revised form 20 April 2007; accepted 25 May 2007

- HFMSE adds 13 clinically relevant items from the GMFM to include ambulant SMA and eliminate a ceiling effect
- Detailed manual with operational definitions and training videos
- Minimal patient burden requiring only standard equipment and taking less than 15 minutes on average

Hammersmith Functional Motor Scale Expanded

Type I | Type II SMA | Type III SMA

HFMSE


Sitting


Rolling


Transitions/ Crawling


Standing


Transitions/ Kneeling


Squat/ Jump


Stairs

HFMSE ITEMS

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33

Sitting without support


Hands and knees crawling

Standing with support

Walking with assistance

Standing alone

Walking alone

World Health Organization

Motor Milestones

Correlation of HFMS with MFM20

Hammersmith Functional Motor Scale and Motor Function Measure-20 in non ambulant SMA patients

E. Mazzone [a], R. De Sanctis [a], L. Fanelli [a], F. Bianco [a], M. Main [b], M. van den Hauwe [c], M. Ash [b], R. de Vries [d], J. Fagoaga Mata [e], K. Schaefer [f], A. D'Amico [g], G. Colia [g], C. Palermo [a], M. Scoto [b], A. Mayhew [h], M. Eagle [h], L. Servais [i], M. Vigo [e], A. Febrer [e], R. Korinthenberg [f], M. Jeukens [d], M. de Viesser [d], A. Totoescu [i], T. Voit [i], K. Bushby [h], F. Muntoni [b], N. Goemans [c], E. Bertini [g], M. Pane [a], E. Mercuri [a,*]

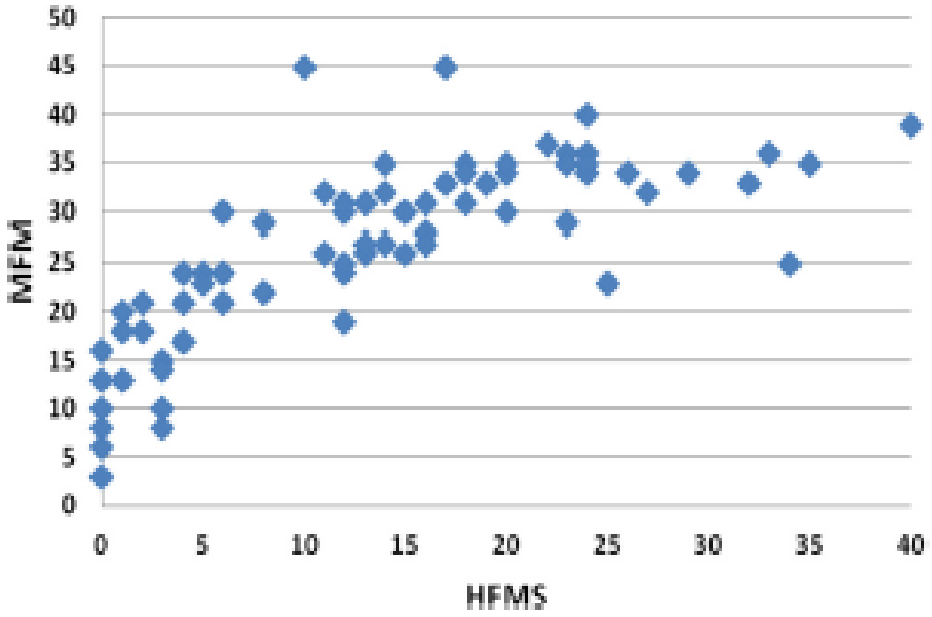
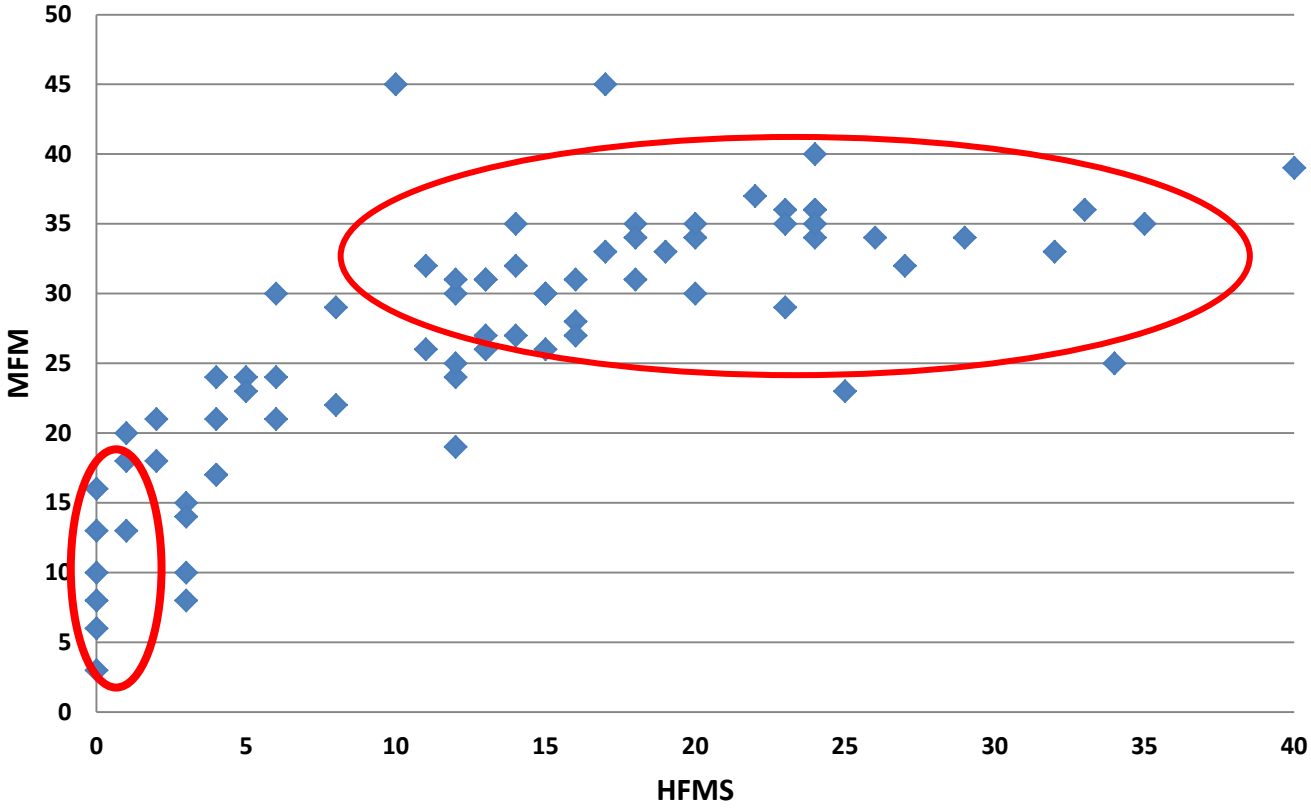


