Rare diseases: Methodology and other challenges

Charlotte Gaasterland

I AM Summer School on Rare Diseases

July 2017

Duchenne Muscular Dystrophy

Rare disease: 1 in 5000 male births

X-linked recessive mutation

No dystrophine is made in the muscle cells

Duchenne Muscular Dystrophy

2007: Prosensa develops a promising new drug: Drisapersen

2009: GSK buys Prosensa

A large phase 3 trial is started (N=186)

First results are all positive:

‘I am able to run, bike, and do a backflip on the trampoline’

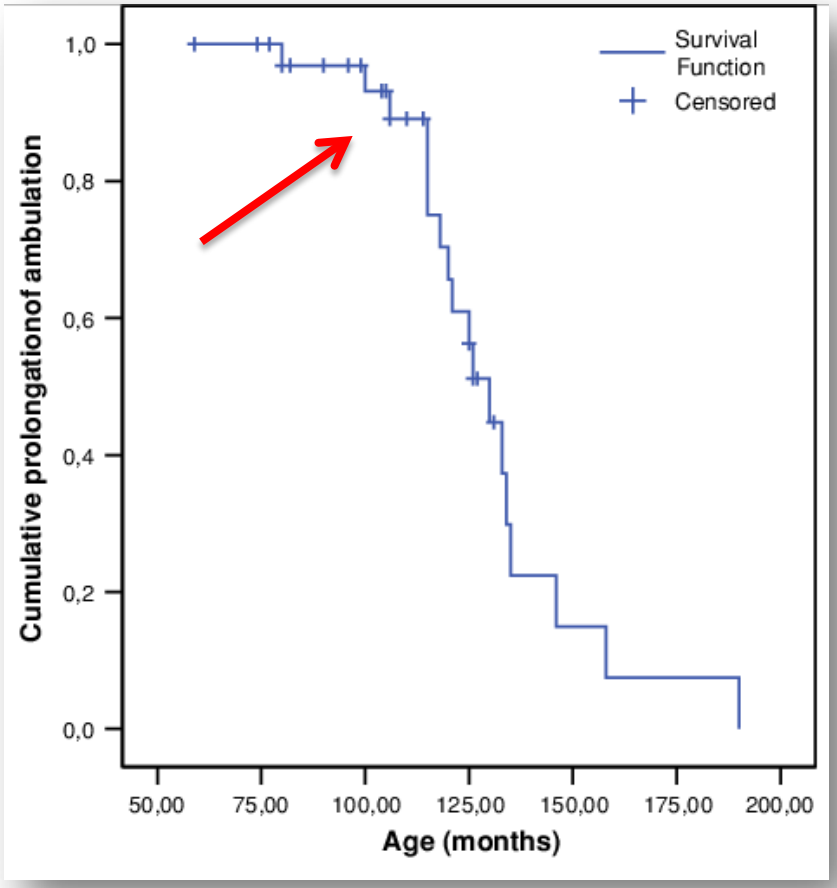
Duchenne Muscular Dystrophy

2013: ‘The results are not what we expected’

Difference on the 6 minute walk test: 10 m.

Clinically relevant?

