

# The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials

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## Background

With the emergence of experimental therapies for DMD, it is crucial to understand the natural history of this disorder to properly design clinical trials

The aims of this study are:

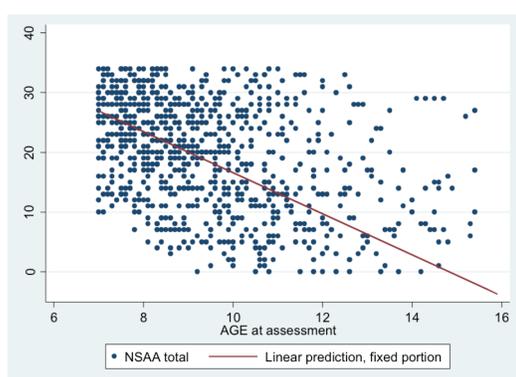
- 1) to assess the motor function decline in DMD boys treated according to the standards of care;
- 2) to describe the rate of motor function decline in DMD boys stratified for genetic mutations;
- 3) to describe the natural history of young DMD boys treated with glucocorticoids below five years of age



Through the UK NorthStar Clinical Network, which encompasses the collaborative efforts of 20 Neuromuscular Centres in the UK, clinical data from 2004-2013 on 513 DMD boys treated on glucocorticoids were included in the analysis

For the analysis of the sub-genotypes, we also included data from 172 DID boys followed-up by the neuromuscular Italian clinical network

## NorthStar Ambulatory Assessment in boys >7 years of age

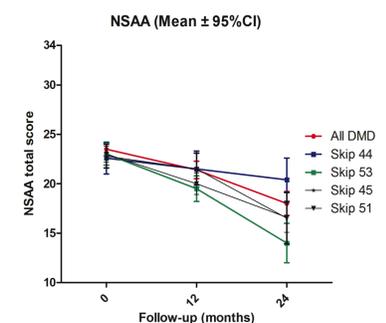


### NSAA total score fitted model for > 7 year-old boys

- DMD boys gain motor function up to age 7, after which they start declining
- The average mean NSAA score at age 7 was 27 out of 34
- The overall slope coefficient was -3.7 (95% CI -4.1, -3.3) per year
- Our DMD population on average lost 4 NSAA units for each year, after age 7

	NSAA 12 months	NSAA 12 + 24 months
ALL DMD (n=395)	-2.1 (-2.7, -1.5) p<0.001	-5.8 (-6.5, -5.1) p<0.001
Skip 44 (n=27)	1.3 (-0.9, 3.5) (p=0.25)	3.9 (1.3, 6.5) (p<0.01)*
Skip 45 (n=31)	0.3 (-1.8, 2.5) (p=0.75)	-0.6 (-3.2, 1.9) (p=0.6)
Skip 46 (n=34)	1.3 (-0.6, 3.3) (p=0.19)	3.5 (1.1, 5.9) (p<0.01)*
Skip 50 (n=8)	1.9 (-2.2, 6.1) (p=0.37)	3.0 (-1.8, 7.7) (p=0.22)
Skip 51 (n=61)	-1.0 (-2.6, 0.6) (p=0.22)	-2.4 (-4.2, -0.5) (p=0.01)*
Skip 52 (n=9)	0.4 (-2.6, 3.3) (p=0.80)	3.0 (-0.4, 6.4) (p=0.08)
Skip 53 (n=41)	-2.0 (-3.8, -0.1) (p=0.04)*	-4.5 (-6.7, -2.3) (p<0.001)**

	Overall slope coefficient
Deletions (n=323)	-0.4 (p=0.7)
Duplications (n=54)	0.7 (p=0.5)
Point Mutations (n=62)	-1.4 (p=0.2)



## Age at loss of ambulation

Centiles LOA	Age (years)	SE	95% CI
10 <sup>th</sup> Centile	9.5	0.1	9.1-9.9
25 <sup>th</sup> Centile	10.9	0.2	10.1-11.1
50 <sup>th</sup> Centile	13	0.3	12.1 - 13.5
75 <sup>th</sup> Centile	16	0.7	15-

