COLLABORATIVE
TRAJECTORY
ANALYSIS
PROJECT

- Pre-competitive
- Multi-national
- All stakeholder groups
- More effective trial design

Collaborative Learning from Patient Data

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Therapy Developers

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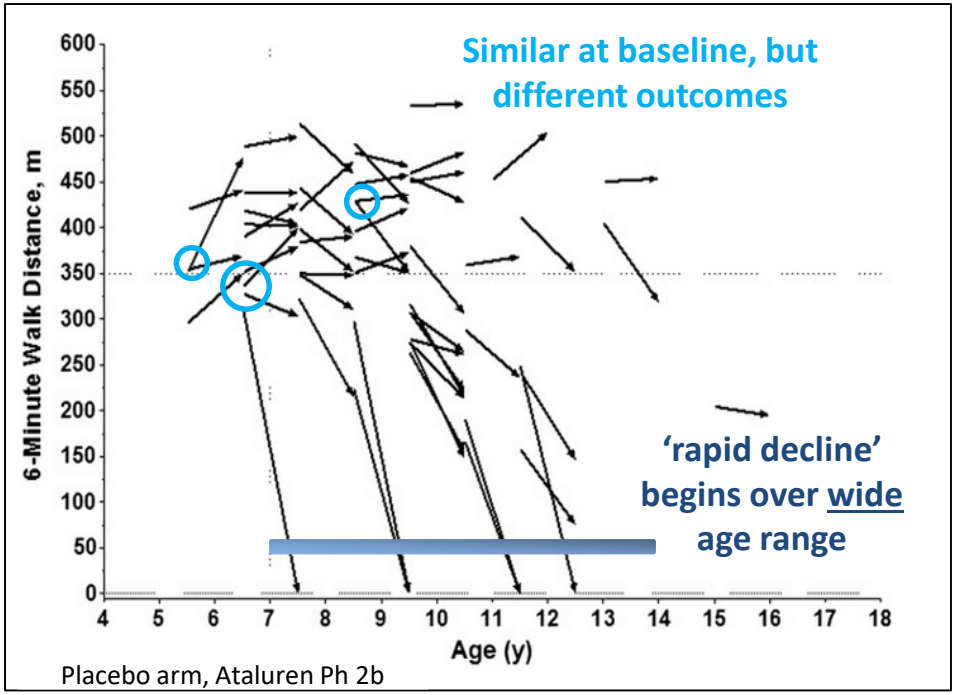
The problem we're trying to solve

PIVOTAL TRIAL	No. Patients in the trial	Met primary endpoint?	Placebo Arm SD
Ataluren Phase 2b	174	no	88
Ataluren Phase 3	228	no	81
Drisapersen Phase 2	69	no	51
Drisapersen Phase 3	186	no	92
Tadalafil Phase 3	331	no	51

