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RARE DISEASE WORKSHOP SERIES
Improving the *Clinical Development Process*

The necessity for improving the accessibility to multi-domain assessments in rare disease treatments

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Evaluation of Multi-system Diseases: An area in need of innovation

- Original targets of drug development
 - Single clear indication (HTN, Asthma, Infection)
 - Driven by single problems/primary endpoints
- Next generation of diseases targets
 - Multisystem complex, heterogeneous diseases
- Does the current paradigm for clinical evaluation make sense for multisystem diseases?



Aldurazyme Phase 3 Study: Composite Endpoint

Placebo

Patient	FVC 11%	6MWT 54m	SHFLEX 20 deg	AHI 10 ev/hr	ACUITY 2-lines
1			Decline		
2					
3		Decline			
4	Decline		Improve		
5		Decline	Not Available		
6		Decline	Improve	Decline	
7		Improve			
8				Not Available	
9	Improve			Improve	
10	Decline			Not Available	
11				Improve	
12		Decline			
13		Decline			
14		Improve			
15	Decline		Decline		
16		Improve			
17			Decline	Decline	
18			Decline		
19			Decline		
20		Decline			
21	Improve			Decline	
22					
23			Decline		

Aldurazyme

Patient	FVC 11%	6MWT 54m	SHFLEX 20 deg	AHI 10 ev/hr	ACUITY 2-lines
24	Improve		Decline		
25	Improve	Improve			Improve
26		Decline			
27		Decline			
28		Improve	Improve		Improve
29				Improve	
30	Decline	Improve	Improve	Not Available	Improve
31	Improve	Improve	Improve		
32	Improve				Improve
33		Improve	Improve		
34			Decline		
35	Improve	Improve	Improve		Improve
36					
37			Not Available	Improve	
38	Improve		Decline		
39	Improve	Improve	Improve	Improve	
40		Decline	Decline		
41					
42			Not Available	Not Available	
43		Decline			
44	Improve		Not Available		
45				Improve	

Clinically
Significant
Changes



Improve
No Change



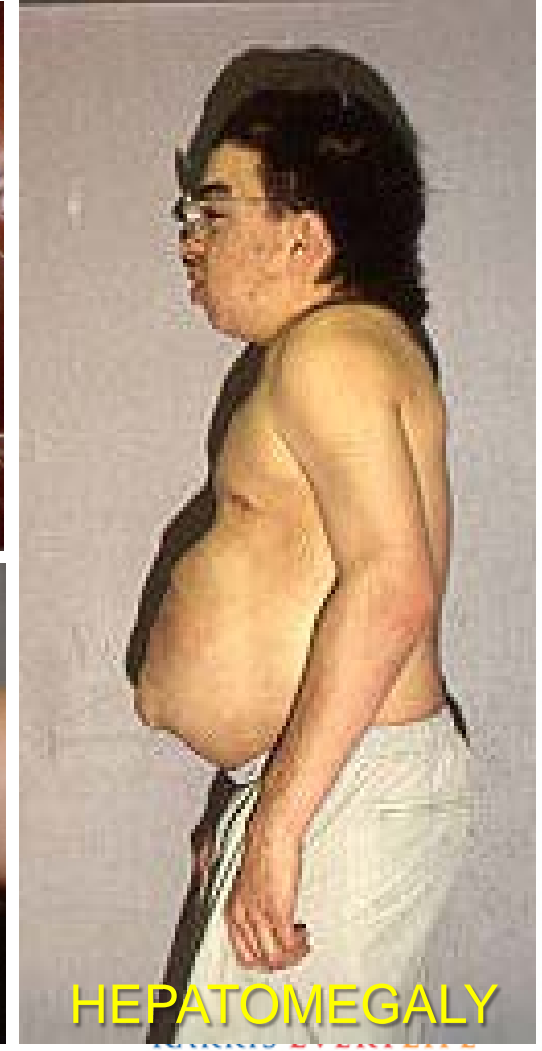
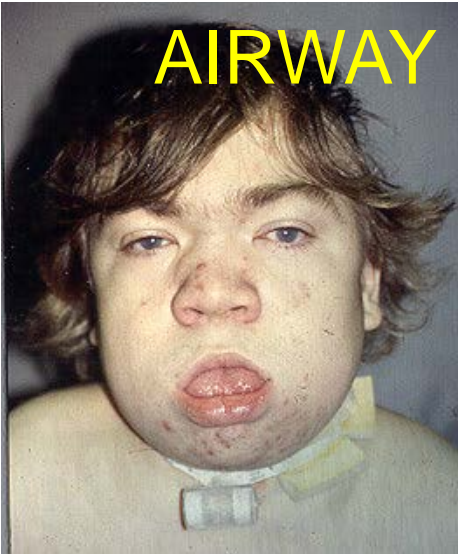
Decline
Not Available



Evaluation of complex heterogeneous diseases will not be simple

- Heterogeneity in disease domain severity
- Hard to know how interplay between clinical domains affects outcomes
- Irreversibility/progression
- Few patients to explore issues

MPS I: Devastating multi-system disorder





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Variability between patients



Patients from the first MPS I enzyme study



How heterogeneous is disease?

- 6 min walk test $\sim 1/3$ rd normal
- Forced vital capacity $\sim 1/3^{\text{rd}}$ normal
- Shoulder ROM $1/2 > 90$ degrees
- Sleep apnea AHI $1/2 < 10$ events/hr
- Visual acuity $2/3^{\text{rd}}$ near normal



Conducting a clinical study

- Pick the endpoint
- Select “right” affected patients
- Study the endpoint
- File for approval
- Get a single claim



What does it really mean?

- Do we understand what the drug does for all aspects of each patient?
- Do we understand the complexity of who benefits?
- Do we understand how disease heterogeneity varies response?
- Do we understand safety in all types?

I have a dream...





New study in a new disease

- **Enroll all patients** except in whom harm or benefit is not justified
- Treat all patients
- Evaluate 5-6 major domains of disease (individual endpoints)
- Analyze data by continuous variable methods for significance



Analysis

- Each patient evaluated only for each disease domain affected
(a priori criteria for subsets)
- Each domain evaluation managed for clinical meaningful in evaluation
- Multi-domain continuous variable analysis completed



Interpretation if positive study

- Each domain evaluated independently using proper affected subset
 - Statistical significance
 - Responder/clinical significance
- Label constructed from positive primary and individual secondaries



Benefits

- Safety in a wide variety of patients
 - No selection based on 1^o Endpoint
- Learn about more domains
- Avoids hazard of picking wrong on a primary (manage multiplicity)
- Capture benefit across multiple domains in variable patients