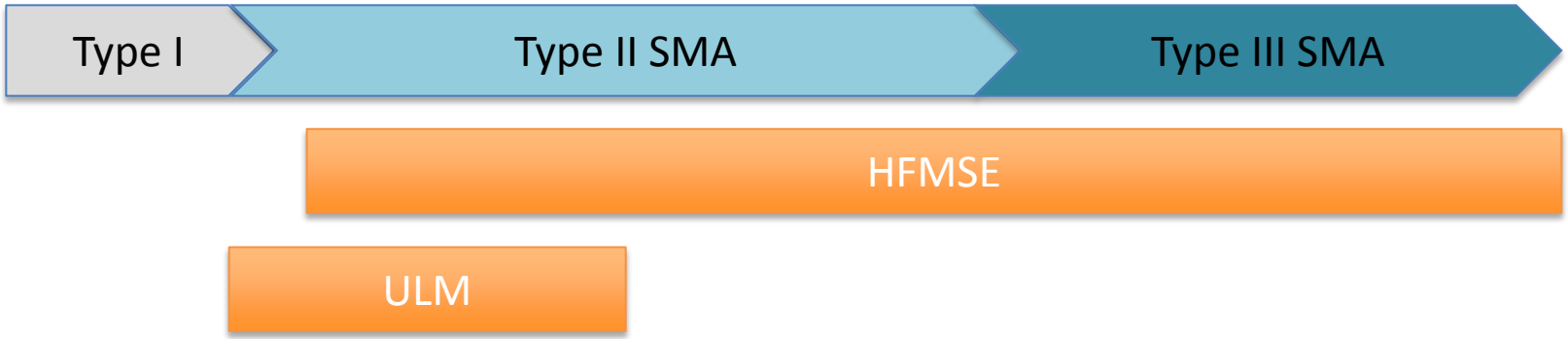
Fig. 2. Correlation of the HFMS and MFM20 baseline scores.

