

Patients and Patient Organisations Involvement in the TREAT-NMD
Milan, 15 September 2010-

Learning about outcome measures and their day to day relevance

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What should be measured?

"Measure what can be measured,
and make measurable what cannot be measured."

Galileo Galilei



Why have outcome measures become so important?

- With ongoing and forthcoming trials we have realised how little experience in this field
- Poor choice of available measures
- Lack of reliability of many of the available ones

The role of TREAT NMD in outcome measures: WP 9

Defining and disseminating outcome measures

- (WP 9.01) selection and elaboration of assessment tools to be used as outcome measures in clinical trials
- (WP9.02) ; performing a systemic review of the available outcome measures

TREAT NMD WP 9.01

- several activities, including workshops, questionnaires and other meetings dedicated to specific aspects of functional abilities,
- better understanding of the existing outcome measures and to identify areas where further work is needed.



Neuromuscular Disorders 18 (2008) 894–903



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

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List and analysis of the existing measures

- A range of good functional outcome measures already exist which are ready for application in trials of SMA and DMD.
- More experience on DMD
- Less experience in SMA

List and analysis of the existing measures

Selection of statistically robust measures

- Clinical use \neq research tool
- clinical prospective \neq statistician prospective
not all the measures used in clinical practice appear to be robust for use in multicentric trials

List and analysis of the existing measures

Selection of statistically robust measures

Identification of measures in need for further validation
and cross validation

What did we learn?

- No one scale can be regarded as relevant across the entire spectrum from babies with severe type 1 SMA to adults with mild diseases or be used in DMD and in distal disorders

Choice of the most appropriate

- The choice of appropriate functional outcome measures will depend on the particular trial, (disease treated, level of disability, age of the patients, expected results)
- Disease specific tools were generally regarded as more sensitive to change but had inherent drawback such as ceiling or floor effects.
- More generic tools avoided these floor and ceiling effects but lack sensitivity.

Some of these measures appear to be more suitable for specific conditions or for specific stages of the disease,

- CHOP-INTEND
- Hammersmith Functional Scale for SMA (HFMS)
- Hammersmith Functional Motor Scale for SMA with 13 items from GMFM (HFMS+GMFM)
- North Star Ambulatory Assessment (NSAA)

others appear to be less specific but can be used in larger studies involving different diseases or patients with different severity

- MFM
- GMFM

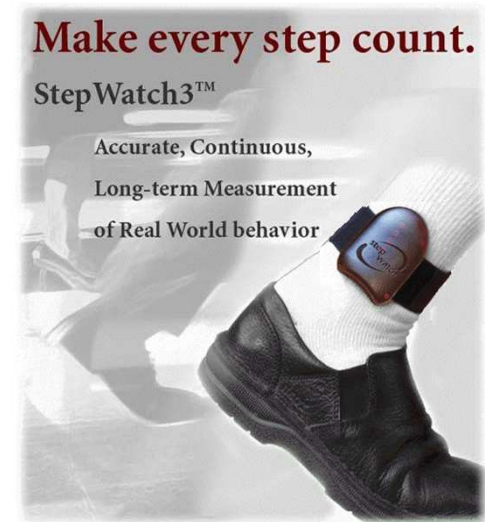
OTHER APPROACHES

- Assessing endurance and stamina
- 6 minutes walk test



Activity monitors

Attached to the ankle they record number of steps, movements etc in long time intervals (days, weeks, etc)



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Working together with the regulatory authorities

- Clinical use \neq research tool
- clinical prospective \neq statistician prospective
- Clinical/ statistical prospective \neq requirements from FDA /EMA

Working together with the regulatory authorities

- When considering an early drug/ therapeutic development program, it is important to engage as early as possible with the regulatory authorities.
- In the last few years regulatory authorities have shown interest to increase their knowledge on specific rare neuromuscular conditions and have been available to help with their extensive knowledge on different requirements for a successful product development.

EMEA Workshop on SMA London,
October 13, 2008

EMEA Workshop on DMD
London, September 25, 2009

Identification of early predictors of life altering events.

Prediction of life altering events

- Retrospective and prospective studies are encouraged to establish the value of timed items or functional scores to predict life altering events such as loss of independent ambulation in DMD.

If life altering events cannot be easily predicted,

- Clinically meaningful changes (Patients and parents' prospective!)
- Mandatory use of quality of life questionnaires and care givers appraisals

Feedback from EMEA

- Suggests to try to show interdependence between scale and QoL (rather than electrophysiology)
- Caregivers burden questionnaires
- try to define responders

- What is clinically meaningful depends on the natural history of the disease
- The changes should reflect real changes in everyday life

Back to the families

- Need to listen to patients/families
- Possible changes not always captured by existing scales

- Now able to switch lights on
- Brings hands on the table
- Can take objects from shelves
- Can lift glass
- Can open a ziplock

- Specific add on modules to explore specific aspects that are relevant to subgroups
- Upper limbs

