BIOMARKERS AND OUTCOME MEASURES IN NEUROLOGY CLINICAL TRIALS

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Disclosures

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- Research funding received from Cytokinetics, Biogen, Synapse, Neuraltus, Biotie, Amylyx, ALS Association, MDA, NINDS

What is a Biomarker?

- generally refers to a measurable indicator of some biological state or condition. (Wikipedia)
- a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (NIH)
- Definition is so broad that a biomarker can be any one of above
- Functional and clinically relevant endpoints can also be a biomarkers

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Six Main Categories of Biomarkers

Biomarker Category	Utility	Examples
Target Engagement	• The drug interacts with its intended molecular target *in vivo*	• PET receptor occupancy studies • Measurement of molecular complexes in vivo • Binding in a surrogate compartment (e.g., lymphocytes)
Pharmacokinetic	• The drug reaches its desired molecular site of action	• Pharmacokinetics in CSF • CNS uptake studies

Pharmacodynamic	• The intended molecular effect produces the desired biological effect.
	  • Useful for determining therapeutic dose range;
	  • potential candidate for becoming a surrogate
		• Effect on Molecular Target:
		• Effect on Presumed Downstream Marker
		• Plasma proteomics
		• Plasma metabolomics

Diagnosis/ Stratification	• The targeted disease state is present, and/or the desired patient population can be stratified to optimize risk benefit ratio and probability of success	• Genetics • Blood-based makers • CSF • Imaging

Disease Outcome	• Assessment of effect on Clinical or Pathological Disease measures	• Clinical Outcome Measures
		• Imaging
		  • Anatomical
		  • Functional

Safety	• Presence and/or severity of potential target organ toxicity is measurable	• Biochemical (common/special labs) Electrophysiological (QTc)

Integration of Biomarker Strategies into Drug Development Decision Making

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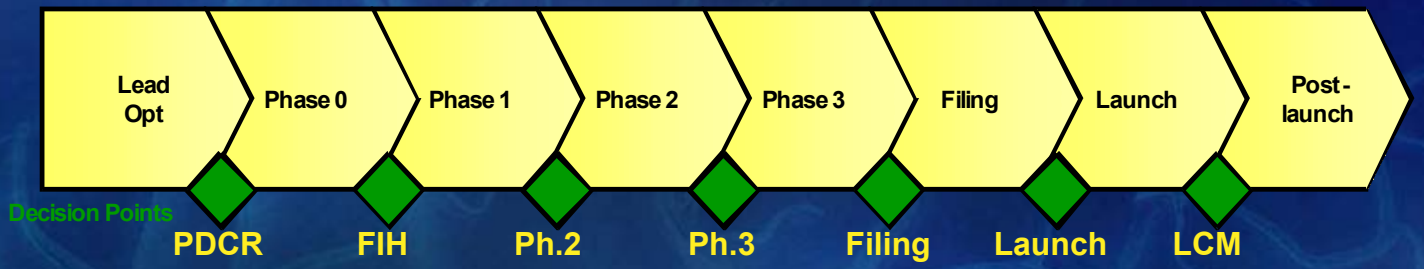

Mechanism of Action								
Pharmacokinetics								
Pharmacodynamics								
Disease Dx/Stratification								
Disease Progression								
Safety								

Courtesy of Jesse Cedarbaum

P_D Markers: measure of compounds ability to interact with its intended target leading to a biological effect.

- P_D type:
  - Biochemical:
    - Enzyme substrate
    - mRNA/ Protein
  - Imaging:
    - PET
    - MRI
    - CT
  - Physiology:
    - Axonal excitability
    - MUNE
- P_D use:
  - Test biological hypothesis in human
  - Combine with P_K
  - Select dose:
    - Efficacious range
    - Safe range

CSF SOD1 as a PD Biomarker for ALS

- SOD1 Antisense Oligonucleotides (ASO) lower SOD1 and prolong survival in animal models
- SOD1 natural history data suggests we will be able to determine benefit
- ASOs safe in prior IONIS/Biogen Phase I in SOD1 ALS

JS1

Antisense Oligos Decrease CSF in SOD1 G93A Rats

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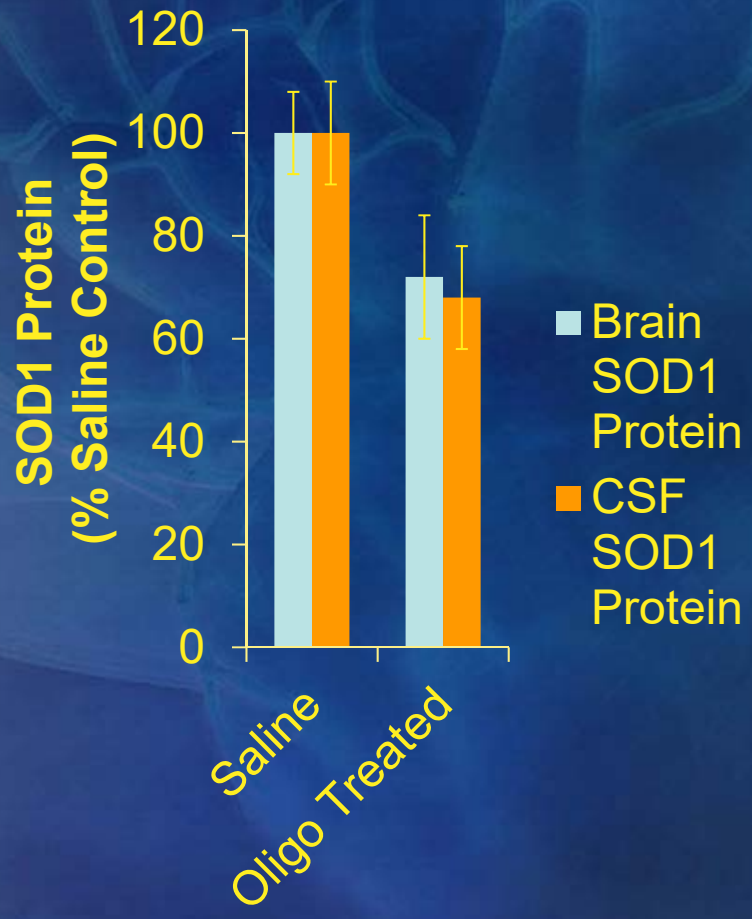

