# Evolution of time to stand velocity in glucocorticoid-using and non-using patients with DMD

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## Objective:

To characterize the evolution of the TTSTAND clinical study endpoint as a function of age in a natural history population of Duchenne muscular dystrophy (DMD) patients using or not using glucocorticoids (GCs).

## Methods:

Data were extracted from the Cooperative International Neuromuscular Research Group (CINRG) natural history study.[1]

- 1273 TTSTAND assessments from 224 patients
- Data before initiation of GCs were used to describe the GC non-user subset, and data after initiation of GCs were used to describe the GC user subset, i.e. the same patient could contribute to only one or both subsets

## Conclusions:

- **TTSTAND velocity is a clinically relevant endpoint** with good statistical properties for evaluating motor function in clinical studies of patients with early-stage DMD
- A velocity of **0.2 rises/second** is a threshold associated with increased probability of losing standing ability
- A change in velocity of **0.05 rises/second** is considered clinically meaningful
- The natural history of TTSTAND velocity indicates that early GC use may delay DMD disease progression by **2–3 years**

**References**

1. McDonald CM, et al. *Muscle Nerve.* 2013;48(1):32–54.
2. McDonald CM, et al. *Eur J Paediatr Neurol*. 2017;21:e237.
3. McDonald CM. *Muscle Nerve*. 2018;58(5):614–7.
4. Arora H, et al. *Muscle Nerve.* 2018;58(5):631–8.

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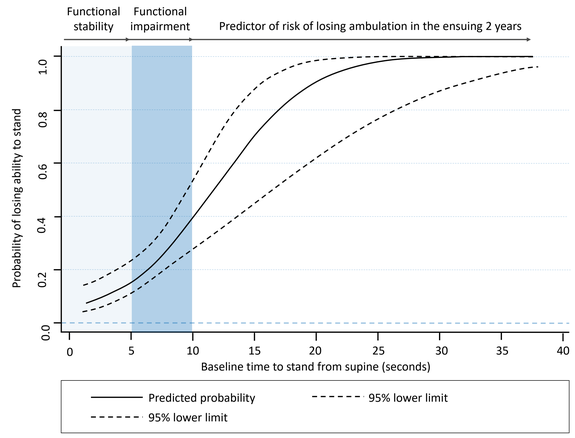
## TTSTAND as a clinical predictor of disease progression

- TTSTAND, or 'time to stand from supine', is a useful functional test in DMD[2] and is often used as a primary or secondary endpoint in clinical studies[3]
- It is a linear measurement expressed as the number of seconds taken to rise from a supine position without assistance[4]
- TTSTAND declines rapidly over time in patients with DMD[4] and has been previously shown to be an early prognostic factor for disease progression and loss of ambulation (**Table 1**)[2,4]
- TTSTAND can have limitations when evaluating declining patients who lose the ability to stand,[3] and endpoints may be skewed by outliers caused by large but clinically meaningless changes in long rise times[3]
- In our CINRG cohort (**Fig. 1**), the probability of losing ability to stand at 24 months correlated with a longer TTSTAND at baseline, in a trajectory that closely aligned to clinical markers of disease progression

**Table 1. Clinical relevance of TTSTAND measurements**

| TTSTAND | Clinical relevance |
|---|---|
| <5 seconds | Suggests functional stability[2,3] |
| ≥5 seconds | Indicates functional impairment[2,3]<br>Shown to predict disease progression over 48 weeks[2,3] |
| ≥10 seconds | Shown to predict risk of losing ambulation in the ensuing 2 years[3] |

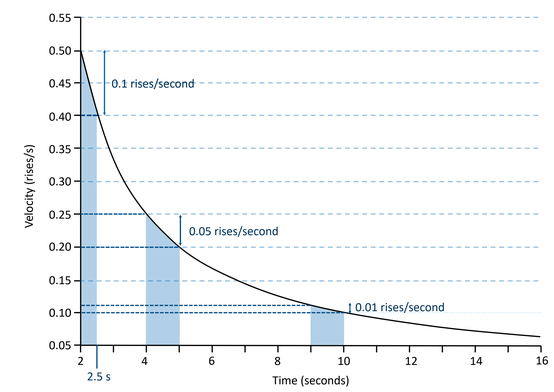
**Fig 1. Predicted probability of losing ability to stand at 24 months given baseline time to stand from supine assessment (TTSTAND). Adjustment made for baseline age and cumulative steroid use at baseline**