Duchenne Muscular Dystrophy

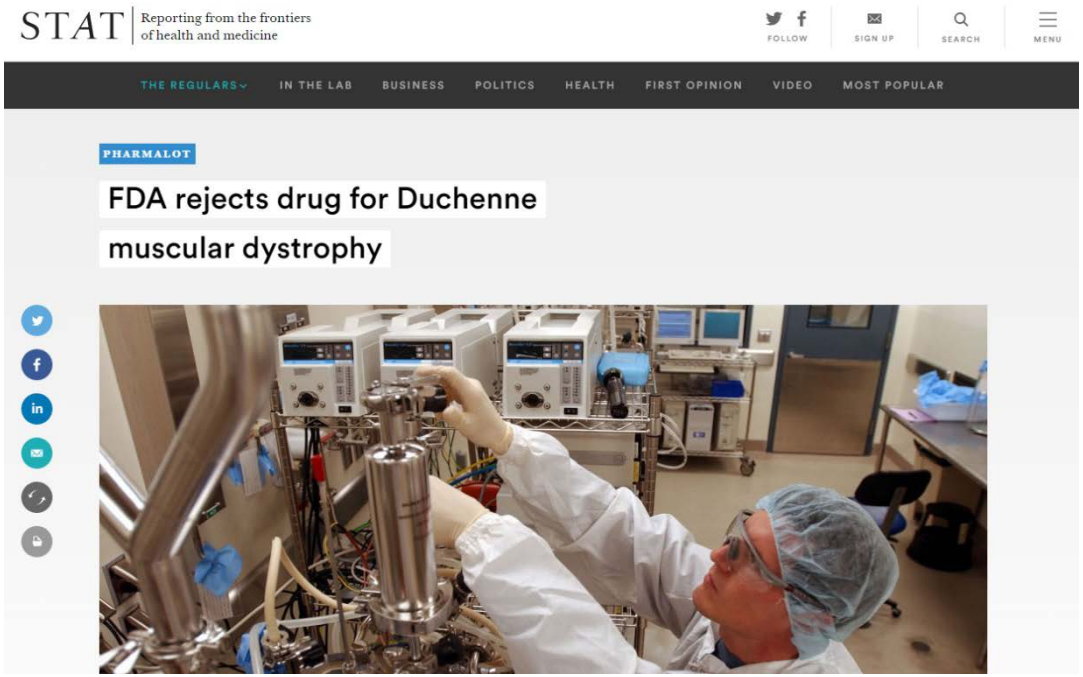


After extra analyses:

Drisapersen works better in young boys

November 2015: FDA declines Drisapersen

Duchenne Muscular Dystrophy

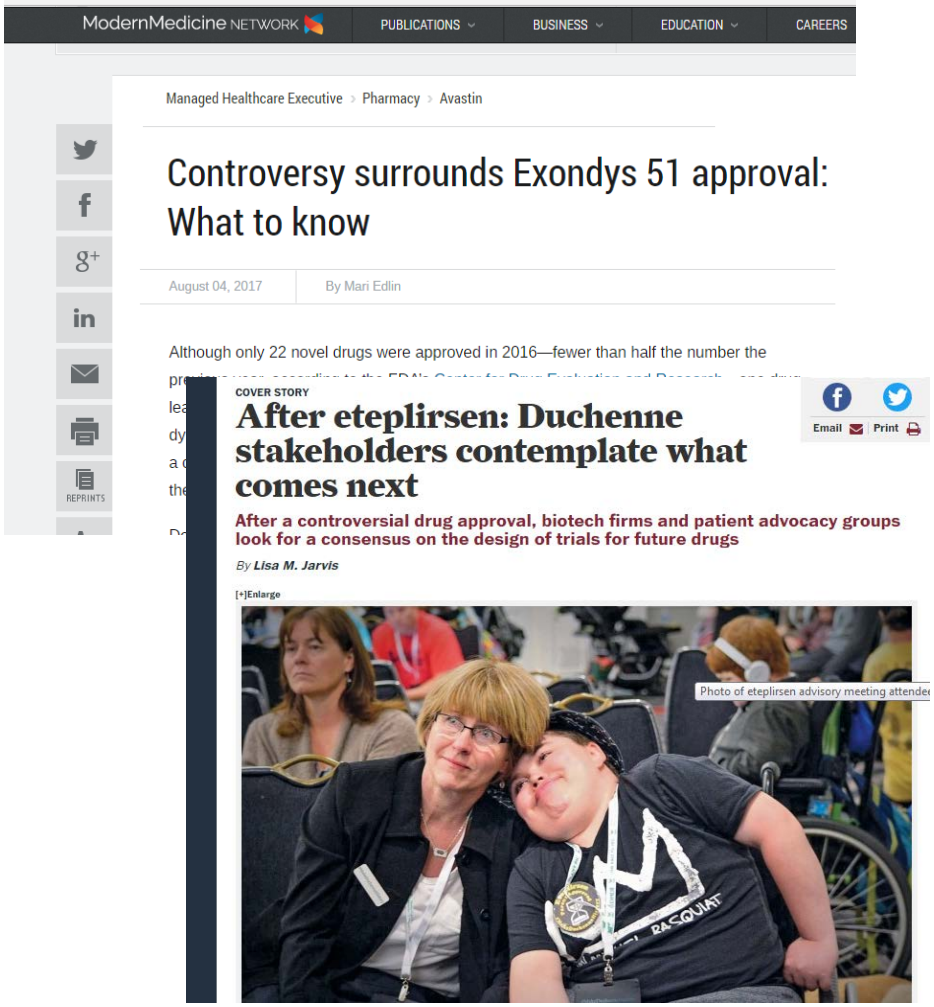


"I am deeply disappointed in the FDA's decision. The FDA did not consider the strong patient voice in favor of this drug. The boys who have been on drisapersen and their parents wanted to see drisapersen approved. The top Duchenne specialists supported the approval of drisapersen. As a mother of a boy with Duchenne and as the leader of an advocacy organization, I feel strongly that drisapersen has substantial benefit to boys with Duchenne."