- *large numbers of patients*
- *drug effects not statistically significant*

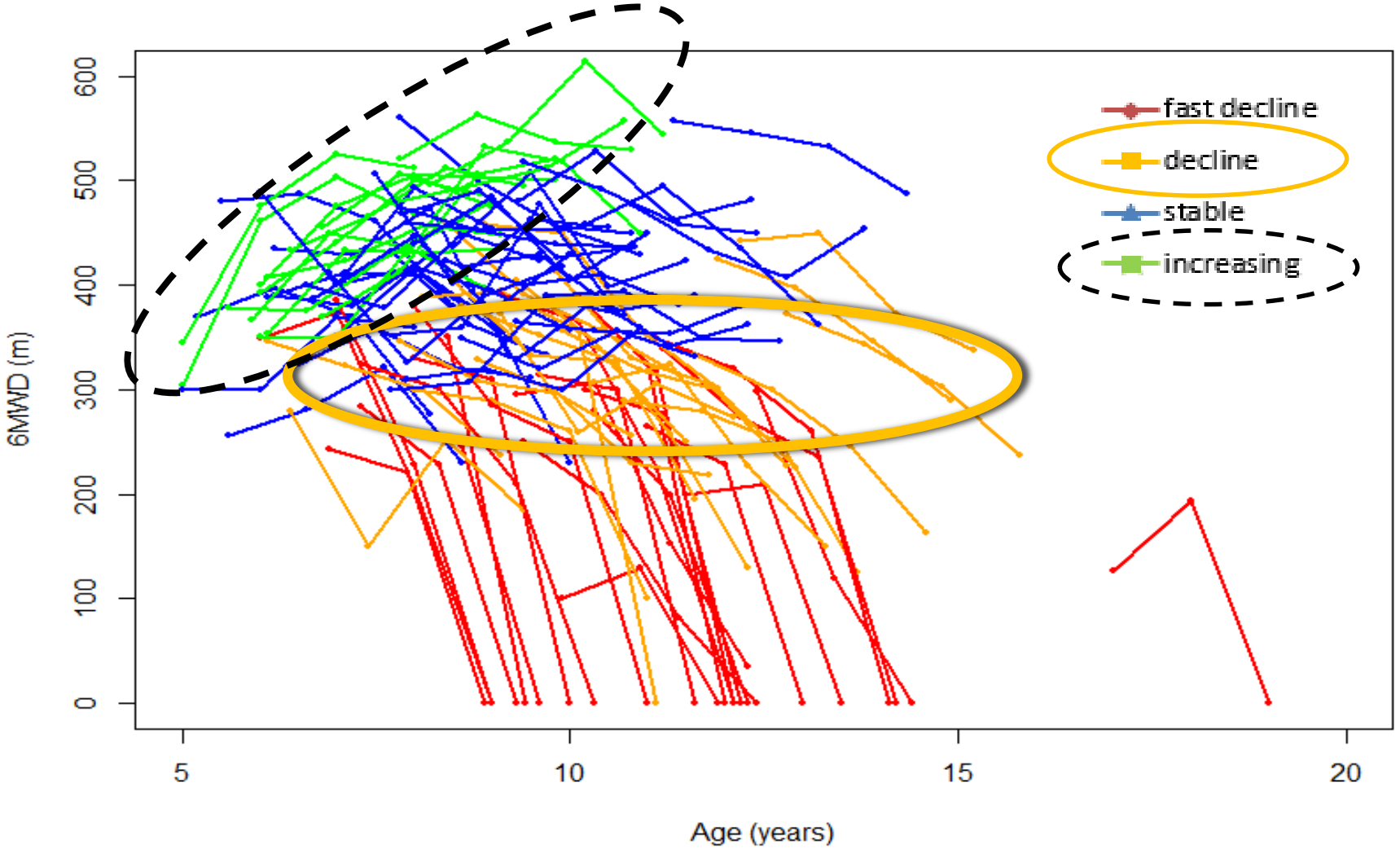
High variance is driven by heterogeneity in longitudinal disease progression



Placebo arm, Ataluren Ph 2b

- Burden and disappointment for patients and families
- Uncertainty and wasted resources for drug development
- Disincentive for investors

Can we select for patients at similar stages of disease?



COLLABORATIVE TRAJECTORY ANALYSIS PROJECT

What to do?