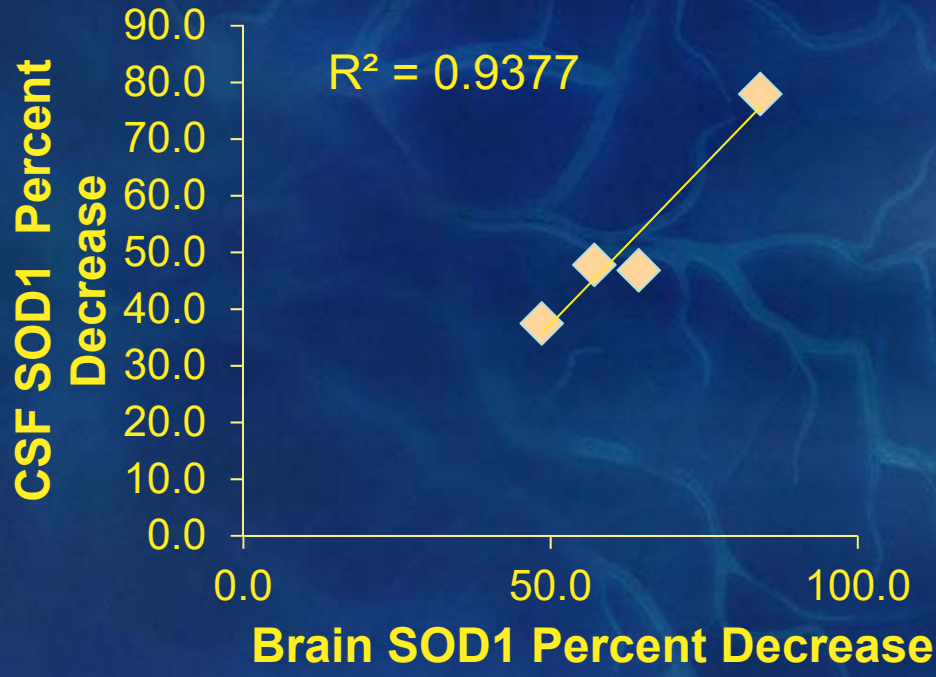

Tim Miller

JS1 Jeremy Shefner, 8/16/2018

SOD1 in CSF Varies Little Over Time

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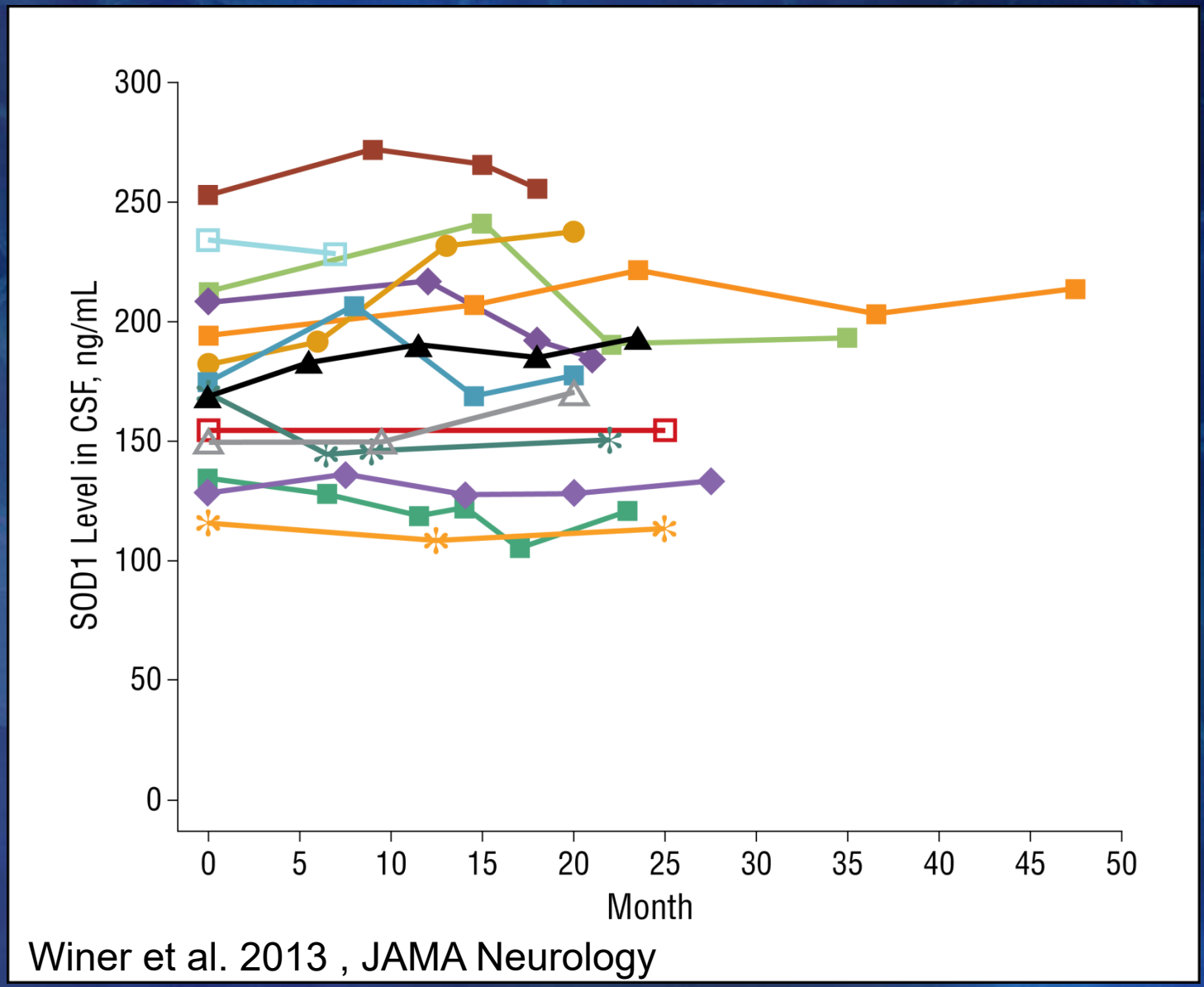
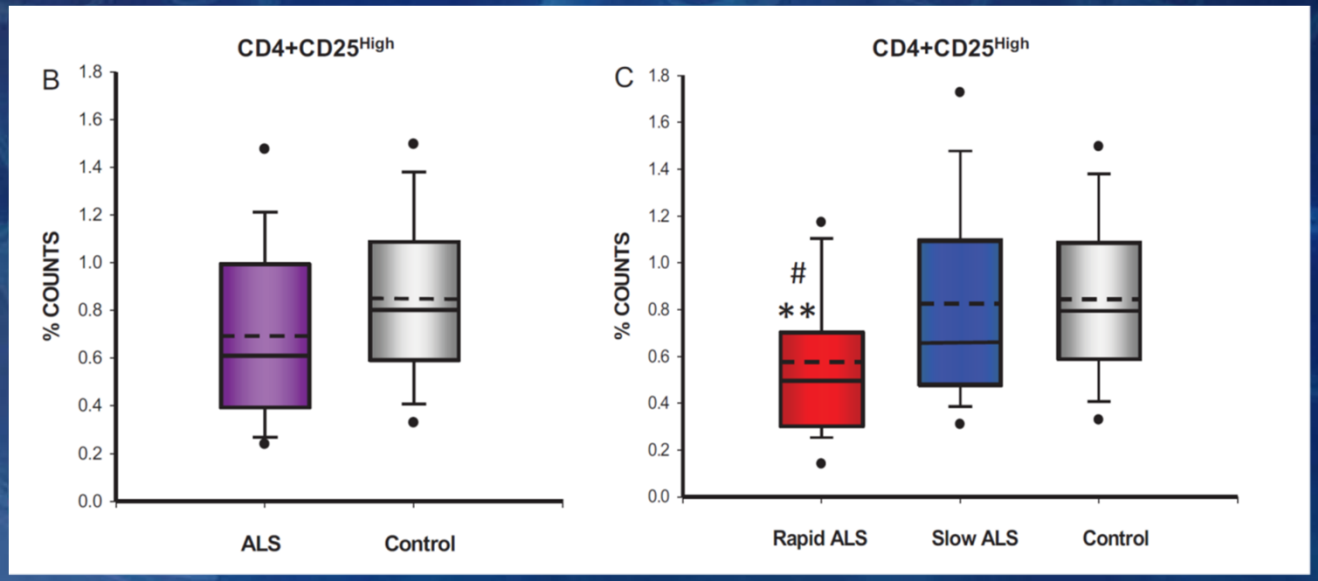
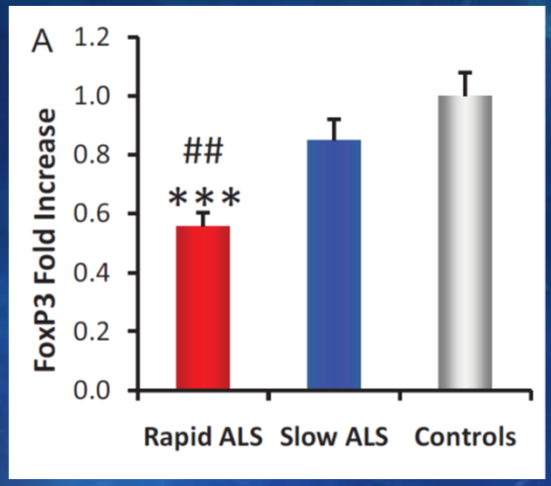


Winer et al. 2013 , JAMA Neurology

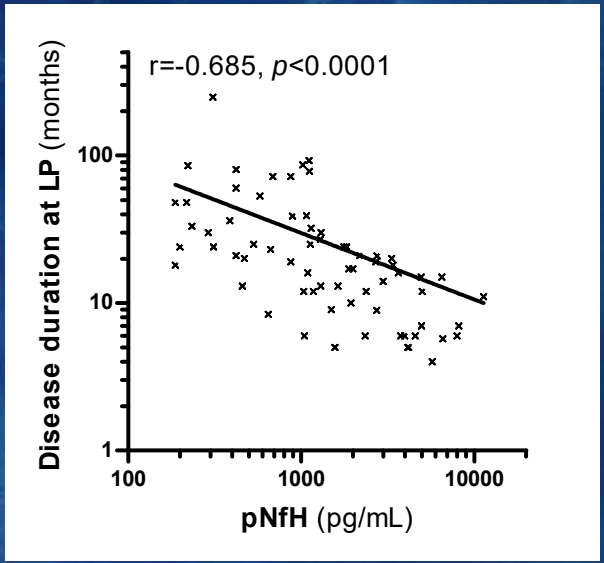
Regulatory T Cell and their function are reduced in ALS



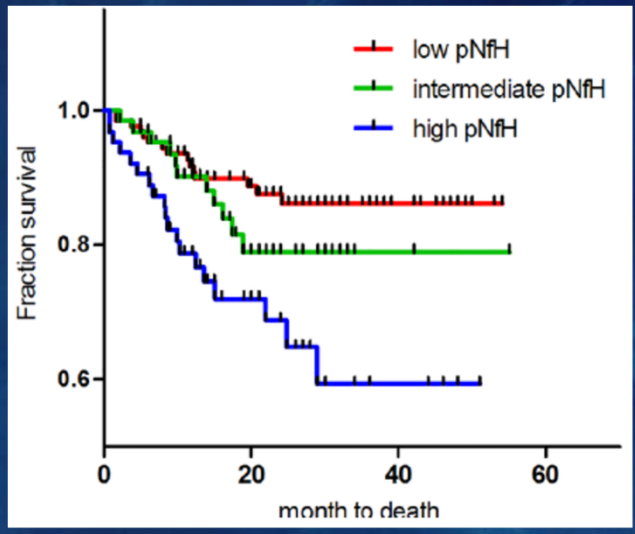


Henkle et al., 2013

pNFH levels correlate to patient survival



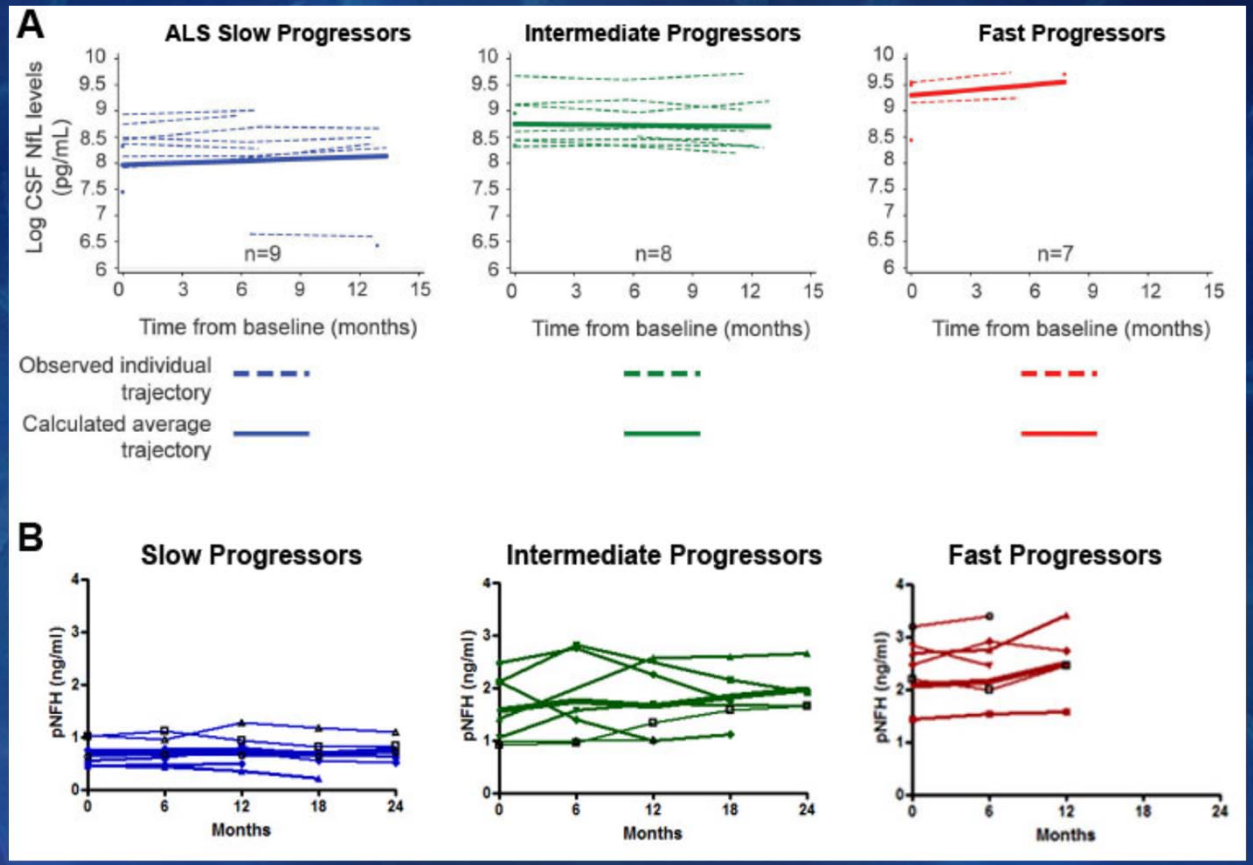
Oeckl et al., (2016): Correlation to survival