## Conversion between rise time and velocity

- TTSTAND velocity is a conversion of TTSTAND. It is calculated as 1/TTSTAND, expressed as rises/second.
- TTSTAND velocity is a clinical study endpoint designed to overcome the limitations of TTSTAND:
  - Patients with long rise times or who can no longer rise without assistance are inputted as zero
  - Better statistical properties reduce the impact of outliers
- The relationship between rise time (as seconds) and velocity (as rises/second) is illustrated in **Fig. 2**
  - The TTSTAND velocity endpoint recognises that a 1-second difference in rise time is more meaningful when the change is from 5 to 4 seconds (i.e. a 1/5 improvement from baseline) compared with a change from 10 to 9 seconds (i.e. a 1/10 improvement from baseline)
  - A clinically meaningful 1-second change in rise time from 5 to 4 seconds equates to a change in velocity of 0.05 rises/second. To achieve this change in velocity from a baseline rise time of 10 secs, an improvement of 3.3 seconds is required. This methodology puts the clinical emphasis on rise times of 5 seconds
- While TTSTAND velocity is a useful measure for patients in functional decline, caution should be exercised when analysing datasets that include rise times shorter than 2.5 seconds. In these instances, small and clinically meaningless changes in rise times may lead to large changes in velocities

**Fig 2. Relationship between absolute rise times (TTSTAND) and TTSTAND velocity**

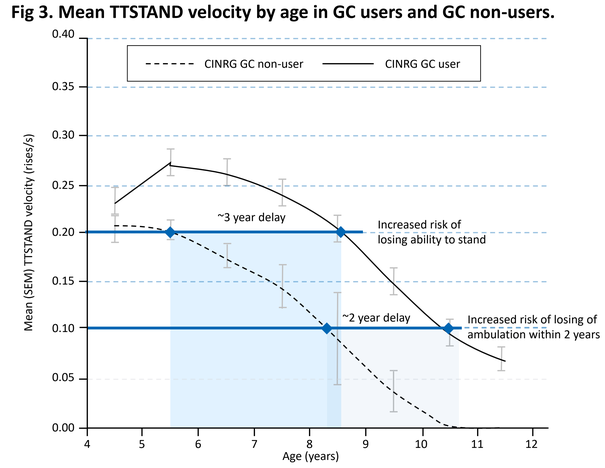



## Natural history of TTSTAND velocity in GC users and GC non-users

- A comparison of the natural history of TTSTAND velocity in GC users and GC non-users from the CINRG cohort confirmed the importance of early intervention for patients with DMD (**Fig. 3**)
  - On average, GC users reached their peak TTSTAND velocity at age 5–6 years, while GC non-users declined consistently from ~4 years of age
  - Once in the decline phase, the trajectory for GC users and GC non-users was similar, and aligned with the well-characterised clinical progression of DMD[4]; however, GC use delayed this decline by ~2–3 years
- Most CINRG patients had lost the ability to rise by age 10 (100% of GC non-users and 45% of GC users), though this milestone was delayed in the GC user group
- A TTSTAND of 5 seconds – or a TTSTAND velocity of 0.2 rises/second – was a threshold below which there was an increased probability of losing standing ability. GC use delayed reaching this threshold by ~3 years (**Fig. 3**)
- A TTSTAND of 10 seconds – or a velocity of 0.1 rises/second – was associated with increased risk of losing of ambulation over the ensuing 2 years. GC use delayed this milestone by ~2 years (**Fig. 3**)

SEM, standard error of the mean

**Fig 3. Mean TTSTAND velocity by age in GC users and GC non-users.**

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