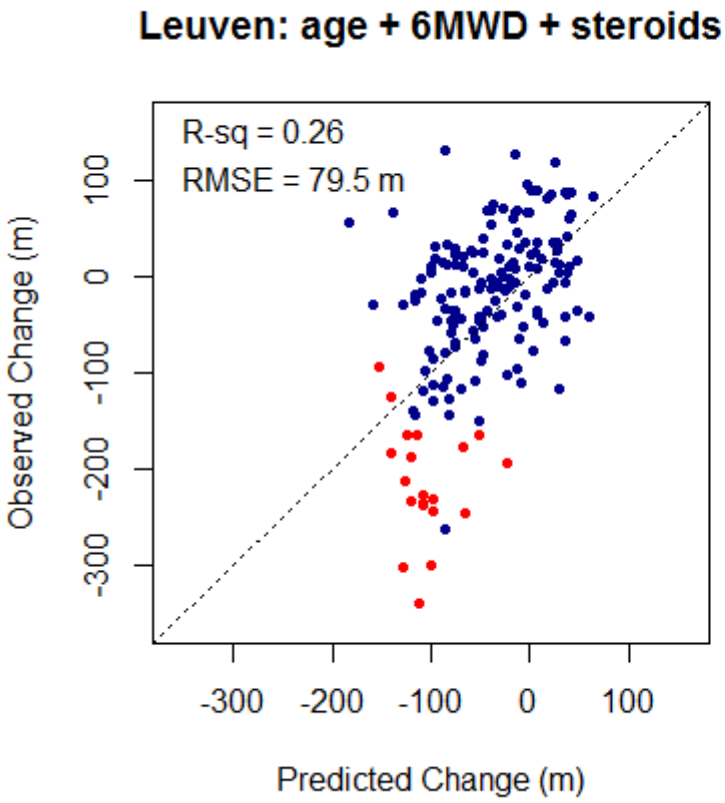
AIMS

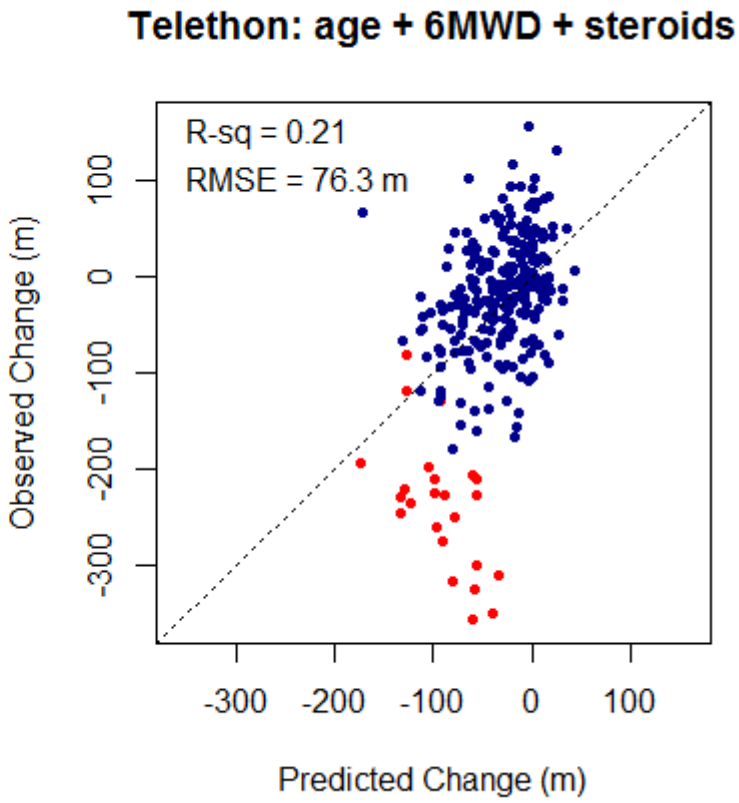
1. Reduce Variance
2. Reduce Size of clinical trials

- Select patients with a similar trajectory of progression
- Identify prognostic factors to predict (and adjust for) different trajectories