Steinacker et al, (2015): 253 ALS Subjects

Level of pNFH in the blood or CSF is a prognostic for patient survival and rate of disease progression

pNFH or NFL levels are relatively stable over time

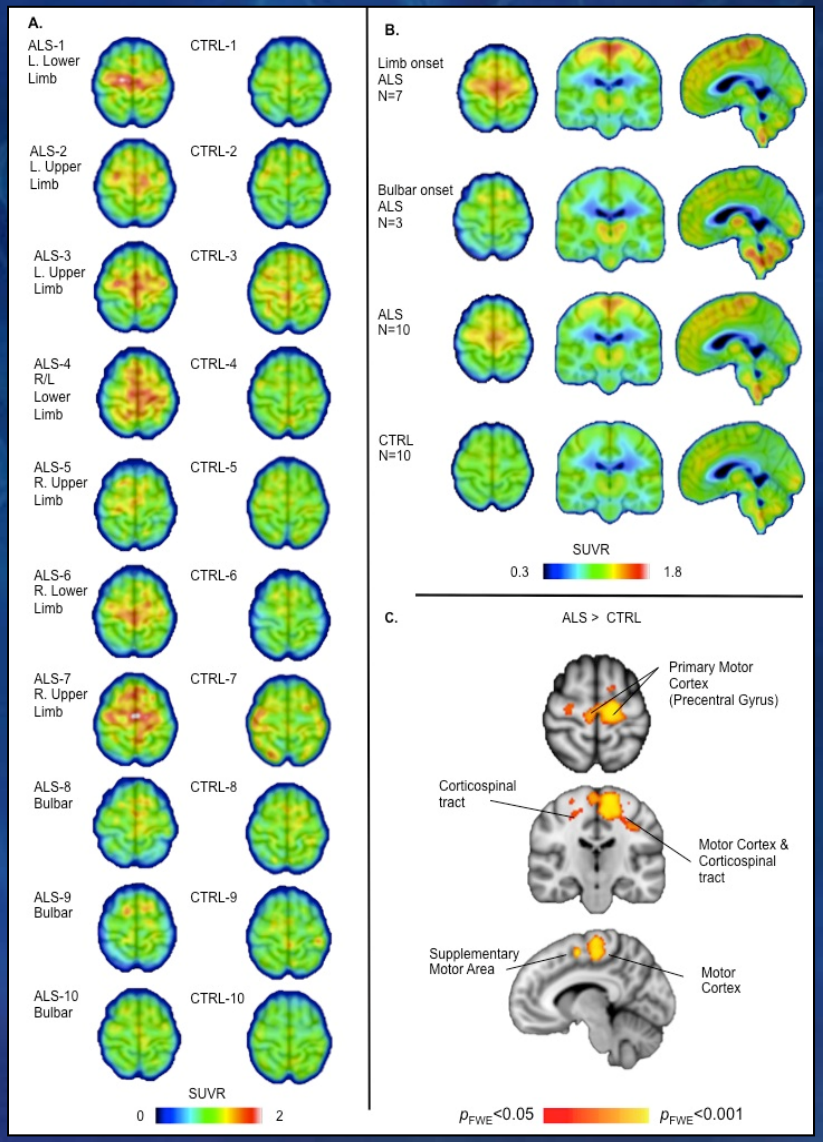


Turner and colleagues (2016)

Bowser lab

Level of pNFH or NFL in blood or CSF could be used to monitor drug effects

[^{11}C]PBR-28 identifies activated microglia in ALS



Increased binding to activated microglia in Motor cortex and other areas of interest for ALS.

Potential use as PD marker in trials that target microglial activation (RNS60, ibudilast)

Zurcher et al. *NeuroImage:Clinical* 7: 409-414 (2015)

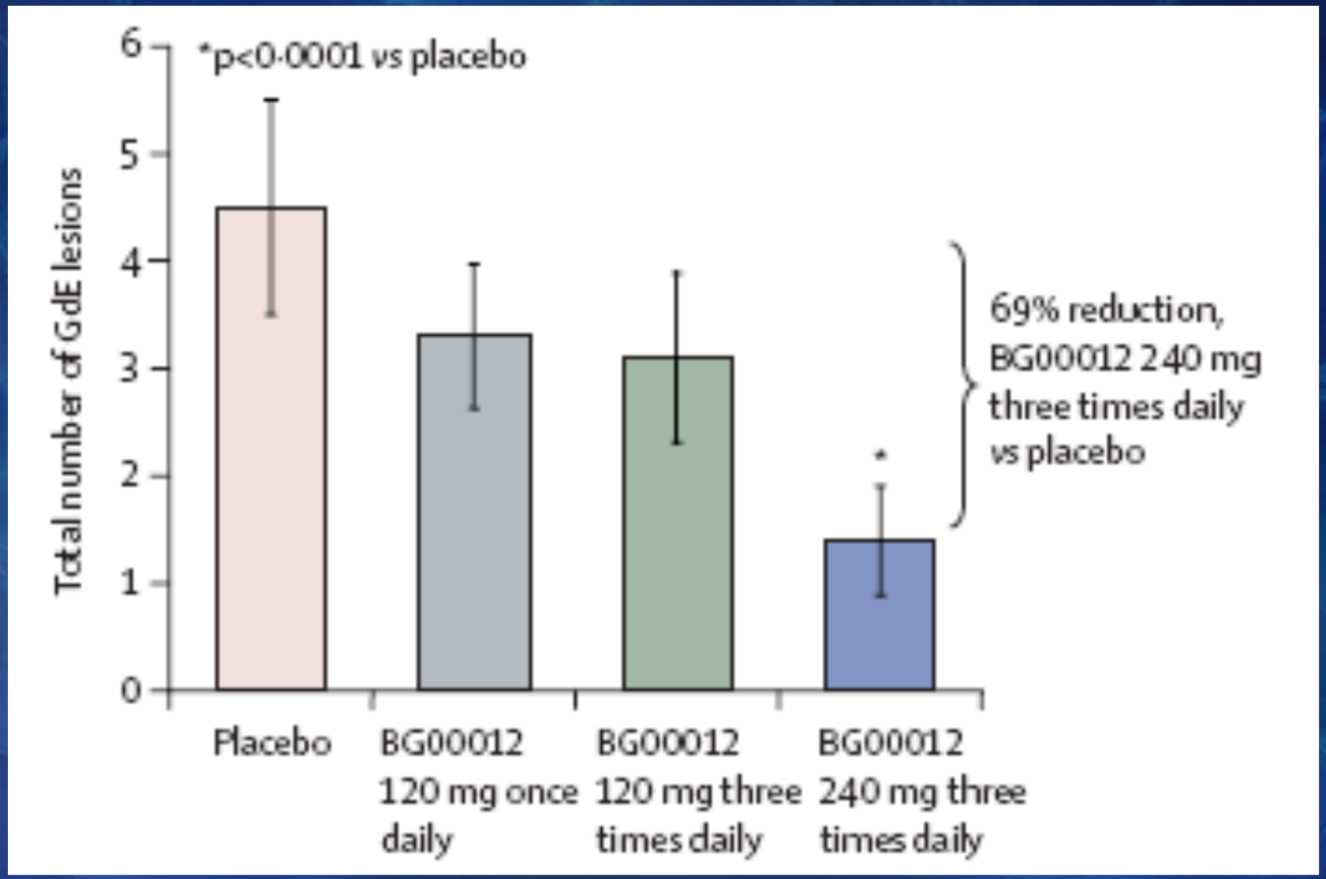
Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study

*Ludwig Kappos, Ralf Gold, David H Miller, David G MacManus, Eva Havrdova, Volker Limmroth, Chris H Polman, Klaus Schmierer, Tarek A Yousry, Minhua Yang, Mefkûre Eraksoy, Eva Meluzinova, Ivan Rektor, Katherine T Dawson, Alfred W Sandrock, Gilmore N O'Neill, for the BG-12 Phase IIb Study Investigators**

- 257 patients, 3 doses vs placebo for 24 weeks
- Primary endpoint: new GdE lesions
  - Clear dose response; lesions reduced by 69% at highest dose
- Secondary endpoint: relapse rate
  - No dose response; overall, relapse rate declined by 32% (p=0.27)

Kappos et al
Lancet 2008

RRMS: Gd+ lesions
A marker of disease activity



Kappos et al
Lancet 2008

Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis

Ralf Gold, M.D., Ludwig Kappos, M.D., Douglas L. Arnold, M.D., Amit Bar-Or, M.D., Gavin Giovannoni, M.D., Krzysztof Selmaj, M.D., Carlo Tornatore, M.D., Marianne T. Sweetser, M.D., Ph.D., Minhua Yang, M.S., Sarah I. Sheikh, M.D., and Katherine T. Dawson, M.D., for the DEFINE Study Investigators*