HFMS assists with sensitivity of MFM in non-ambulant population



MFM assists with floor of HFMS – distal dimension

Upper Limb Module (ULM)



- Assessment of arm function has been specifically designed as an add on module (Mazzone 2011)
- The ULM is intended to capture performance of activities of daily living not typically included in measures of gross motor function
- 9-item scale can be reliably performed in children - 10 minutes to complete
- Used in a multicentric setting and in clinical trials (Darras, WMS, 2016)

Assessing upper limb function in nonambulant SMA patients: Development of a new module

Elena Mazzone [a,1], Flaviana Bianco [a,1], Diego Martinelli [a], Allan M. Glanzman [b], Sonia Messina [a,c], Roberto De Sanctis [a], Marion Main [d], Michelle Eagle [e], Julaine Florence [f], Kristin Krosschell [g], Gessica Vasco [a], Marco Pelliccioni [a], Marilena Lombardo [a], Marika Pane [a], Richard Finkel [h], Francesco Muntoni [d], Enrico Bertini [i], Eugenio Mercuri [a,*]

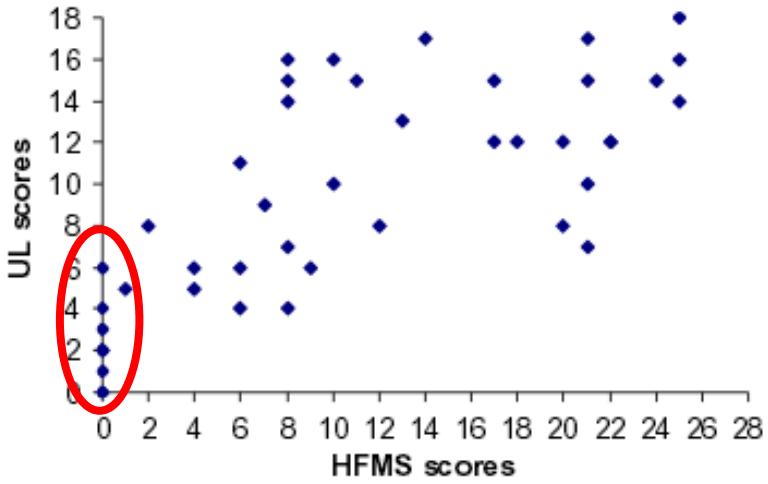


Fig. 5. ULM and HFMS scores.

- ULM can detect changes in the weaker SMA patients
- Used to expand the range HMFSE

www.elsevier.com/locate/nmd

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 [a,*], Enrico Bertini [b], Francesco Muntoni [c], Eugenio Mercuri [d] on behalf of t
ENMC SMA Workshop Study Group [1]

[a] Nemours Children's Hospital, Orlando, USA
[b] UCL Institute of Child Health, Dubowitz Neuromuscular Centre, London, UK
[c] Bambino Gesu Children's Research Hospital, Rome, Italy
[d] Pediatric Neurology Unit, Catholic University, Rome, Italy

Received 2 March 2015

Suitability of Functional Scales

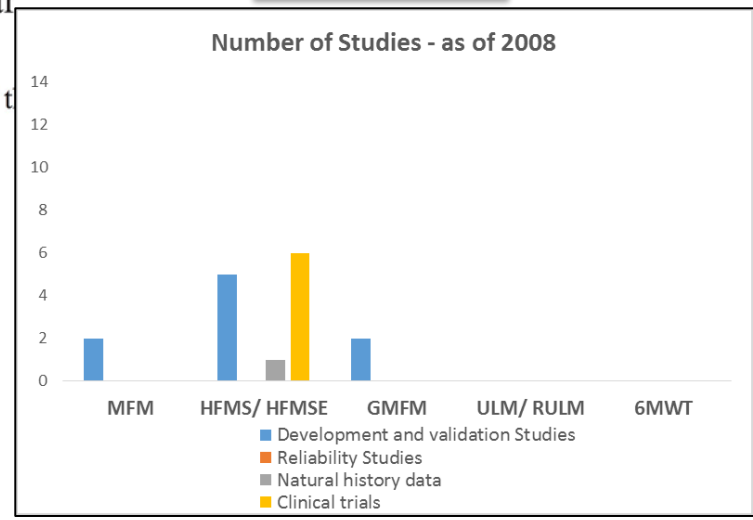
Table 2A
Outcome measures for clinical trials in SMA: motor function scales, electrophysiological biomarkers and strength testing.