### Loss of ambulation

- Ambulation was lost in 137/513 boys, including all glucocorticoid treatment regimens. The median LOA was 13 years (95% CI: 12.1, 13.5)
- The mean NSAA score was 13 and 9 units 24 and 12 months before losing ambulation

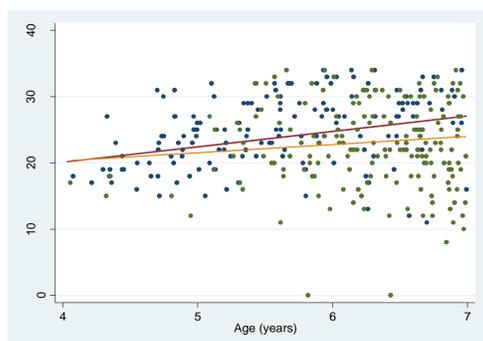
### NSAA mean score for sub-genetic mutations

- A possible trend for duplications declining slower and point mutations declining at a faster rate did not meet significance
- We observed variability of clinical course between the skippable subpopulations especially at 24 months: 1) boys skippable for exons 44 and 46 did better, declining at a slower rate; 2) while boys skippable for exons 53, 51 and 52 showed a faster decline

## NorthStar Ambulatory Assessment in boys < 7 years of age

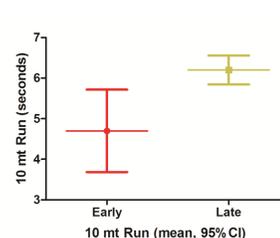
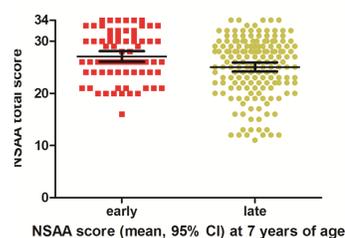
### NSAA total score fitted model for < 7 years old

Boys with DMD improve their motor function, with an overall gain of 1.5 units (95%CI 0.6, 2.1) per year



### Effects of glucocorticoid therapy in young DMD boys

- When compared:
- 78 DMD boys who started daily or intermittent glucocorticoids early (in RED), before the age of 5 (mean age at start = 4.5 years)
- with 163 boys who started GC between ages 5 and 6.5 indicated as late (in YELLOW) (mean age at start = 5.7 years)
- the coefficient of interaction in our analysis was 1.3 (95%CI 3.0, 0.3, p = 0.1), favouring early starters by almost 1.5 NSAA units a year.
- By age 7, the mean total NSAA was different between the two groups (p<0.01): 27 (95%CI 24.6, 29.4) in early starters and 25 (95%CI 23.2, 26.9) in the late starters group
- 10 meter run was 4.7 seconds and 6.2 seconds respectively (p=0.05)



NSAA item	Early vs late mean sub-score
Stand	ns
Walk	ns
Stand up from chair	P= 0.04
Stand on one leg (R+L)	ns
Climb box step (R+L)	P= 0.009
Descend box step (R+L)	P= 0.009
Gets to sitting	P=0.008
Rise from floor	ns
Lifts head	P=0.009
Stands on heels	P=0.002
Jump	P=0.004
Hop right + left leg	P=0.001
Time rise from the floor	ns
Run	ns

## Conclusions

Our study provides insights on the current natural history in a large cohort of DMD boys, which helps for the design of clinical trials and inclusion criteria

- Including all the steroid treatment groups after age 7, we observed a large variability of motor function. Overall the rate of decline was **4 NSAA units per year**.
- Median loss of ambulation was **13 years**; two years prior to losing ambulation the average total NSAA score was **13 units** (out of 34)
- When compared to the general DMD population, over a 24 month period boys with mutations skippable for exons 44 and 46 decline at a slower rate (by overall 4 units less); while boys with mutations skippable for exons 53 and 51 decline faster (2.5 to 4.5 additional units)
- Young DMD boys gain motor function up to age 7 (~1.5 NSAA unit a year); starting glucocorticoids before age 5 confers an advantage of an additional of ~2 NSAA units by age 7



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