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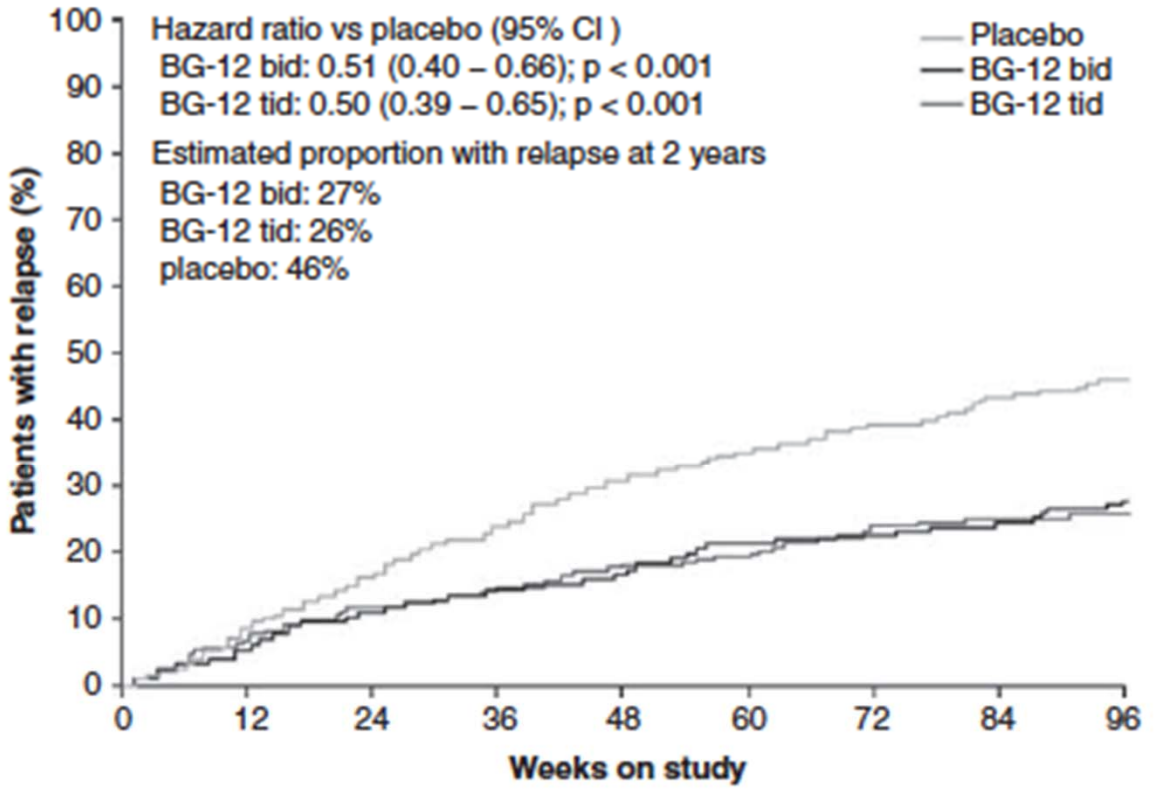


No. at risk

Placebo	408	356	321	282	243	224	205	190	115
BG-12 bid	410	353	324	303	286	267	255	243	154
BG-12 tid	416	346	322	301	286	270	251	244	166

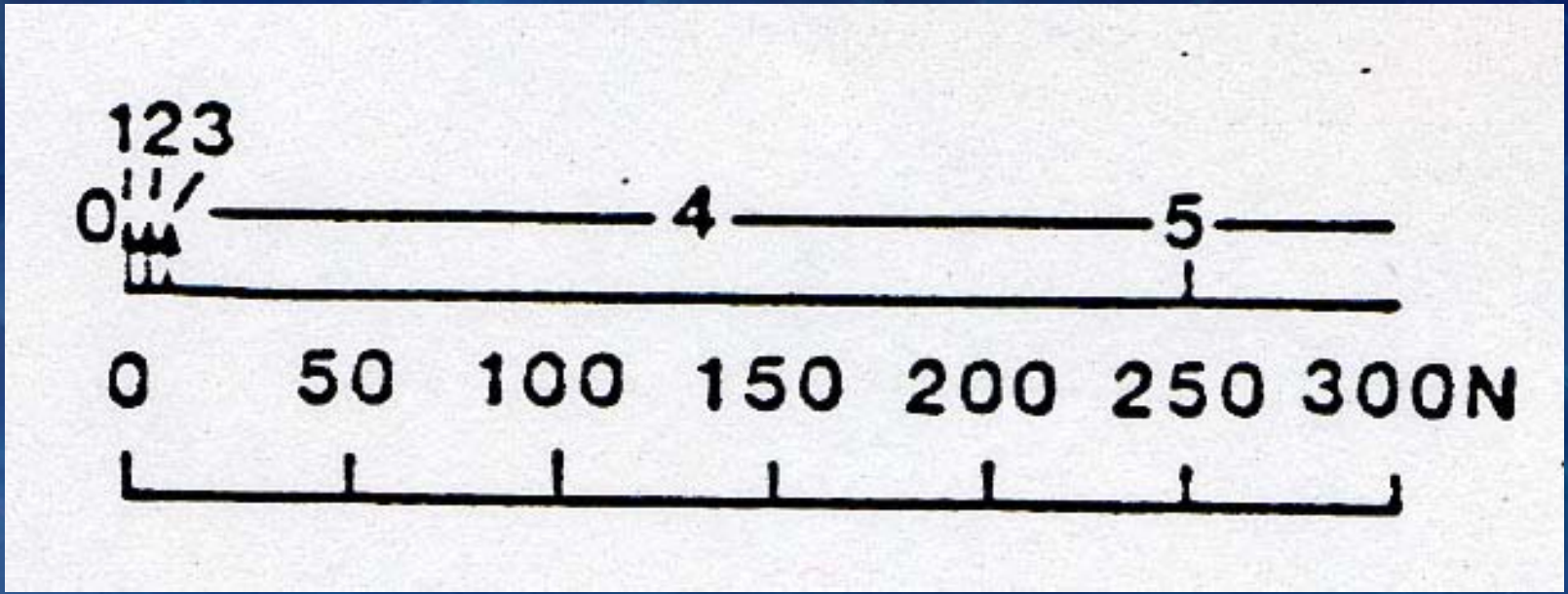
Functional markers serve as intermediate stage endpoints

- Strength
- Pulmonary function
- 6 minute walk
- Timed up and go
- Many others

Methods of assessment can be very important

- Strength is a functional marker that may be important in studying many diseases
- However, how it is measured affects it's utility
  - Single muscle group
    - Vital capacity
    - Handgrip
  - Global Assessment
    - MRC manual muscle testing
      - Any number of muscle can be tested on a 0-5 ordinal scale
    - Quantitative muscle testing
      - TQNE
      - HHD

Uneven Steps Between MRC Grades

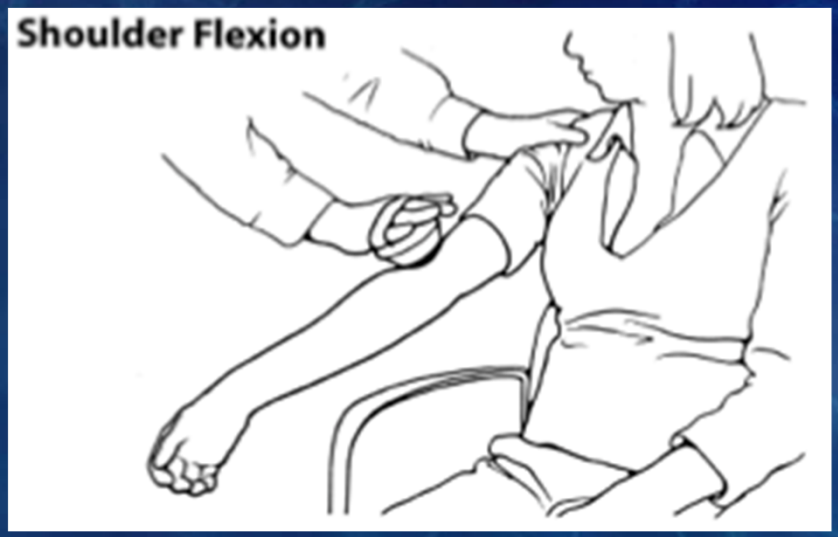


MMT scale compared with actual dynametric force measurement of the biceps brachii

(modified from van der Ploeg: J Neurol, 1984)

Quantitative Muscle Testing: Standardized Training and Validation

- Standardized positions
- Video and hands on training
- Requirement for demonstration of adequate training
- Test-retest reliability criterion



Decline in individual muscle groups

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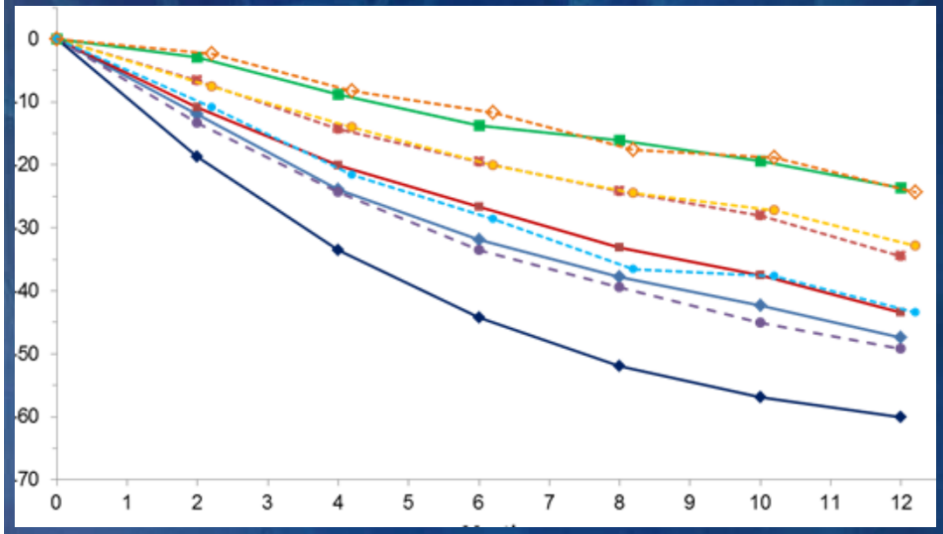
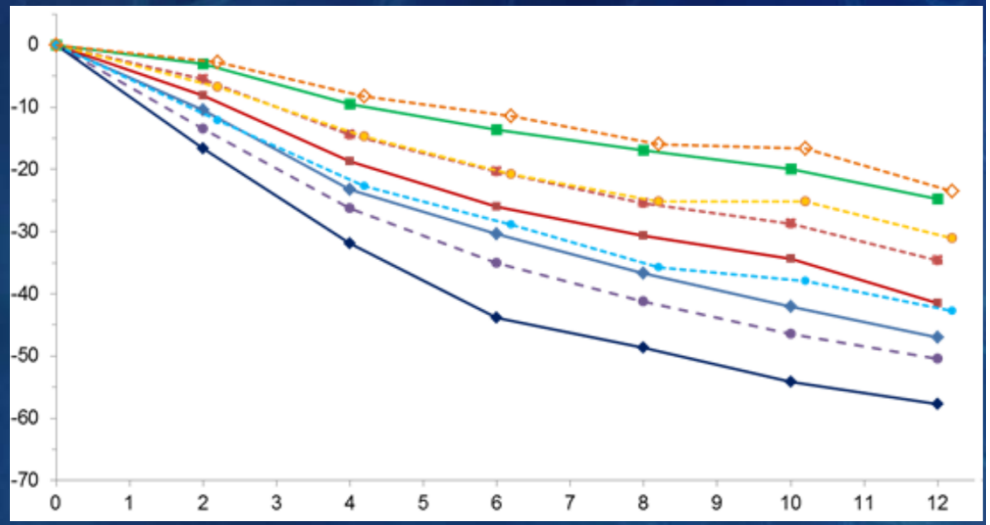
RIght