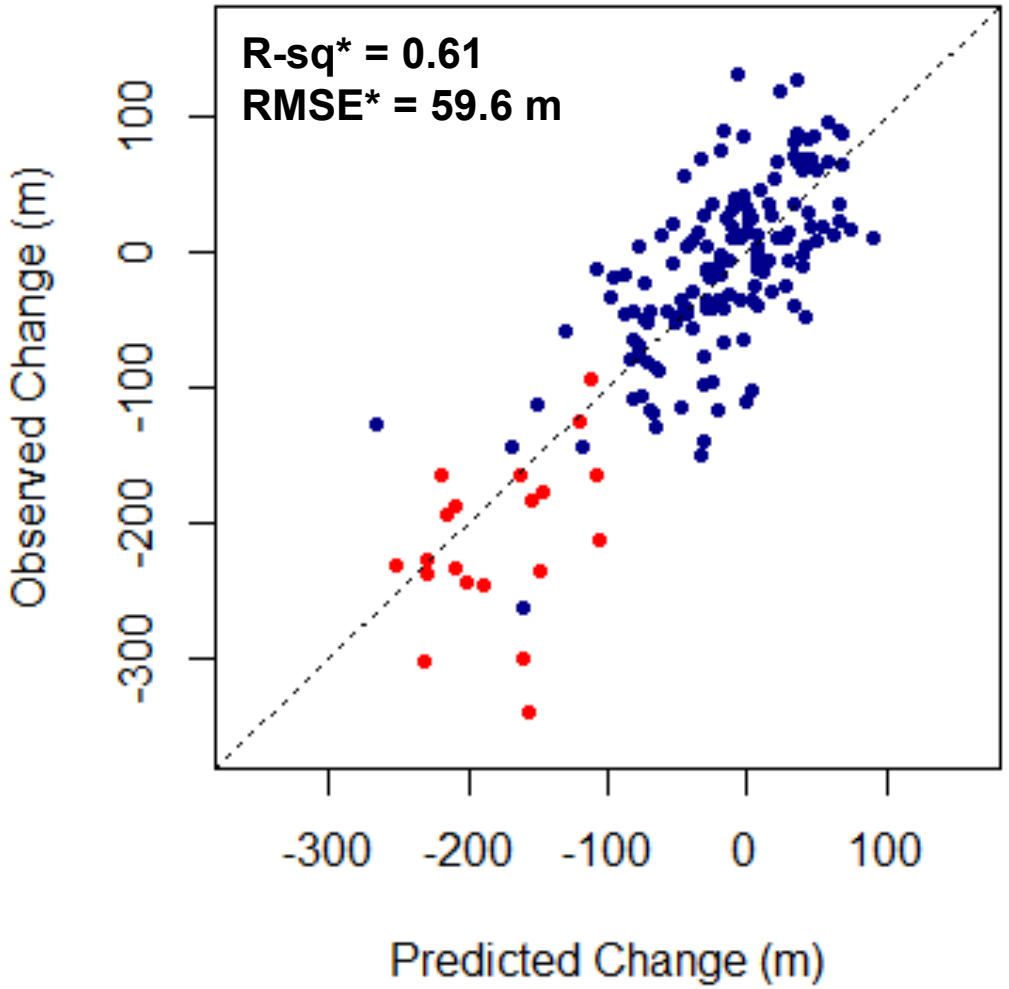
Better trial design, good therapies to patients sooner

Conventional Prognostic Factors account for only one quarter of observed variance in 1 yr Δ6MWD