	HFMSE	MFM	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 intrarater								
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	✓	✓	×	✓	✓	✓	✓	✓

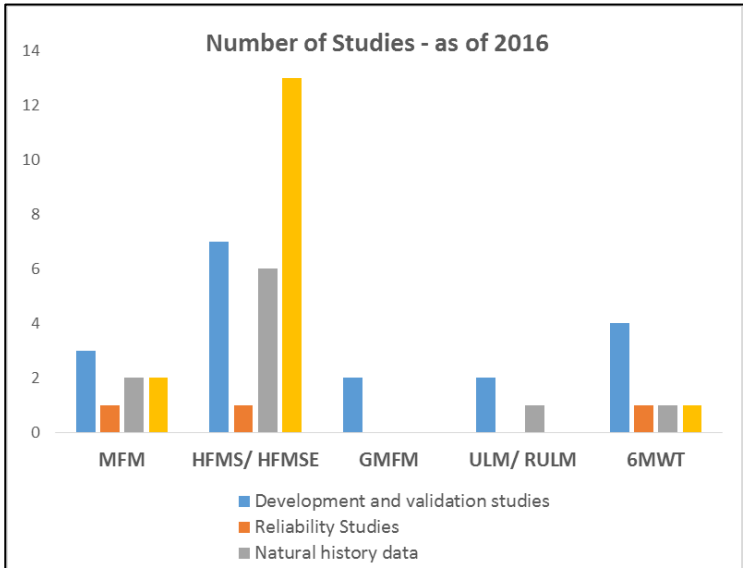
HFMSE: Hammersmith Functional Motor Scale Expanded, MFM: Motor Function Measure, 6MWT: 6-minute walk test distance, ULM: upper limb module for SMA, CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, TIMPSI: Test of Infant Motor Performance Screening Items, CMAP: 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

2008



2016



Scale requirements

- Conceptual framework fits SMA ✔
- Suitability for multicentric studies ✔
- Reliability ✔
- Validation with other measures
- Natural history data
- Responsiveness to traeatment
- Clinical meaningfulness

	Hammersmith Functional Motor Scale	Motor Function Measure
Method studies (description, validation, reliability etc)	Main et al, 2003 Mercuri et al, Kroschell et al, 2006 Kroschell et al, 2011 O' Hagen et al, 2007 Glanzmann et al, 2011 Chen et al, 2013 Chiriboga et al, 2016	Berard et al, 2005 Berard et al, 2006 Vuillerot et al, 2012 Vuillerot et al, 2013 De Lattre 2013 Vuillerot et al, 2014

Scale requirements

- Conceptual framework fits SMA
- Suitability for multicentric studies
- Reliability
- Correlation with other measures ✔
- Natural history data
- Responsiveness to treatment
- Clinical meaningfulness

	Hammersmith Functional Motor Scale	Motor Function Measure
Correlation	**Quality of life** (De Oliviera et al, 2011) **MFM** (Mazzone et al, 2013) **6MWT (**Montes et al, 2010; Dunaway Young et al, 2016) **ULM** (Mazzone et al, 2012) **Timed Up and Go** (Dunaway et al, 2013) **DXA scans** (Sproule et al, 2010) **CMAP** (Lewell et al , 2010) **SMN2 copy number** (Tiziano, 2007)	**UL measures** (Werlauff et al, 2014) **HFMSE** (Mazzone et al, 2014)

- Conceptual framework fits SMA
- Suitability for multicentric studies
- Reliability
- Correlation with other measures
- Natural history data ✔
- Responsiveness to traeatment ✔
- Clinical meaningfulness

HFMS etc	Pz	MFM	Pz
Valproic acid		**Trophos** (Clinicaltrials.gov NCT02628743)	
Swoboda et al, 2009 (SA)	42		
Swoboda et al, 2010 (RPCT)	61		
Darbar et al, 2011 (OA)	22		
Kissell et al, 2011 (OA)	33	**Riluzole**	
Kissell et al, 2014 (RPCT)	33	Abbara et al, 2011	
Albuterol/Salbutamol			
Pane et al, 2008 (OA)	23		
Tiziano et al, 2013 (RPCT)	45		
Hydroxyurea			
Chen et al, 2010 (OA)	28		
Phenylbutyrate			
Mercuri et al, 2004 (OA)	10		
Mercuri et al, 2007 (RPCT)	107		
Nusinersen			
Chiriboga et al, 2016 (OA)			
Olesoxime (Clinicaltrials.gov NCT02628743)			
4-Aminopyridine (Clinicaltrials.gov NCT01645787)			

	HFMS etc	Pz	MFM	Pz
Natural history data Longitudinal	Mercuri et al, 2007	90	Vuillerot et al 2013	31
	Kauffman et al, 2012	79	Mazzone et al, 2014	74
	Kauffamn et al, 2013	65		
	Mazzone et al, 2013	40		
	Mazzone et al, 2014	74		
	Mercuri et al. 2016			