Duchenne Muscular Dystrophy

2016: a different drug, Eteplirsen, is allowed on the market by FDA

After a trial in 12 boys, without placebo arm



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Controversy surrounds Exondys 51 approval: What to know

August 04, 2017 | By Mari Edlin

Although only 22 novel drugs were approved in 2016—fewer than half the number the

COVER STORY

After eteplirsen: Duchenne stakeholders contemplate what comes next

After a controversial drug approval, biotech firms and patient advocacy groups look for a consensus on the design of trials for future drugs

By ***Lisa M. Jarvis***

[+]Enlarge

Photo of eteplirsen advisory meeting attende

Hurdles to take for a rare disease patient

1. Find a diagnosis and a network of patients

2. Find people who will research your disease

3. Find a possible new drug

4. Find other patients who want to be included in a trial

5. Get the agency to allow the drug on the market (EMA, FDA)

6. Get your country to reimburse the drug

Rare diseases – a field of problems

Do potential drugs for rare diseases need the same quality of evidence?

How do we know we have chosen the right inclusion criteria for a trial?

Is a Randomized Controlled Trial always the best possible solution?

What is the proper outcome measure and measurement instrument?

How do we make sure that drugs reach patients as soon as possible?

Should we collaborate on a larger (European) scale?

How much money are we willing to spend on rare disease drugs?

Three European collaborations

asterix

IDeAl

Integrated DEsign and AnaLysis of small population group trials

InSPiRe

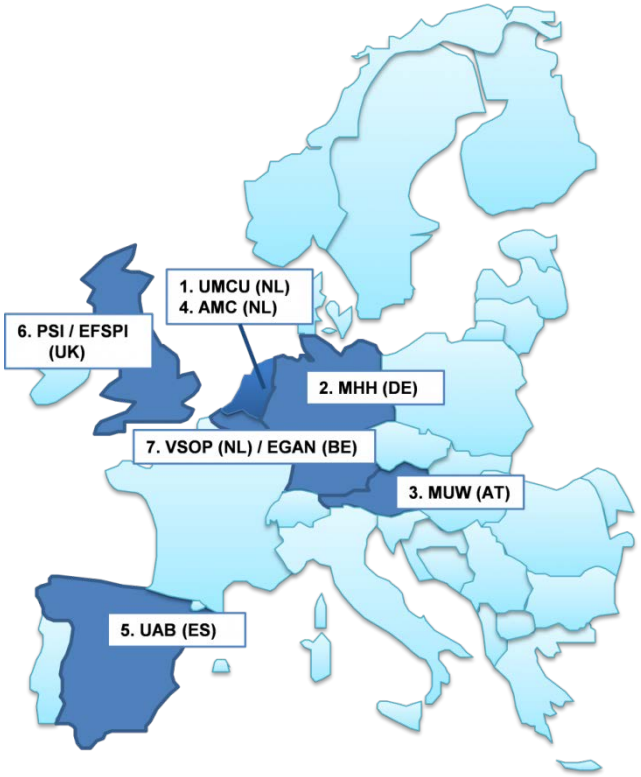
Innovative methodology for small populations research

Should we collaborate on a larger (European) scale?

YES!

The Asterix project

Advances in Small Trials dEsign for Regulatory Innovation and eXcellence



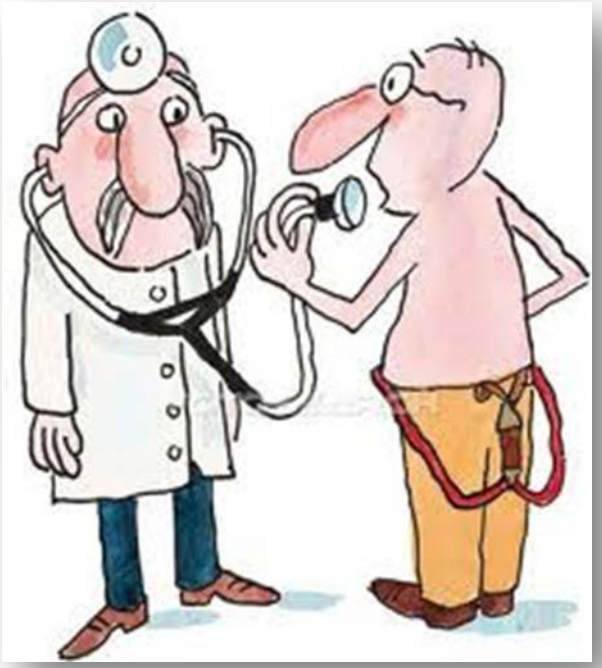
Patient Think Tank

Ten patient representatives, from various disease groups

Qualitative research

We interviewed ten members of the Patient Think Tank:

What aspects of trial design are important to patients?