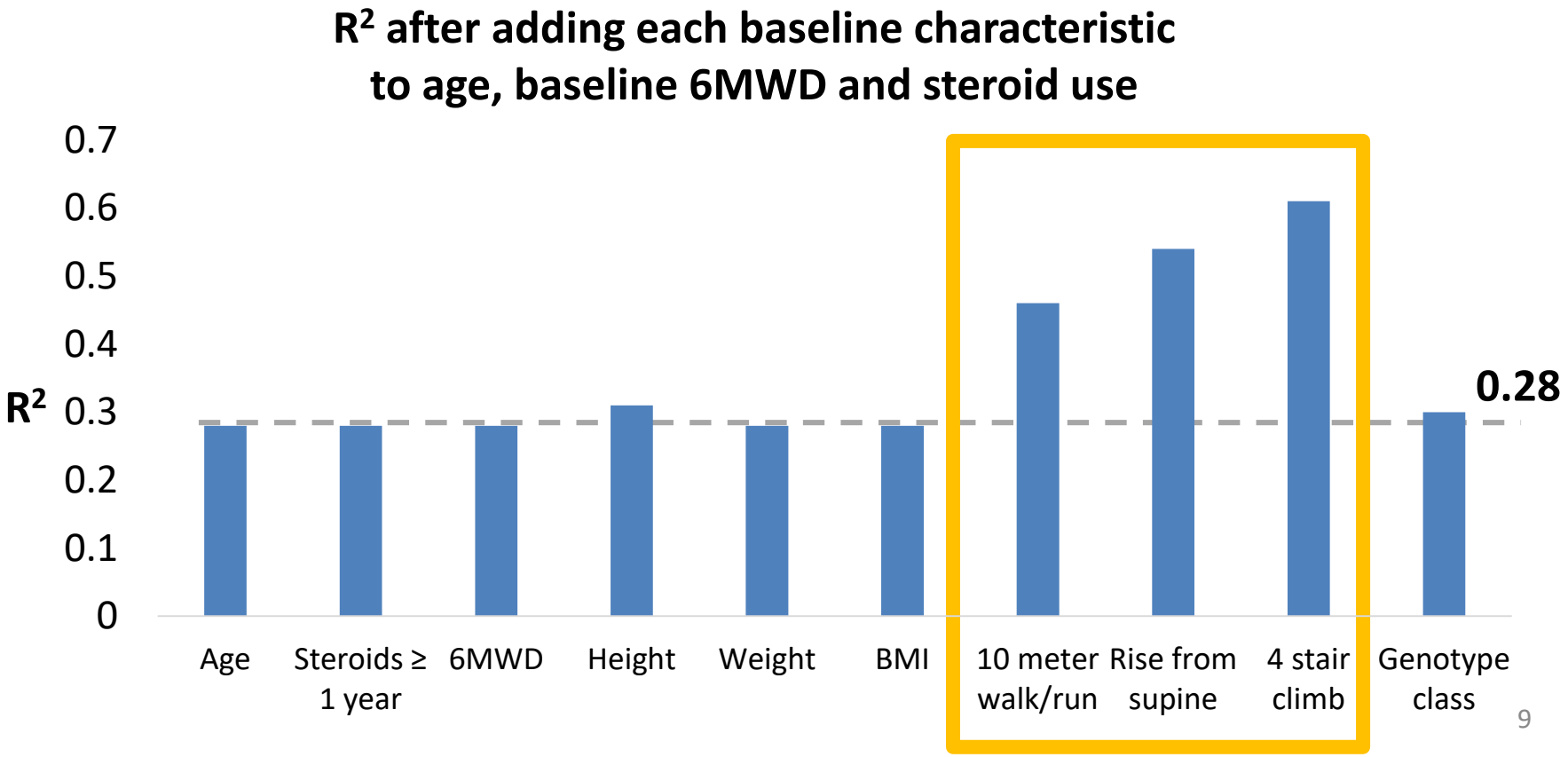
Composite prognostic model more than doubles prognostic accuracy, reduces unaccounted for variance