2014

RASCH ANALYSIS OF CLINICAL OUTCOME MEASURES IN SPINAL MUSCULAR ATROPHY

STEFAN J. CANO, PhD,[1] ANNA MAYHEW, PhD,[2] ALLAN M. GLANZMAN, DPT,[3] KRISTIN J. KROSSCHELL, DPT,[4] KATHRYN J. SWOBODA, MD,[5] MARION MAIN, MA,[6] BIRGIT F. STEFFENSEN, PhD,[7] CAROLE BÉRARD, MD,[8] FRANÇOISE GIRARDOT, PT,[8] CHRISTINE A.M. PAYAN, MD,[9] EUGENIO MERCURI, MD, PhD,[10] ELENA MAZZONE, PT,[10] BAKRI ELSHEIKH, MBBS, FCRP,[11] JULAINE FLORENCE, DPT,[12] LINDA S. HYNAN, PhD,[13] SUSAN T. IANNACCONE, MD,[14] LESLIE L. NELSON, MPT,[15] SHREE PANDYA, PhD,[16] MICHAEL ROSE, MD,[17] CHARLES SCOTT, PhD,[18] REZA SADJADI, MD,[19] MACKENSIE A. YORE, MD,[20] CYNTHIA JOYCE, MS,[20] and JOHN T. KISSEL, MD,[21] on behalf of the International Coordinating Committee for SMA Clinical Trials Rasch Task Force

Methods

Data from children with SMA Type 1, 2, and 3 were available for HMFS/E, MFM. GMFM, NSAA, EK, CHOP, TIMP

Results

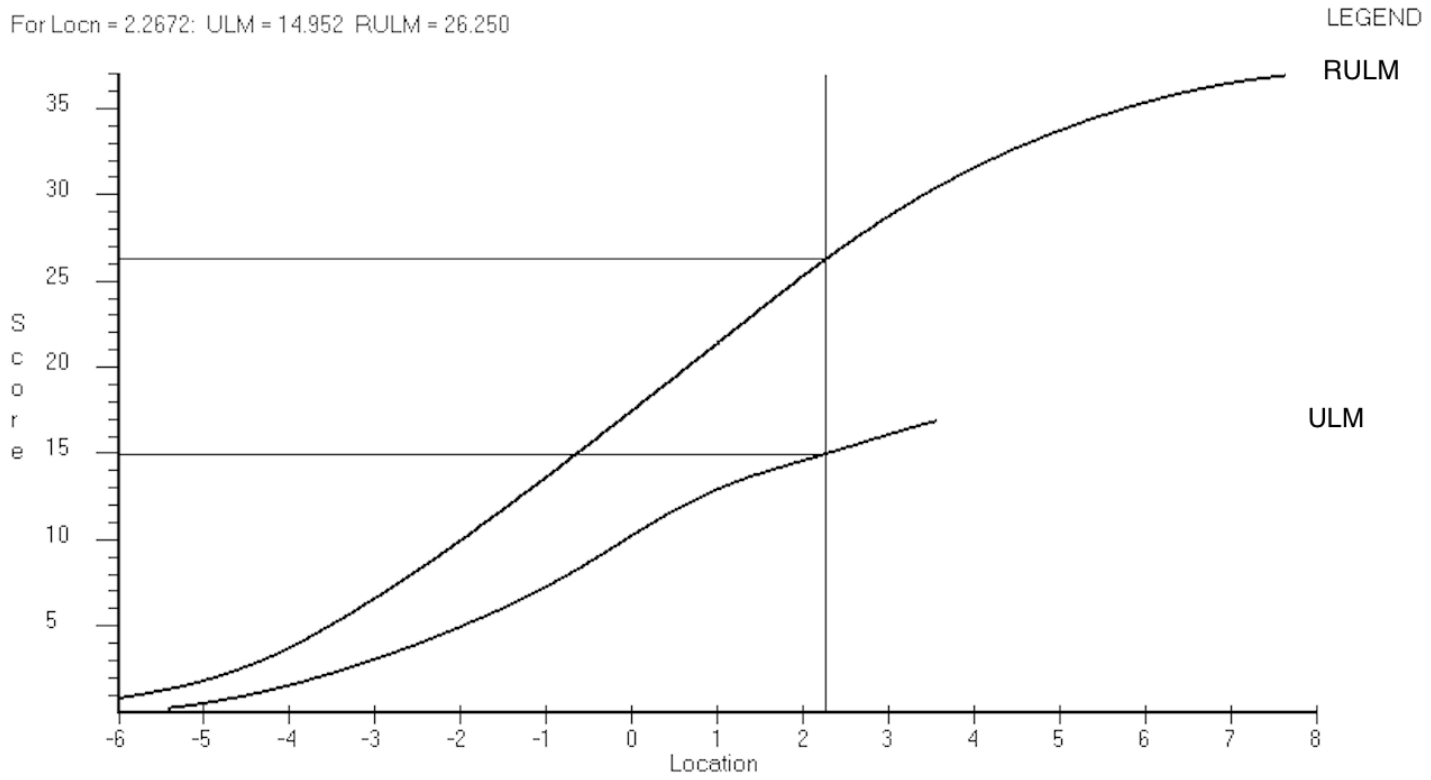
Each scale had good reliability but several issues impacting scale validity, including the extent that items defined clinically meaningful constructs and how well each scale measured performance across the SMA spectrum.