Left



Months

Biogen Empower Study

Ceftriaxone

Empower

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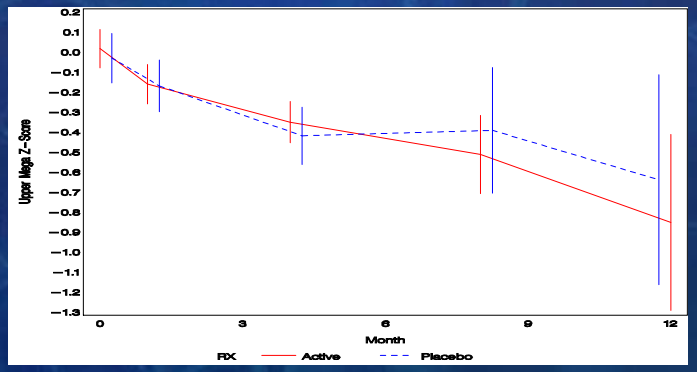
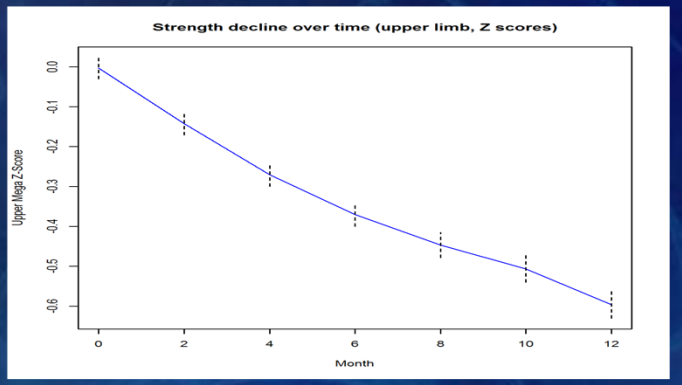
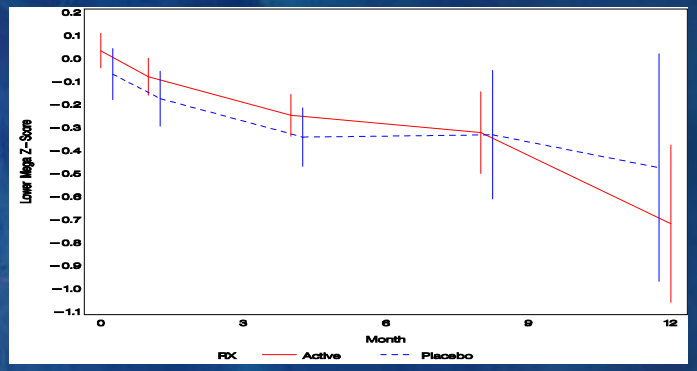
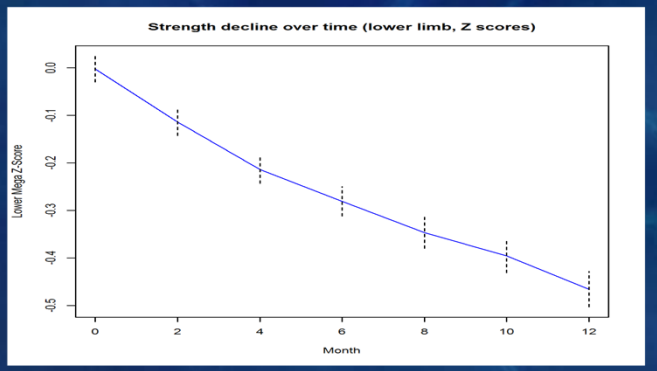
Upper



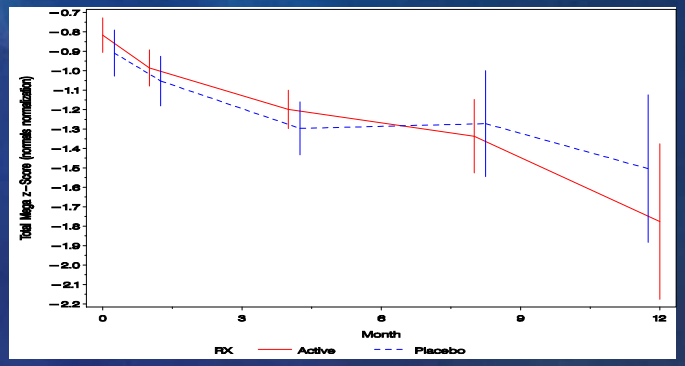


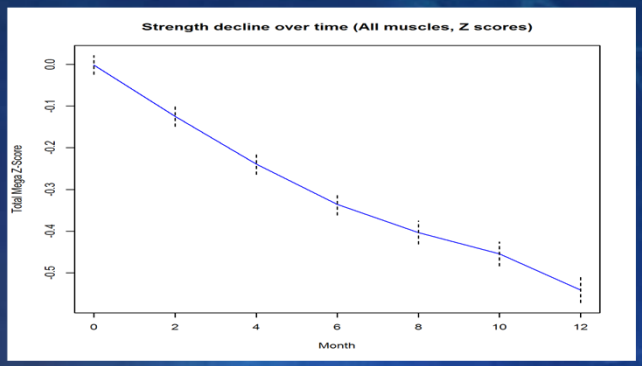
Lower





Total





Proportion of zero force per muscle

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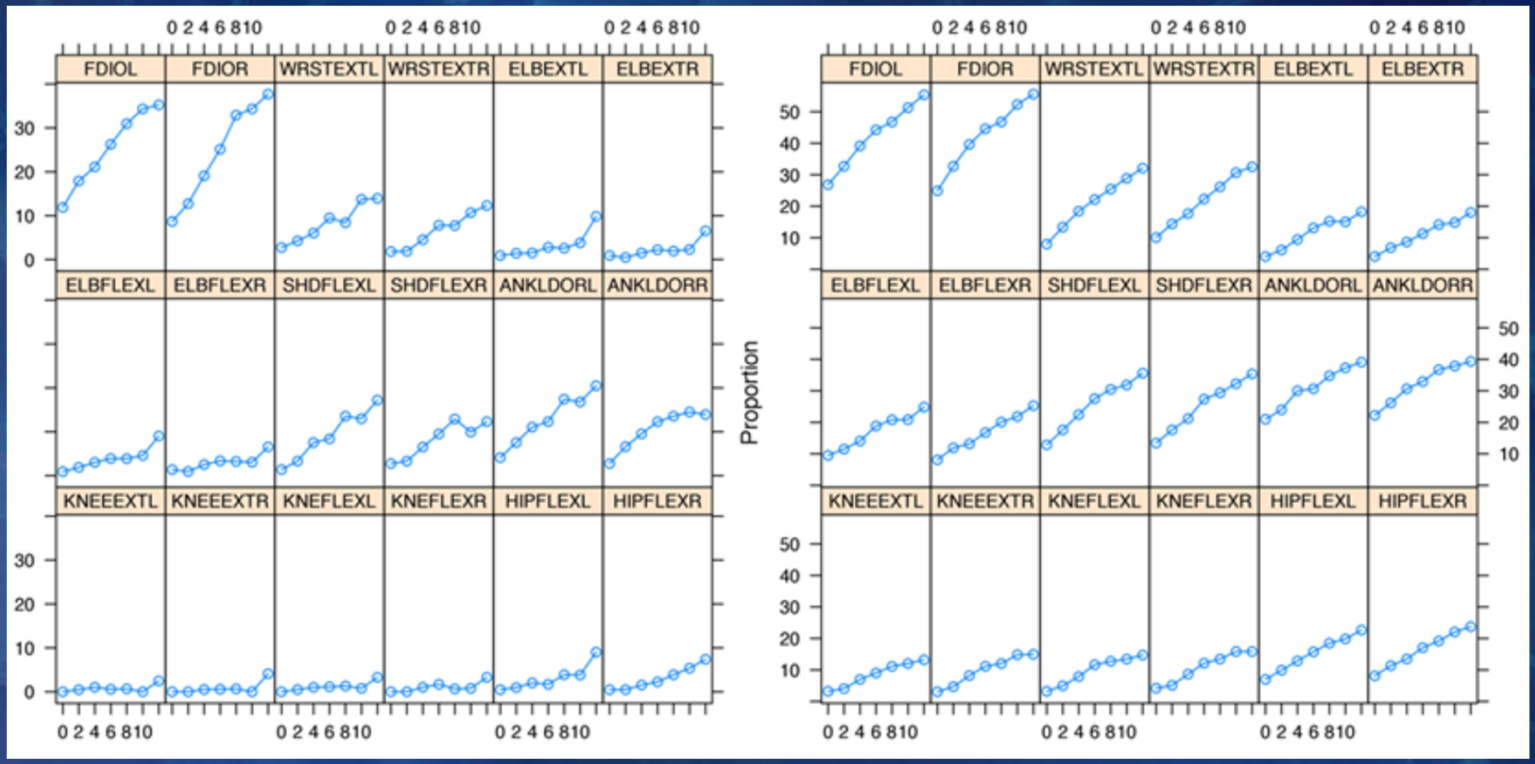
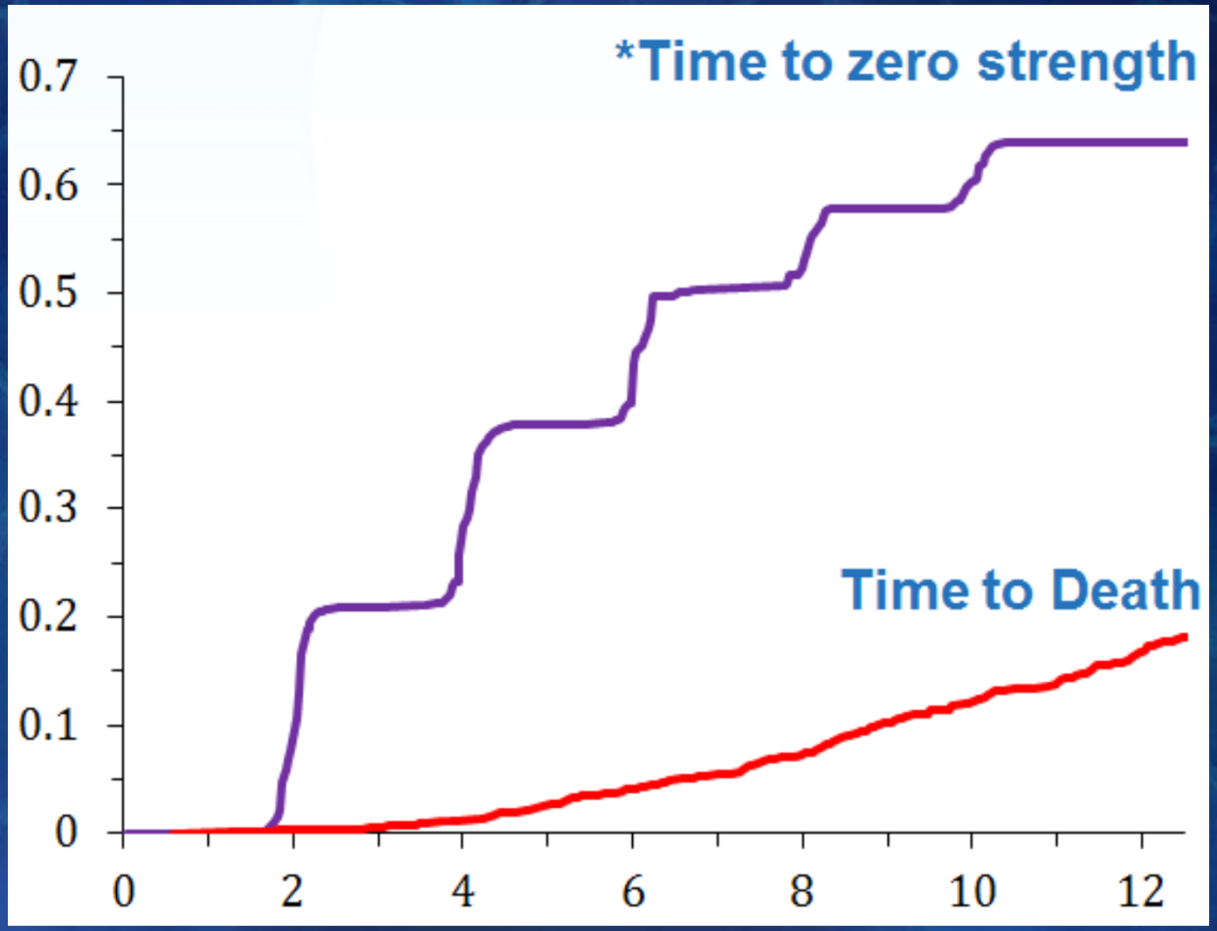
Bulbar Onset