SCORING SHEET








UPPER LIMBS GROSS MOTOR FUNCTIONAL SCALE

Date of assessment:
Patient's name:
Preferred side: R L

Dob:

Evaluator:
Diagnosis:

Starting position	Task	0	1	2
Same position as above	Make a fist three times	Does not make a fist	Attempts fist but does not complete movement	Makes a fist 3 times
Seated on the chair with elbow resting on table, hand on sheet of paper next to the coin. Material: standard sheet of paper with drawn: 2 circles 10 cm apart	Grasp coin on a circle, lift it and bring it inside other circle	Does not pick up coin	Grasps coin and slides it	Grasps and lifts coin to other circle
Seated on the chair with elbow resting, finger placed on centre of CD	Go round inner and/or outer edge of the CD with finger	Not able	Able only to follow inner edge	Goes round inner and/or outer edge
Seated on the chair with elbow resting on table, hand on surface next to a sheet of paper (size A4)	Turn over and show paper	Not able	Does not complete movement	Turns paper to show drawing
Seated on the chair with elbow resting on table, cup placed on the table at wrist length lying horizontally and, if the child can bring the coin, vertically	Bring coin to cup on table	No elbow extension	Brings coin to cup lying horizontally	Brings coin into vertical cup
Seated on the chair with elbow resting on table, cup placed by the examiner at wrist length with upper border of cup at shoulder height	Bring coin into cup	No elbow extension	Extends elbow does not able to put coin	Puts coin into cup

Seated on the chair with elbow resting on table, hand on sheet of paper with pencil, Material: Standard sheet of paper with drawn paths, lines 2 cm apart	Complete the paths	Doesn't grasp pencil and/or doesn't mark paper.	Doesn't complete path	Completes path
				
Seated on the chair with elbow resting, paper cup next to hand	Lift the glass at shoulder height, keep elbow in	Not able to lift cup	Lifts cup below shoulder height	Lifts the glass at shoulder height
Seated on chair with support, arms at sides	Place hands on table	No elbow flexion	Flexes elbows but doesn't complete movement	Places hands on table
Seated with support, hands on thighs	Touch ear with one hand	Not able	Touches ear by flexing head	Touches ear
Seated with support, hands on thighs	Touch ears with both hands	Not able	Touches ears by flexing head	Touches ears
Seated with support, arms at sides. Testing shoulder abductors.	Bring extended arm out and above head	Lifts elbows below shoulder height	Lifts elbows shoulder height	Completes movement
				
Seated with support, arms at rest, back against wall. Testing arm elevation	Bring extended arm in front and above head	No shoulder flexion	Lifts below shoulder height	Lifts at shoulder height or above
				
				TOTAL /26





List and analysis of the existing measures

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Working together with the regulatory authorities

Improving available measures,
further validation and cross validation

Where do we stand now?

Clinical measures

- Library of available measures ranging from general ones covering all the aspects of motor function to specific modules

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- Library of available measures ranging from general ones covering all the aspects of motor function to specific modules
- Increased collaboration with advocacy groups in order to further validate existing scales

SMA

- ICC/TREAT NMD effort to harmonise existing data and improve statistical analysis of most commonly used scales
- Rasch analysis

Where do we stand now?

Clinical measures

- Library of available measures ranging from general ones covering all the aspects of motor function to specific modules
- Increased collaboration with advocacy groups in order to further validate existing scales
- Collect more longitudinal normative data

More data on natural history of the diseases using these measures are necessary

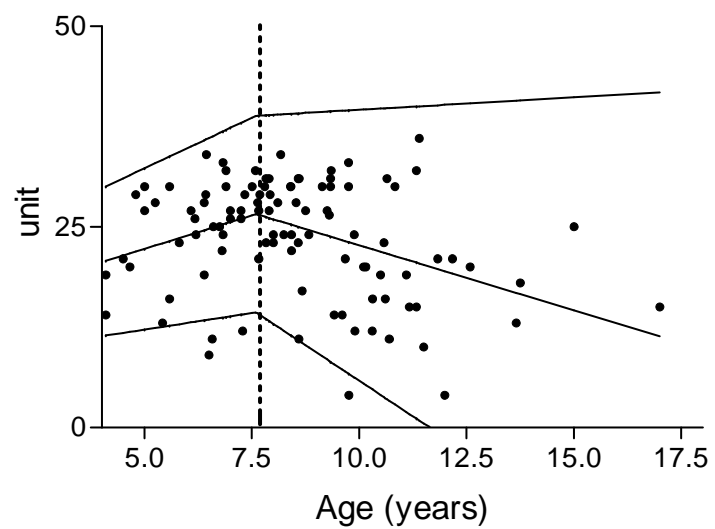
Sma Europe

- Collaborative effort to collect longitudinal data in ambulant and non ambulant SMA
- Eight European countries
- Training
- Data collection