Conclusions

The utility of each SMA scale could be improved by establishing clear definitions of what is measured, reconsidering items that misfit and items whose response categories have reversed thresholds, and adding new items at the extremes of scale ranges.

Revised Upper Limb Module (RULM)

Mazzone et al – 2016



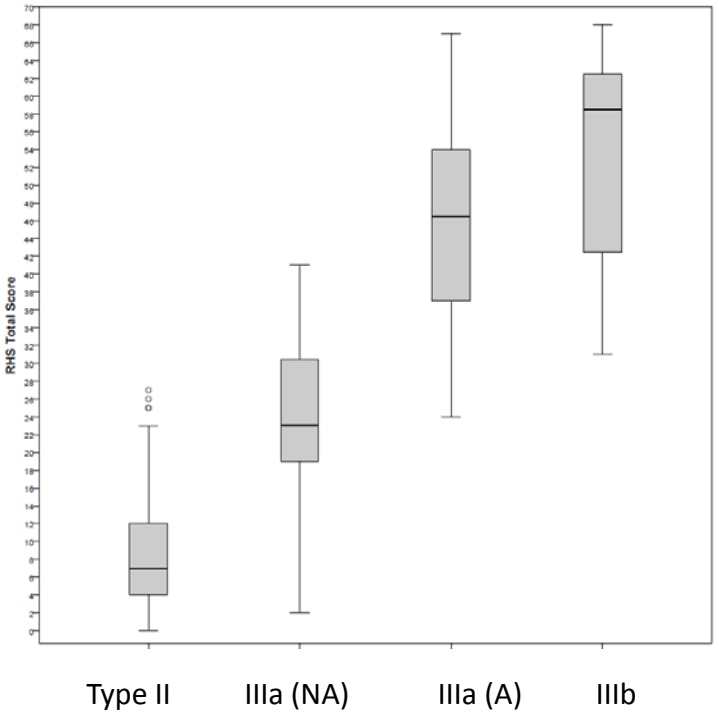
Type I | Type II SMA | Type III SMA

ULM

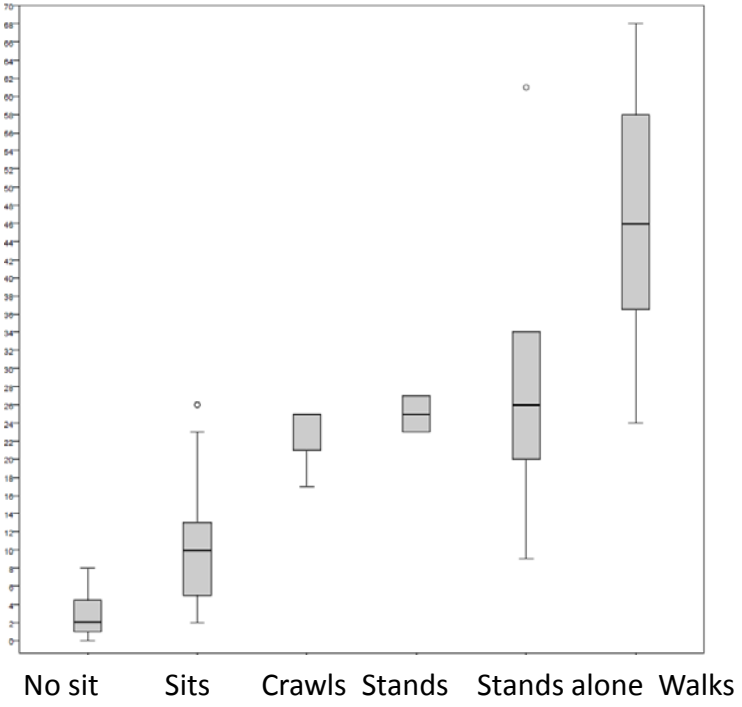
RULM

Revised Hammersmith Scale (RHS)

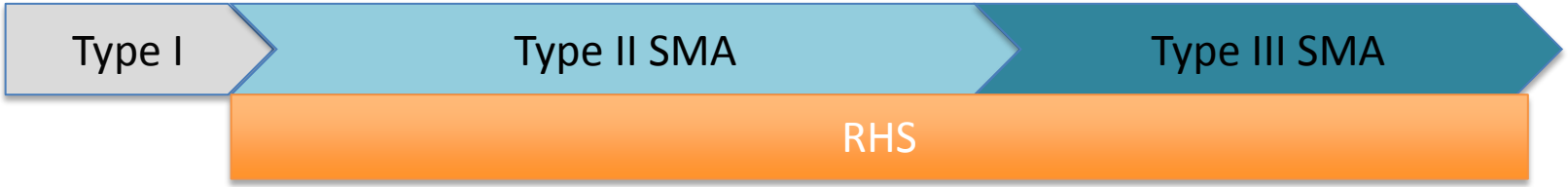
SMA Type & Current Ambulatory Status $p < 0.001$