*Estimated using cross-validation

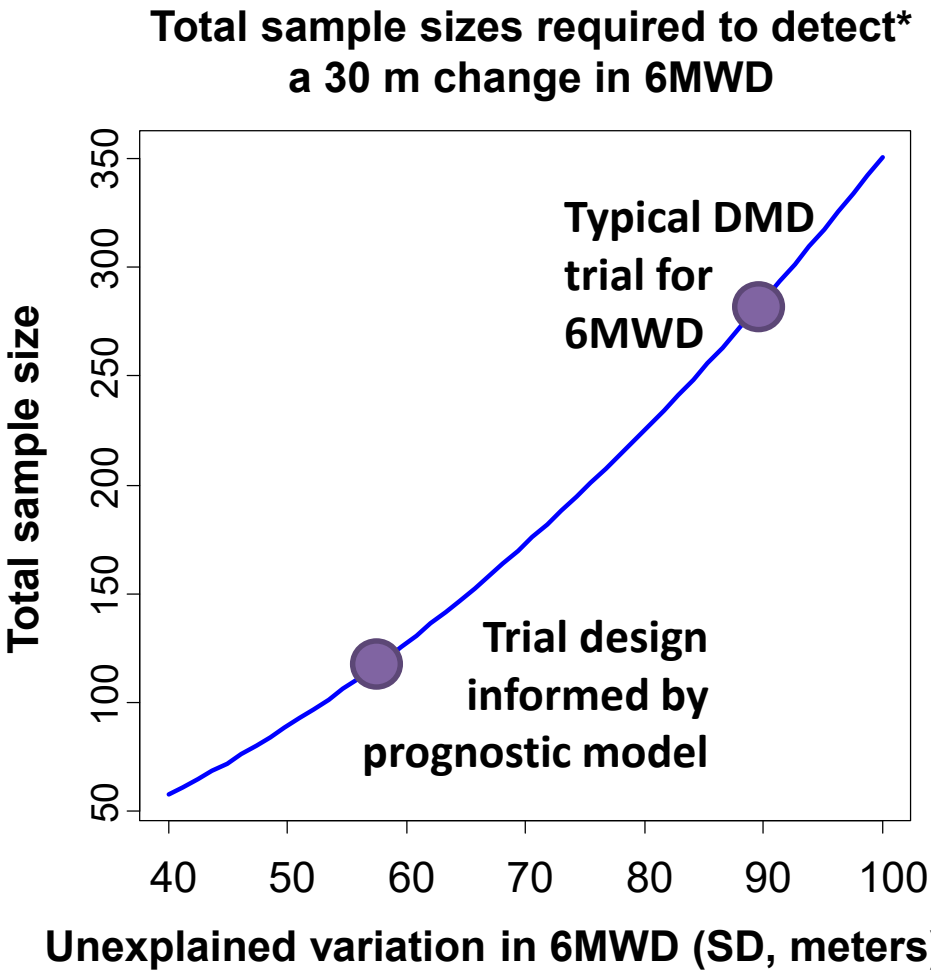
Contributions to prognostic accuracy

- The timed function tests contributed most to additional prognostic accuracy
- Genotypic class for dystrophin mutations (duplication, deletion, point mutation) did not explain significant additional variability in outcomes



Impact of selection/enrichment guided by a prognostic score

- An accurate prognostic model helps explain and reduce variability in outcomes
- Less unexplained variability leads to clearer trials: greater power to detect drug effects and/or smaller sample sizes
- The performance of the current prognostic model can enable smaller trials with 100s fewer patients



**with 80% power and equal allocation to two groups*

What to do?

AIMS

1. **Variance Reduced**
2. Reduce Size of clinical trials

- Identify prognostic factors to predict (and adjust for) different trajectories

Can we use natural history to replace (or augment) placebo arms in clinical trials?

Natural History as control - Considerations

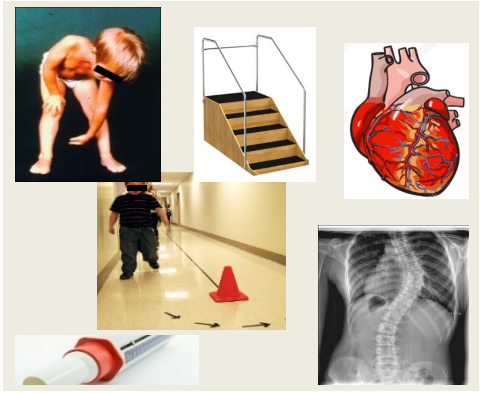
- Ambulatory tests e.g. 6MWD "is not a 'hard' endpoint
  - can be influenced by motivation and other factors
- *"It has been well documented that untreated historical-control groups tend to have worse outcomes than apparently similarly chosen control groups of randomized studies"*
- One could hypothesize that 6MWD outcomes are better in a trial setting vs. natural history in DMD due to:
  - Greater motivation or hope for improvement
  - More frequent follow-up
  - Optimized steroid therapy and physical therapy.

How consistent is natural history versus placebo?

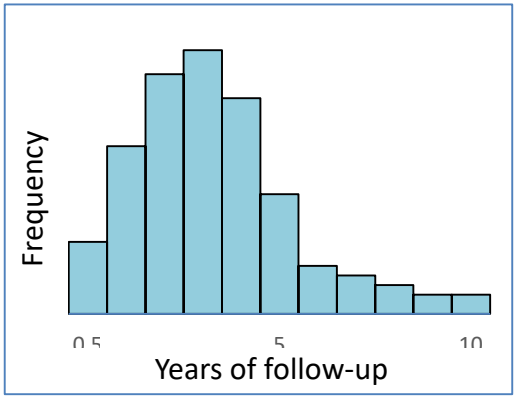
Can we access sufficient patient data?