Extremity Onset



Liu et al., 2017

Sensitivity of time to first zero muscle compared to survival



Liu et al., 2017

HHD0 vs other measures

Hazard Ratio of Treated versus Control	Cumulative Proportion of Zero Score Events at Month 12		Sample Size Required* per Treatment Group for 90% Power)
	Control*	Treatment	
0.5	64%	40%	96
0.4	64%	33%	59

Hazard Ratio	Cumulative Proportion of Deaths at Month 12		Sample Size Required* per Treatment Group for 90% Power
	Control*	Treatment	
0.6	17%	11%	610
0.5	17%	9%	366
0.4	17%	7%	237

Difference at Month 12	Mean Change from Baseline over 12 Months		Sample Size Required* per Treatment Group for 90% Power
	Control*	Treatment	
1.5	-11	-9.5	599
2.0	-11	-9	338
2.2	-11	-8.8	279

Liu et al., 2017

Electrical Impedance Myography (EIM)

- Pioneered by Seward Rutkove
- Technique based on the application of high-frequency electrical current to localized areas of muscle with measurement of resulting voltages.
  - Painless
  - Non-invasive
  - Can apply to virtually any superficial muscle
    - Tongue, paraspinals, proximal muscles all possible
- Sensitive to alterations in muscle composition, structure, atrophy

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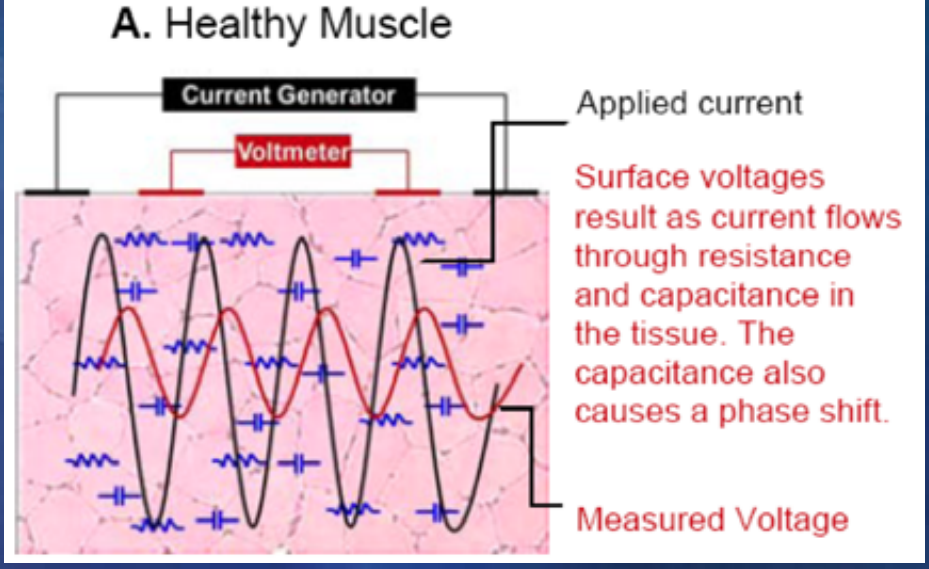

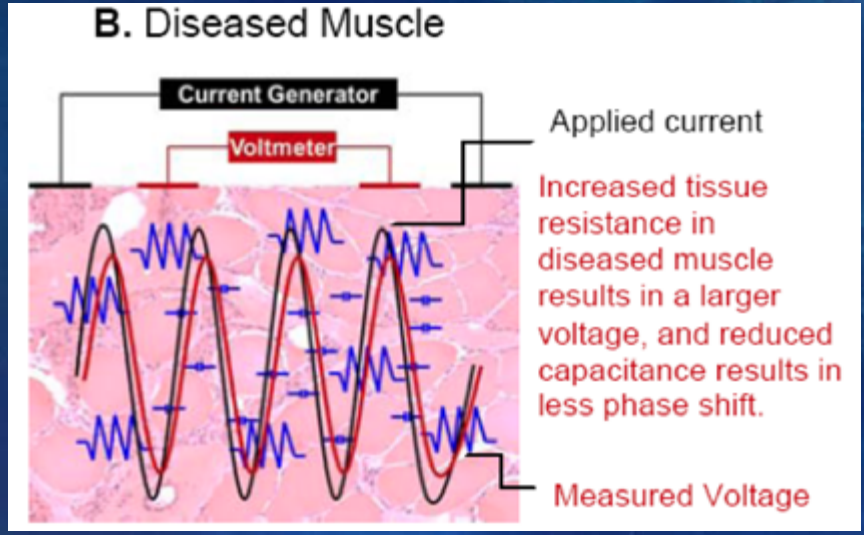

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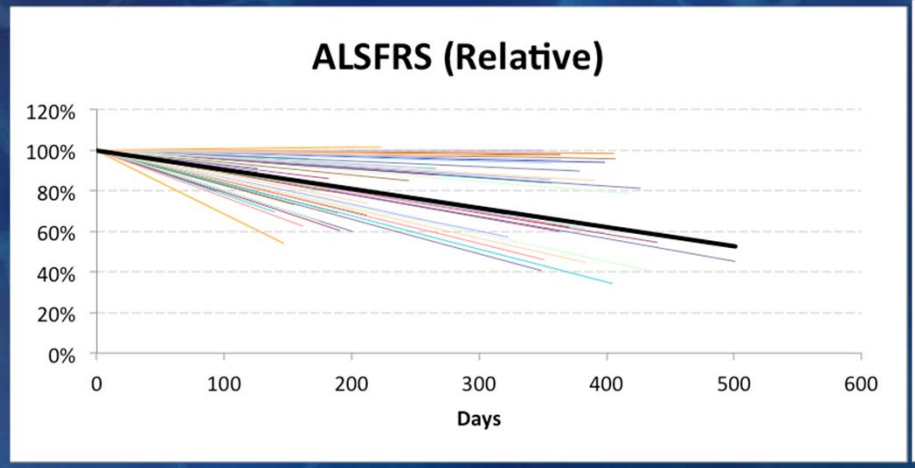
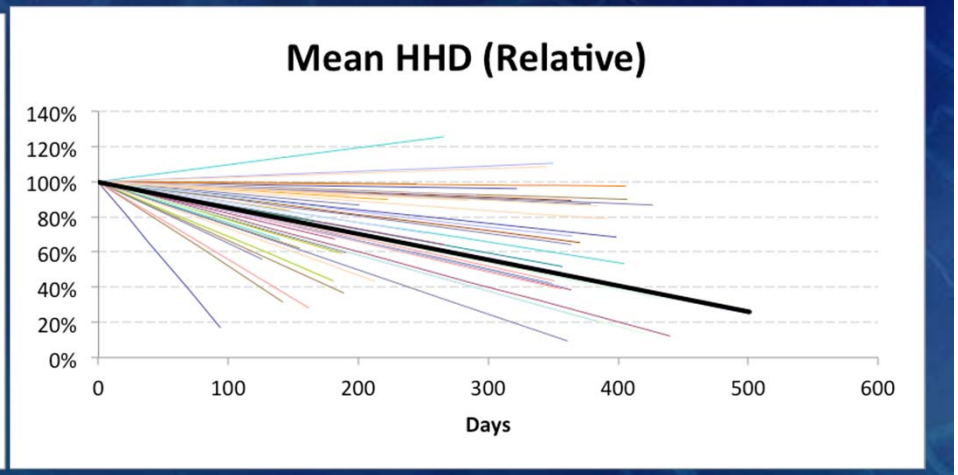
EIM has been studied in several NM diseases

- ALSA-funded Longitudinal Study in ALS
- Ongoing SBIR
- Neuralstem study of stem cells in ALS
- SMA
- Animal models
- A variety of muscle diseases