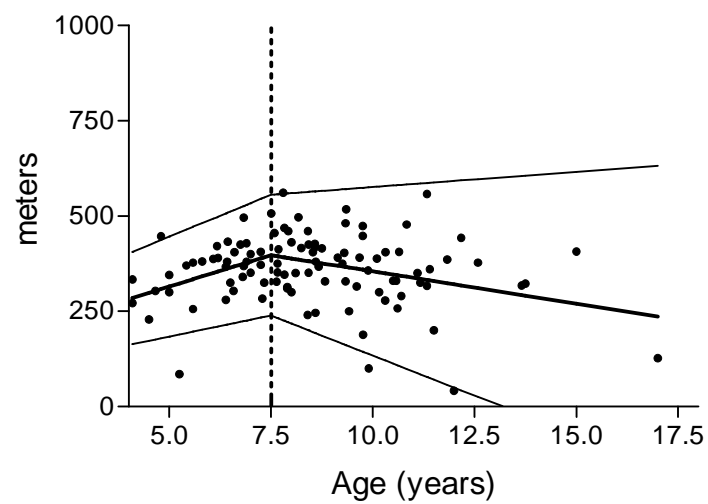
DMD

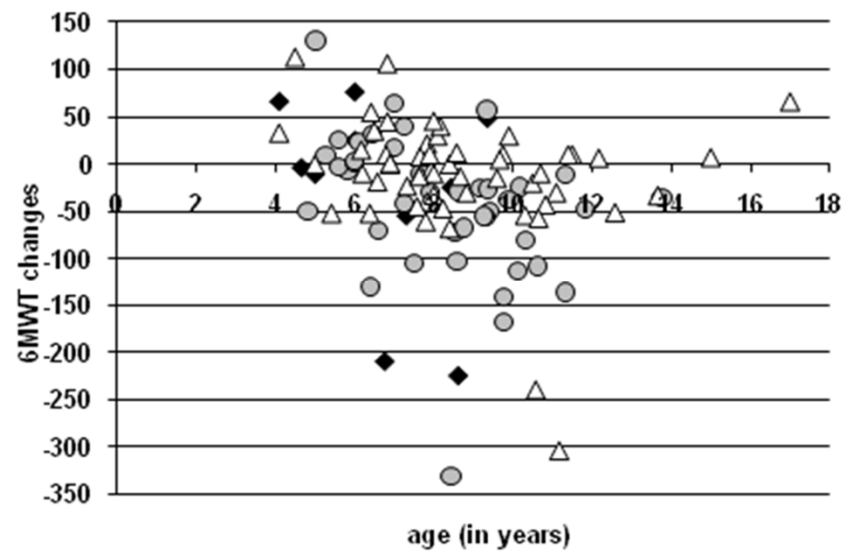
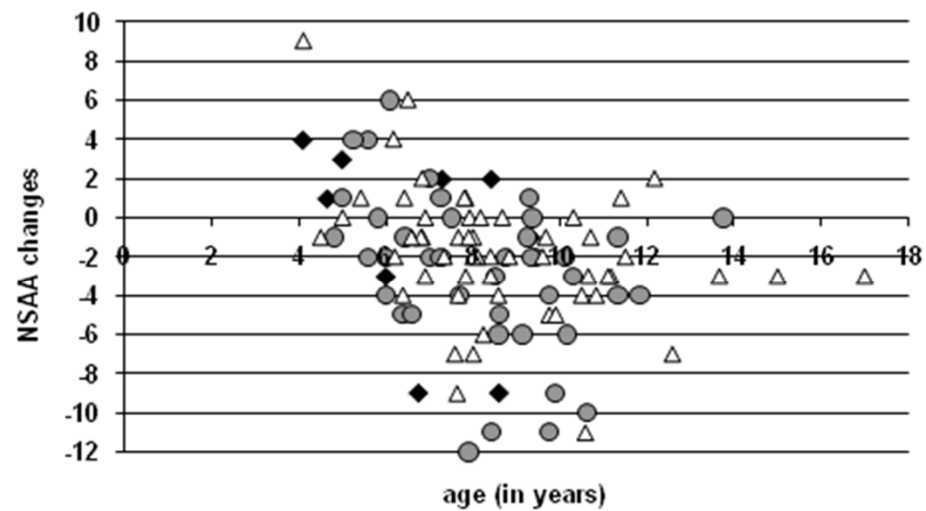
- National networks validating measures for ambulant DMD
- US, Italy, UK
- New recent data are needed for designing clinical trials and for a better idea of what we should expect in day to day life

North Star



6MTW





- International effort to coordinate these data and to have larger numbers to show the NATURAL HISTORY of the disorder and its progression at DIFFERENT AGES and with recent data reflecting RECENT STANDARDS OF CARE

What's next?

- Need to develop and validate new measures for very young children and non ambulant DMD
- Ongoing/planned studies to establish how to measure different aspects of function
- Attempt to use similar protocols
- Need for coordination and structured support (similar training, common databases etc)

Improving available measures,
further validation and cross validation

- Collect more longitudinal normative data
- Disease specific add-on modules
- Translation and validation of quality of life questionnaires
- Cross validation with functional measures