Results

1. Involve patients in the choice of outcomes

‘Yeah, I suppose that’s the key thing really, is.. is making sure that patients have the chance to give their views, and then that those views are listened to.. Patients want to make sure that.. the kind of outcomes are relevant in their life’

Results

2. Minimize placebo groups

‘We of course think it’s a waste.. all those children who are in a placebo group. The smaller the placebo group, the better.’

Results

3. Double blind is not always double blind

‘There are parents who in that way try to unblind the study, so to speak. So who say: yes, but my child has spots where he was injected and yours doesn’t, so probably yours isn’t and mine is.. well, those kind of things.[…] People will compare.’

Conclusion

Outcome measures

Duchenne community:

‘6 minute walk test is not relevant to us’

Why is this so important for regulators?

‘The six minute walk test is less relevant to us than being able to use our hands’

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy

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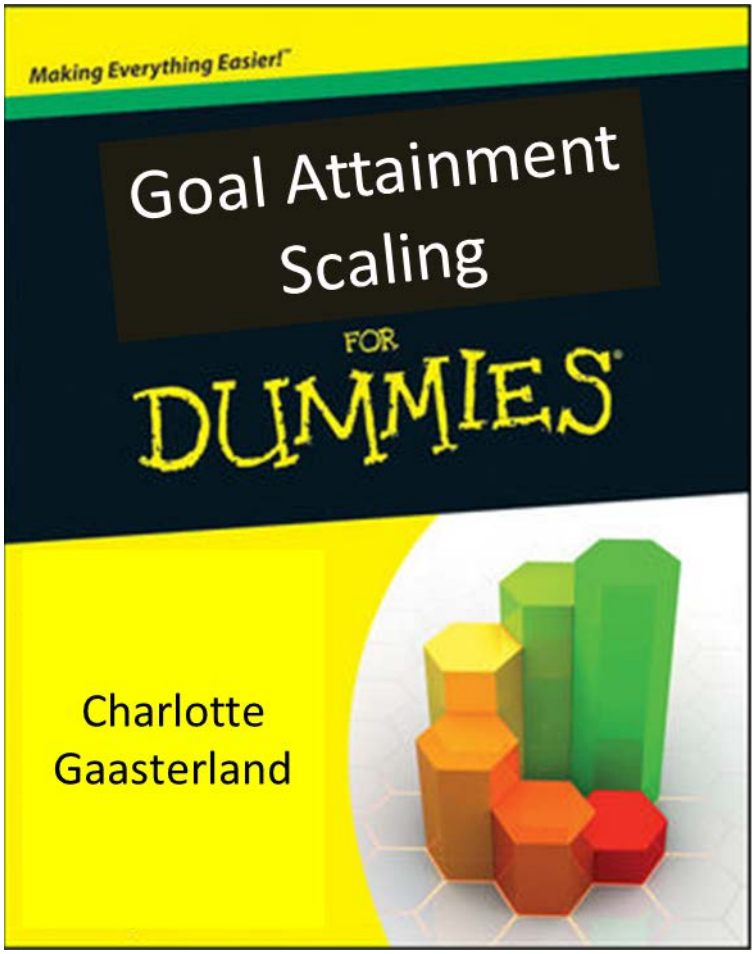
ABBREVIATIONS

6MWT	6-minute walk test
ADL	Activities of daily living
ClinRO	Clinician-reported outcome
DMD	Duchenne muscular dystrophy
MFM	Motor Function Measure
NSAA	North Star Ambulatory Assessment
PUL	Performance of the Upper Limb
SMA	Spinal muscular atrophy

AIM An international Clinical Outcomes Group consisting of clinicians, scientists, patient advocacy groups, and industries identified a need for a scale to measure motor performance of the upper limb. We report the steps leading to the development of the Performance of the Upper Limb (PUL), a tool specifically designed for assessing upper limb function in ambulant and non-ambulant patients with Duchenne muscular dystrophy (DMD).
METHOD The development of the PUL followed a number of steps, from the systematic review and a preliminary study exploring the suitability of the existing measures, to the application of a pilot version in a multicentric setting, with Rasch analysis of the preliminary results, leading to a revised pro forma.
RESULTS The PUL was specifically designed for DMD, with a conceptual framework reflecting the progression of weakness and natural history of functional decline in DMD. Modern psychometric methods were used to create a scale with robust internal reliability, validity, and hierarchical scalability; males with DMD and their families were involved iteratively throughout the process of the clinician-reported outcome assessment tool development to establish clinical meaningfulness and relevance of individual PUL items to activities of daily living.
INTERPRETATION The module was developed using innovative approaches and will be useful

Research on Goal Attainment Scaling



Imagine 3 boys with Duchenne disease:

‘I want to walk’

‘I want to eat independently’

‘I want to breathe independently’

How do we measure improvement?