>2,300
boys

>15,000
clinic visits



>1,000
patient-years



LARGE & REPRESENTATIVE

RELEVANT & COMPREHENSIVE

DISEASE PROGRESSION

Assess consistency – study design

Published placebo-controlled trials using 6MWD

- Ataluren Phase 2b
- Ataluren Phase 3
- Drisapersen Phase 2
- Drisapersen Phase 3
- Tadalafil Phase 3

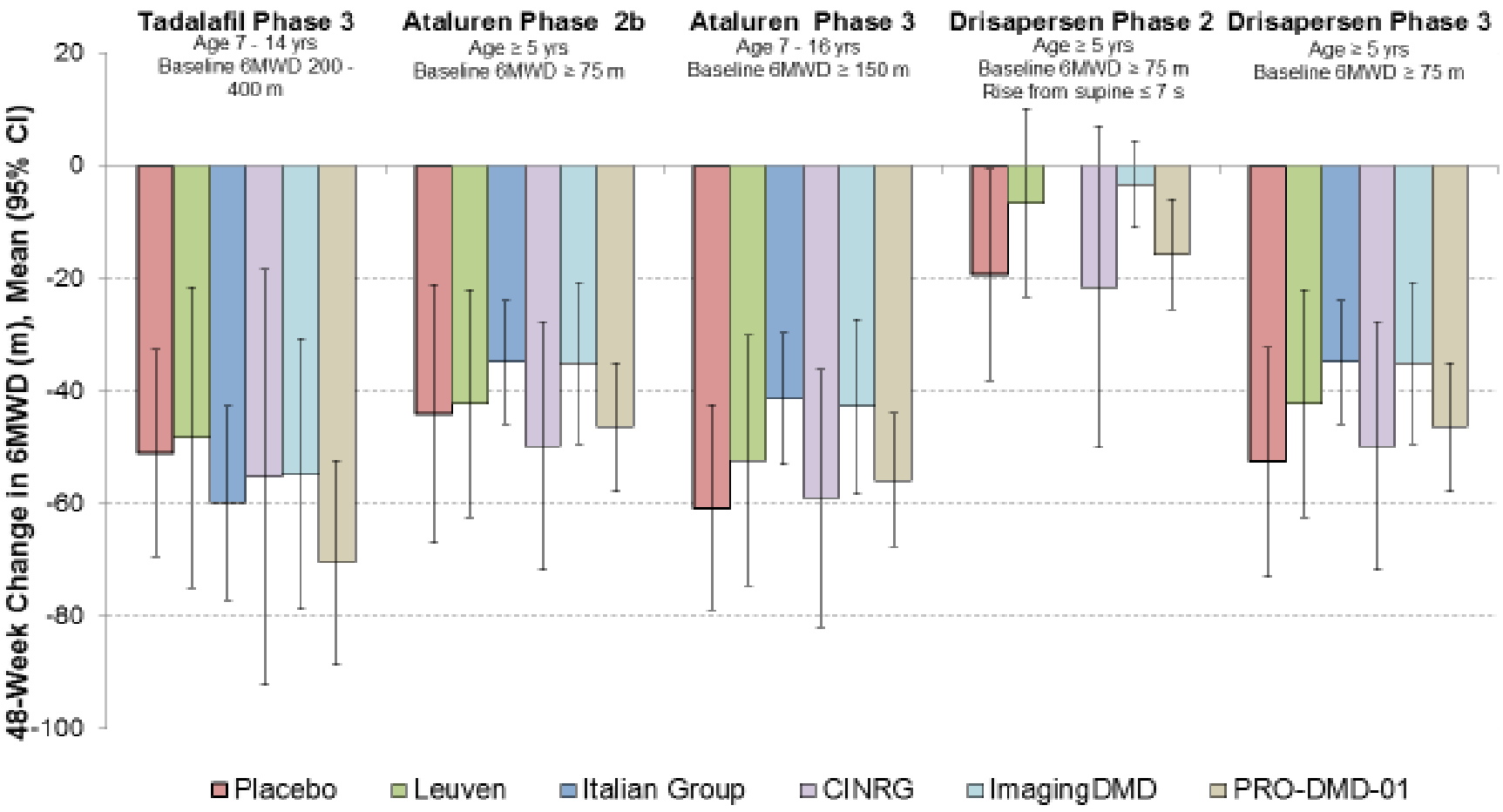
Natural History datasets, Clinical practice, clinical registries

- Telethon Italy
- Goemans, UZ Leuven
- McDonald, CINRG
- Vandenborne, iDMD
- Muntoni, iMDEX