Current Functional WHO Motor Milestones $p < 0.001$



- Improving psychometric measurement properties of the HFMSE additional items from NSAA, and the WHO Motor Milestones
- International development: n = 138 SMA 2 & 3, Longitudinal changes under investigation



Six Minute Walk Test (6MWT)

Type I | Type II SMA | Type III SMA

6MWT

SIX-MINUTE WALK TEST IS RELIABLE AND VALID IN SPINAL MUSCULAR ATROPHY

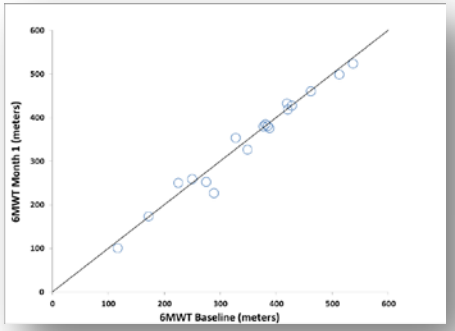
SALLY DUNAWAY YOUNG, PT, DPT,[1,2] JACQUELINE MONTES, PT, EdD,[1,2] SAMANTHA S. KRAMER, BS,[3] JONATHAN MARRA, MA,[1] RACHEL SALAZAR, PT, DPT,[1] ROSANGEL CRUZ, MA, BS,[1] CLAUDIA A. CHIRIBOGA, MD, MPH,[1] CAROL EWING GARBER, PhD,[3] and DARRYL C. DE VIVO, MD[1]

[1] Department of Neurology, Columbia University Medical Center, New York, New York, USA
[2] Department of Rehabilitation and Regenerative Medicine, Columbia University Medical Center, New York, New York, USA
[3] Department of Biobehavioral Sciences, Teachers College, Columbia University, New York, New York, USA

Accepted 22 March 2016

Test-retest reliability at 1 month was excellent for all participants (n = 18)

ICC: 0.984; 95% CI: 0.959–0.994



Convergent validity

Table 2. Associations between the 6MWT and measures of motor function and strength.

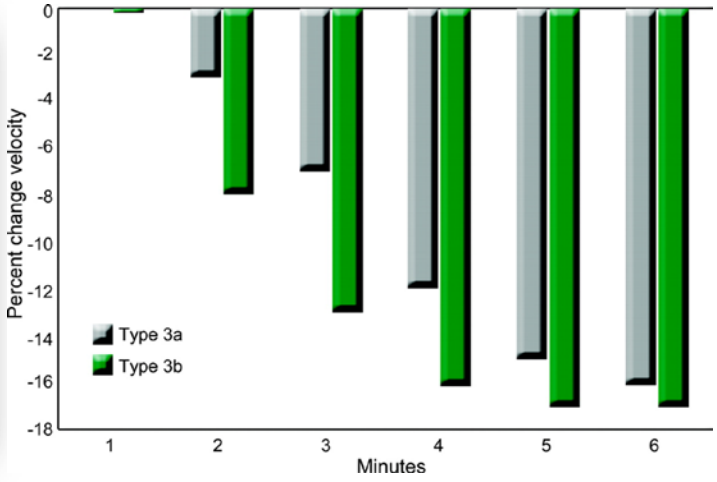
	n	Pearson correlation coefficient (*r*)	*P*-Value
% Fatigue	30	−0.505	0.004†
Stride length	18	0.789	0.000‡
TUG	16	−0.535	0.033*
10 meter walk/run	14	−0.937	0.000‡
HFMSE	30	0.755	0.000‡
MMT (total score)	19	0.691	0.001‡
MMT (upper score)	19	0.407	0.084
MMT (lower score)	19	0.676	0.002†
HHD - knee extensor	19	0.377	0.112
HHD - knee flexor	19	0.622	0.004†
FVC	14	0.246	0.397

Neurology®

Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy

J. Montes, M. P. McDermott, W. B. Martens, et al.
Neurology 2010;74;833
DOI 10.1212/WNL.0b013e3181d3e308

6MWT captures fatigue



Mean velocity walked during the 1st and 6th minute were significantly different (p = 0.0003)