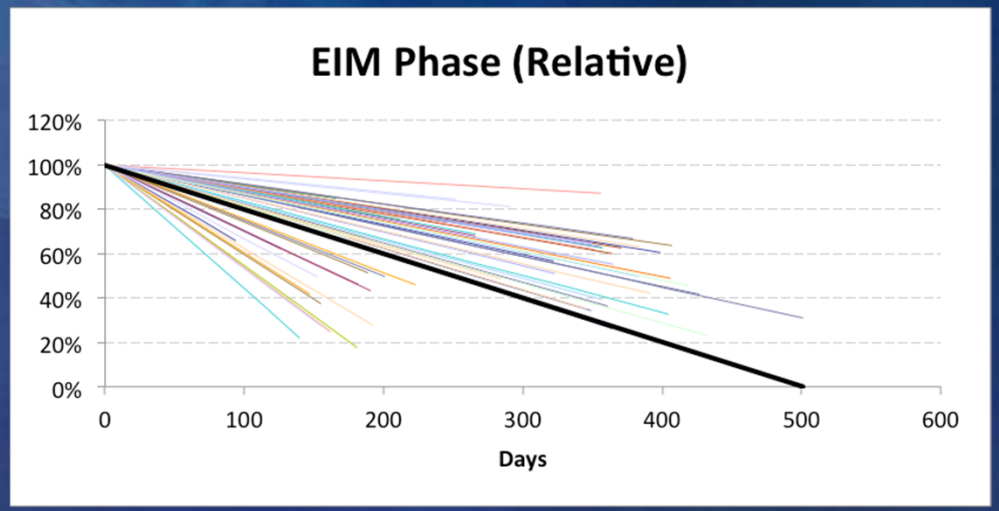
EIM vs other measures



Coefficient of Variation: 0.81



Coefficient of Variation: 0.93



Coefficient of Variation: 0.62

MUNE
Coefficient of Variation: 0.72

From: Rutkove et al., 2012
Shefner et al., 2011

Clinically Relevant Endpoints

- Clinically relevant endpoints are required for phase 3 trials
  - May be subjective (I feel better) or objective (I can walk across the room better)
  - Survival
  - Time to event
- However:
  - Clinical Relevance is often a fuzzy target
    - Is vital capacity clinically relevant?
    - Is strength clinically relevant?
  - Clinical relevance does not necessarily imply relevance to potential therapeutic mechanism
  - Issues of variability may limit utility
    - Disease related
    - Measure related

Functional Scales

- Functional Scales are considered clinically relevant
  - They directly ask patients about functional capacity, or assess these functions by observation
  - However, size of effect that is important is not always clear
  - The scale properties are critical and often undefined
    - Interval Scaling
    - Continuous vs discrete

Functional Scales

- Can be disease or attribute specific
- Scoring of individual items should have characteristics of an interval scale: i.e., a change of 1 unit should be the same anywhere on the scale
- Often comprised of well defined domains capable of assessing different aspects of function

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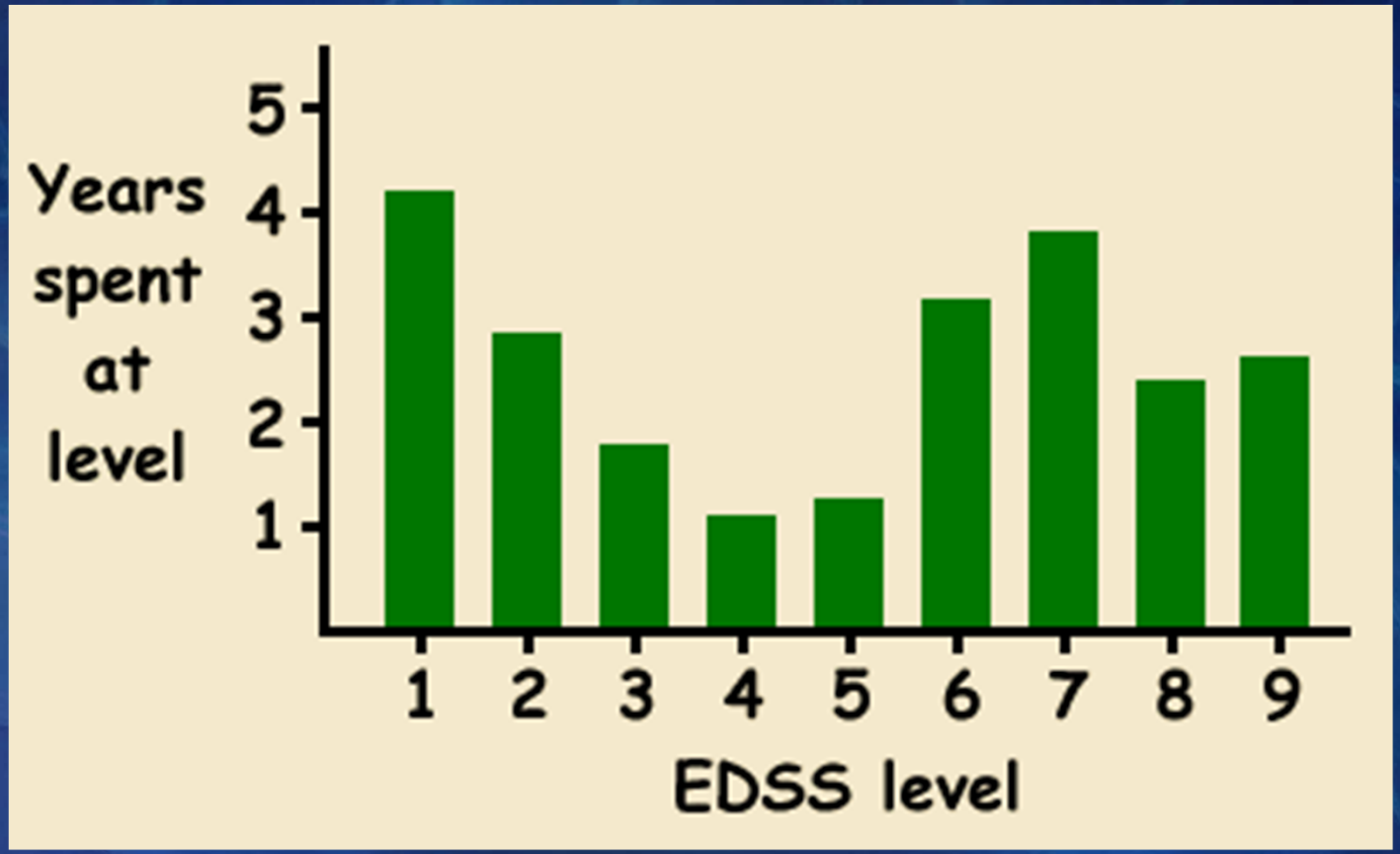
Limitations of Functional Scales

- Often combine attributes so it is difficult to attribute a change to a specific function
- The minimum clinically significant change is undetermined
- Lack of interval scaling may mask small changes
- Variability of scoring may limit use or increase sample size
- Individual items are usually strikingly non-linear; averaging many items together can create appearance of linearity

Commonly Used Functional Scales

- Kurtzke EDSS
- ALS Functional Rating Scale- Revised (ALSFRS-R)
- Unified Parkinson's Disease Rating Scale (UPDRS)
- Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)
- Modified Rankin Scale

Disability Scores do not linearly decline in MS



From: www.mult-sclerosis.org

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ALSFRS-R

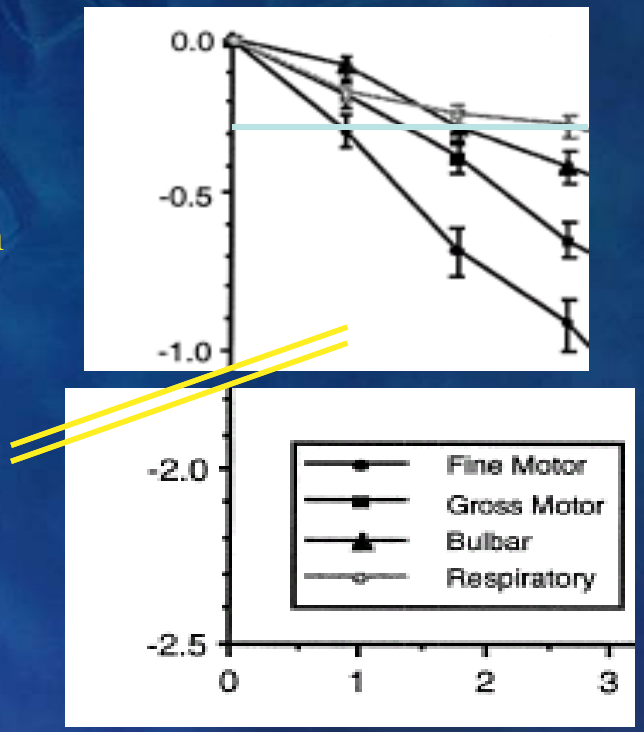
- Speech
- Salivation
- Swallowing
- Handwriting
- Cutting food, handling utensils
- Dressing and Hygiene
- Turning in bed and adjusting bed clothes
- Walking
- Climbing stairs
- Dyspnea
- Orthopnea
- Respiratory insufficiency

From: Cedarbaum et al, 1999

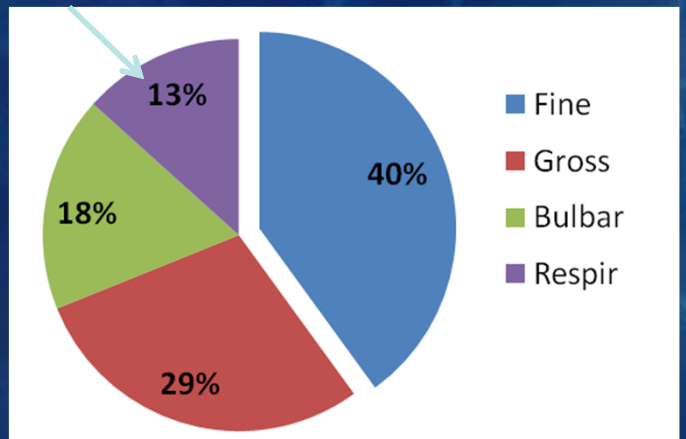
ALSFRS-R Sub-Domains

- Changes in sub-domain scores validated across two studies conducted a decade apart in time