Compare 1 year change in 6MWD

- from each clinical trial
- Versus each natural history using clinical trial inclusion/exclusion criteria

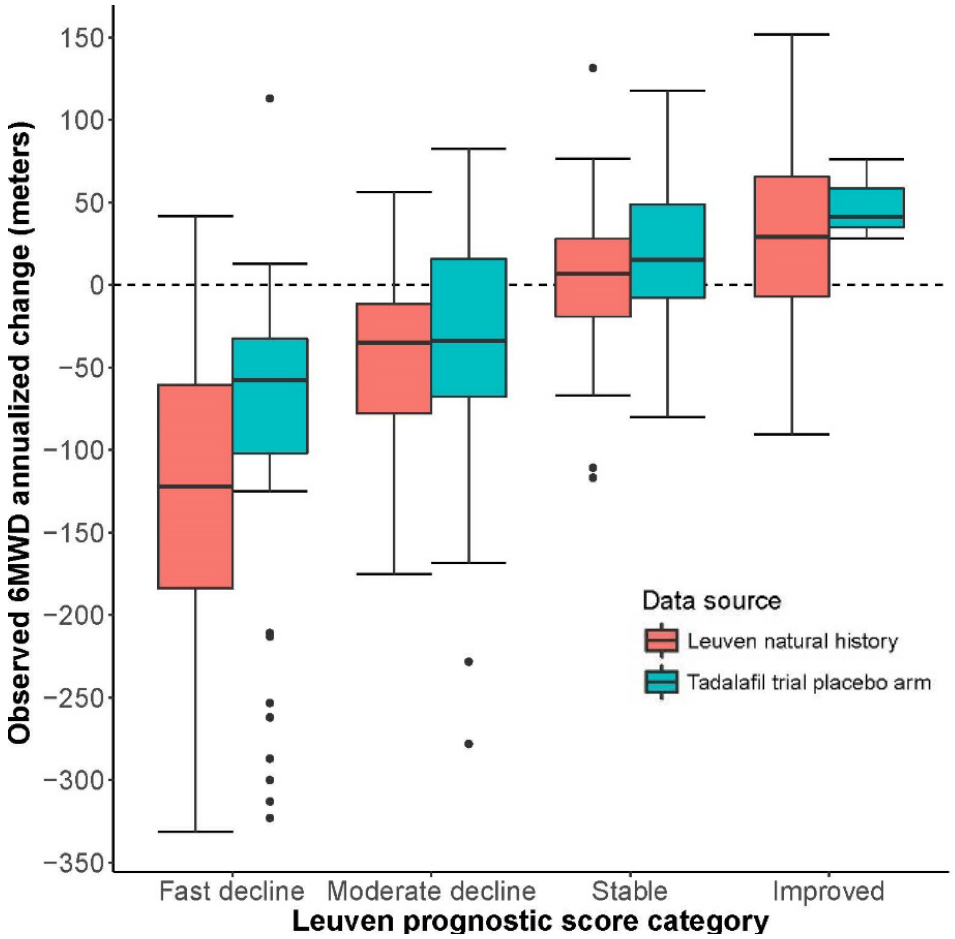
Results



No statistical difference between placebo and natural history

Prognostic model validation in placebo

- Placebo arm data from the tadalafil phase 3 trial
- No statistically significant differences in Δ6MWD between data sources within any baseline prognostic category (all p > 0.05).



No statistical difference between model performance in placebo versus natural history

Regulatory Feedback

- **FDA encouraged**
  - Replicate using other outcome measures
  - Use Natural History to supplement, not entirely replace, placebo
  - Work closely with drug companies to apply prognostic models
- **Review with EMA 2019**

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Summary

AIMS

1. Reduce Variance
2. Reduce Size of clinical trials

- Prognostic model more than doubles prognostic power
  - Replicates in placebo data
- No evidence of statistical difference between natural history and placebo
- Positive Regulatory Feedback

Better trial design, good therapies to patients sooner

Collaboration

- Importance of all patient clinical data
- LEARNing from patient data
- Collaborative learning
- Apples to apples analysis enabled
- Non-proprietary, neutral - Credibility with Regulators
- Teamwork, sum is greater than parts

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