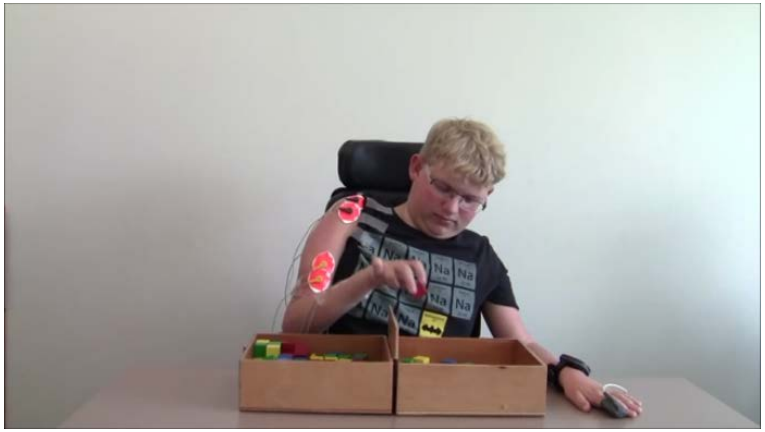
Six minute walk test (6MWT)

- Reliable and valid functional assessment in patients with SMA (Dunaway Young 2016)
- Capture fatigue (Montes 2011, 2013)
- Fatigue was demonstrated by a 17% decrease in gait velocity from the first minute to the last during the 6MWT (Montes 2010). Not observed in patients with other neuromuscular conditions and weakness (Montes 2013)
- Longitudinal experience of the 6MWT in SMA has been reported (Mazzone 2013).

Efforts underway to capture fatigue in non-ambulant individuals

Endurance Shuttle Nine Hole Peg Test

Endurance Shuttle Box and Block Test



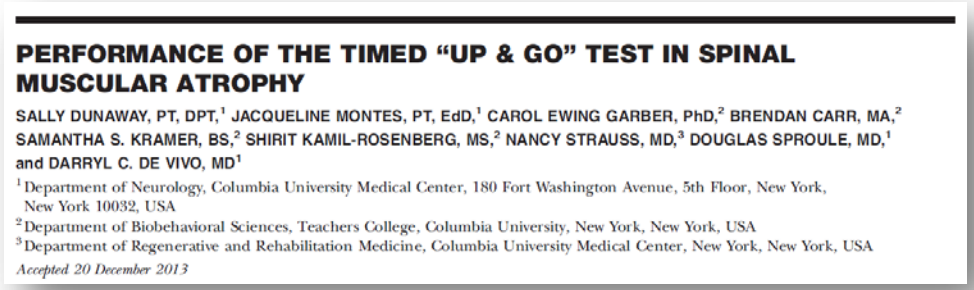
Endurance Shuttle Ride Test

Endurance Shuttle Walk Test

Courtesy of Bart Bartels, Utrecht, Netherlands

Under current development

- Timed Up and Go (TUG) - Quick, meaningful, and applied objective measure of balance, gait speed, and functional mobility, has been applied to ambulatory SMA patients (Dunaway 2014)



PERFORMANCE OF THE TIMED "UP & GO" TEST IN SPINAL MUSCULAR ATROPHY

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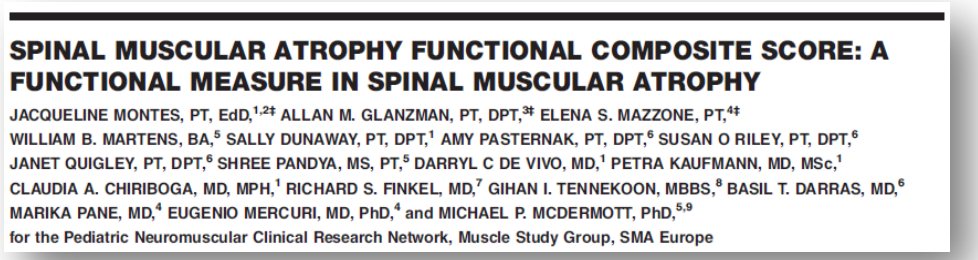
- Composite score – ULM, HFMSE, 6MWT (Montes 2015)



SPINAL MUSCULAR ATROPHY FUNCTIONAL COMPOSITE SCORE: A FUNCTIONAL MEASURE IN SPINAL MUSCULAR ATROPHY

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Patient Reported Outcome Measures in SMA - exploratory

- Limited disease specific PROMs
- Pediatric Evaluation of Disability Inventory Computerised Adapative Test
- PEDICAT applied modern psychometrics to this scale to review its use in SMA (Pasternak 2016)
  - Measure mobility and daily activity skills in children
- ACTIVLIM – Generic PROM for NMD (Sebiyo Batcho 2016)

Functional scales relate to everyday life