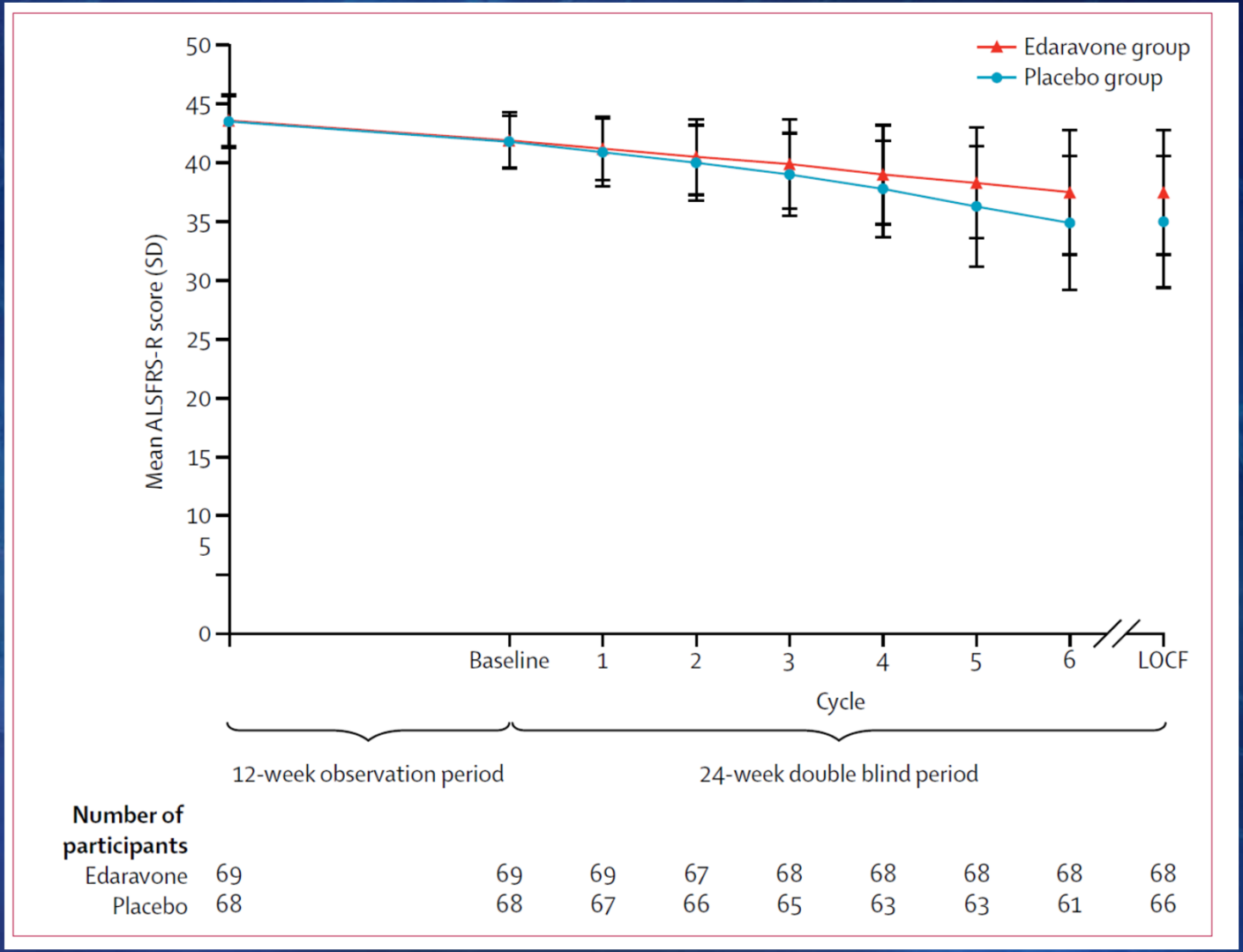
Cedarbaum et. al 1999



Respiratory questions are 25% of the scale, but only 13% of the change over time



Edaravone Phase 3 Trial



Number of participants									
Edaravone	69	69	69	67	68	68	68	68	68
Placebo	68	68	67	66	65	63	63	61	66

Edaravone ALS 19 Study Group, 2017

Binary/Time to Event

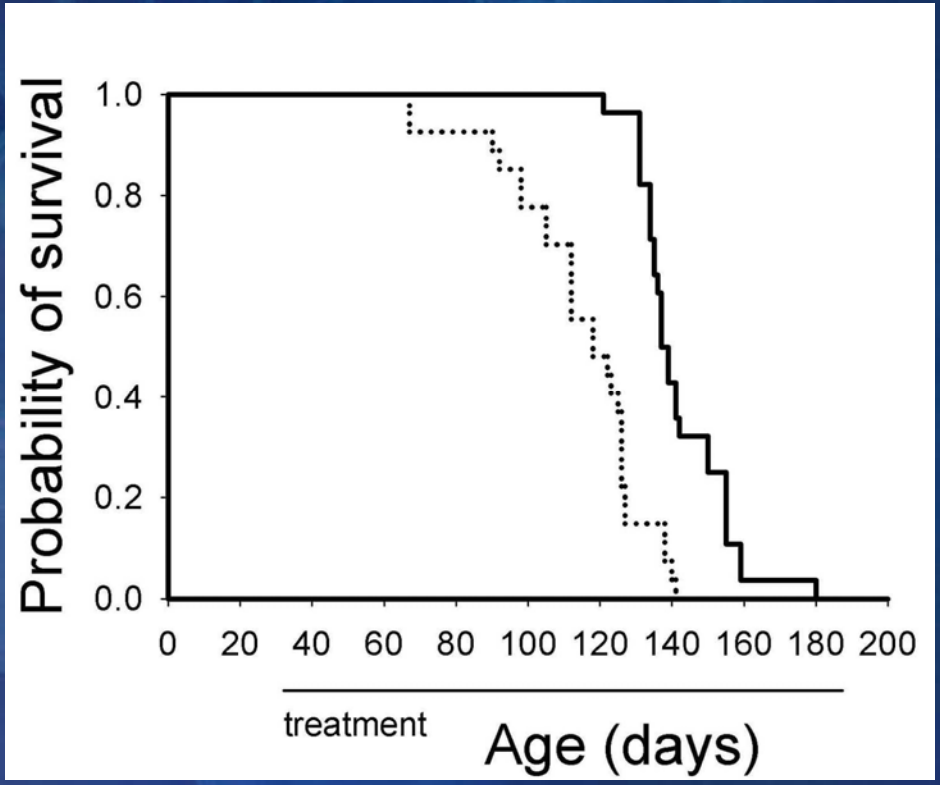
- Advantages
  - Easy to understand
  - Power calculations are straightforward
- Disadvantages
  - Only subjects who reach endpoint are useful
  - Only 1 change of state is deemed important

Time to Event: Survival

- Useful only when events are likely to occur
  - Stroke
  - SAH
  - ALS
- Depending on disease state and target, may not be sensitive to experimental intervention
  - Nuedexta for Emotional Lability
    - Approved for ALS, but unlikely to impact survival

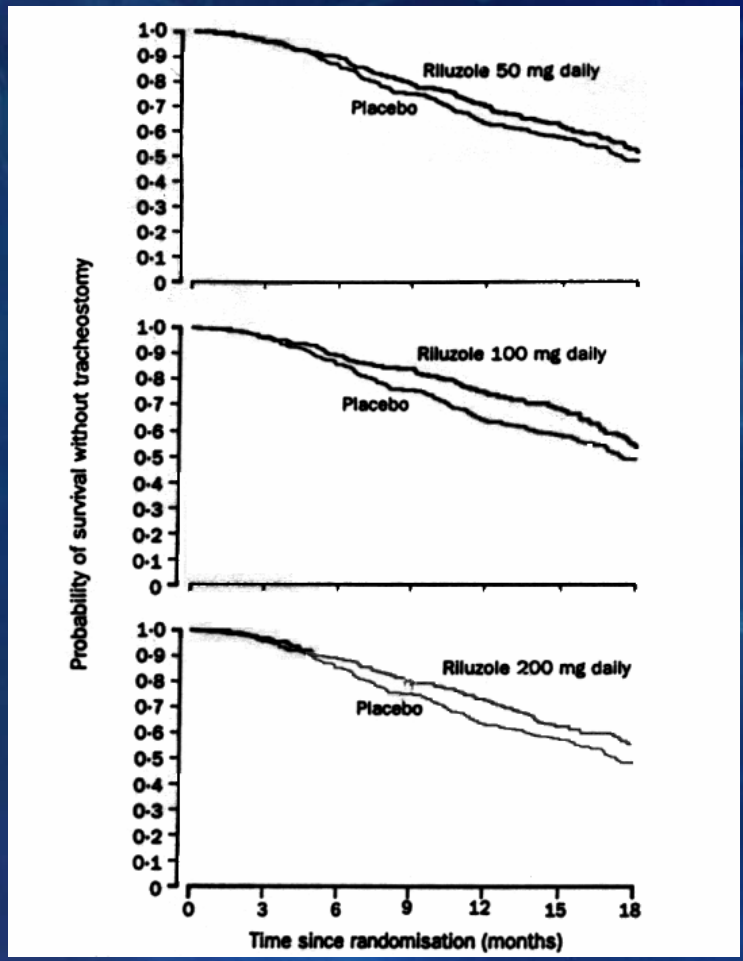
Survival as an outcome measure in ALS

MICE



From: Drachmann et al., 2000

PEOPLE



From Lacomblez et al., 1996

Time to event is an example of a binary endpoint

- Time to event endpoints
  - Survival
  - Hospital readmission
  - Time to new vascular event
  - Time to initiation of NIV
- Other binary endpoints
  - Achieving functional independence
  - Achieving independent ambulation

Binary outcomes

Adapted from Saver, 2007

Table 1. Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities, but able to take care of self without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

A 7 point scale is often dichotomized (0-2 vs 3-6) for primary analysis

How does one choose which biomarker/endpoint is most appropriate?

- Development stage
- Qualities intrinsic to marker/endpoint
  - Relevance to clinically important endpoints
  - Variability
    - Measurement related
    - Disease related
  - If a binary endpoint, how many events expected?

BARROW
Neurological Institute

Summary

- The choice of endpoint is critical in the design of clinical trials
- Endpoints should be reliable, meaningful, and sensitive to disease modification
- An appropriate choice of endpoint should increase the probability of correctly determining whether the goals of the study are met
- The currently available toolbox of measures is not adequate to meaningfully shorten trials or reduce sample size for most neurological diseases