-2 Adam is unable to walk

-1 Adam can take 3 steps

0 Adam can walk for 5 minutes

1 Adam can walk for 15 minutes

2 Adam can walk longer distances

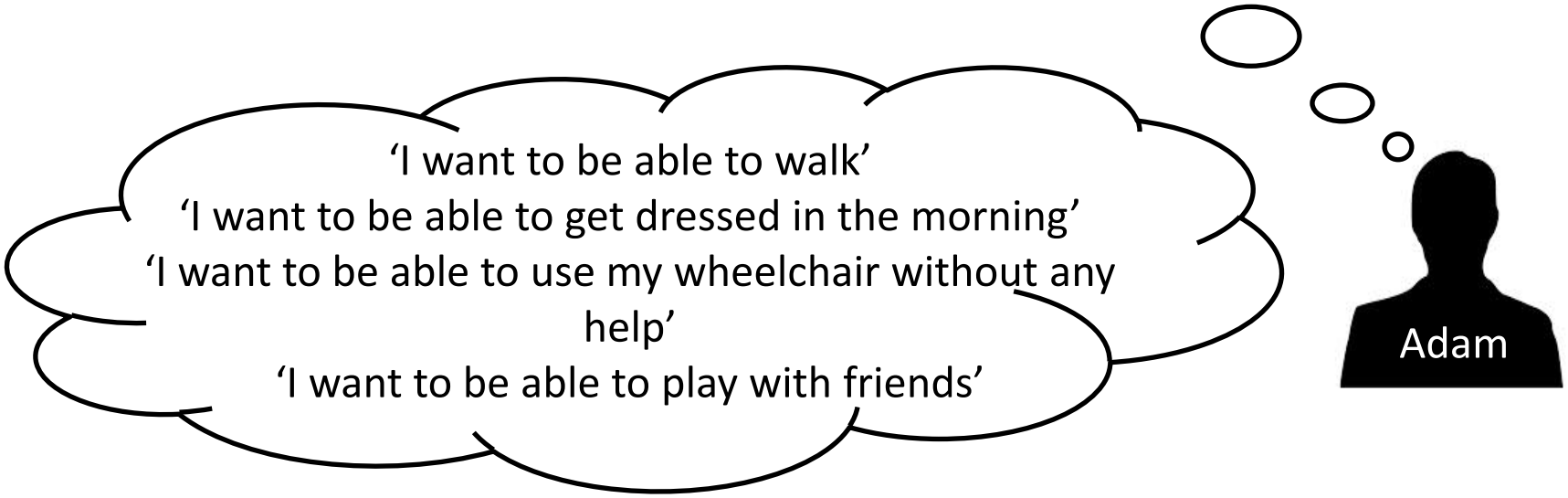
-2 Chris is unable to breathe independently

-1 Chris can breathe for 10 minutes

0 Chris can breathe for one hour

1 Chris can breathe for two hours

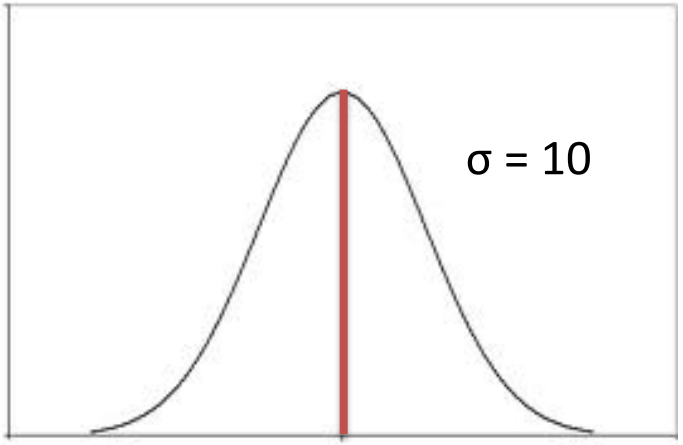
2 Chris can breathe for at least three hours



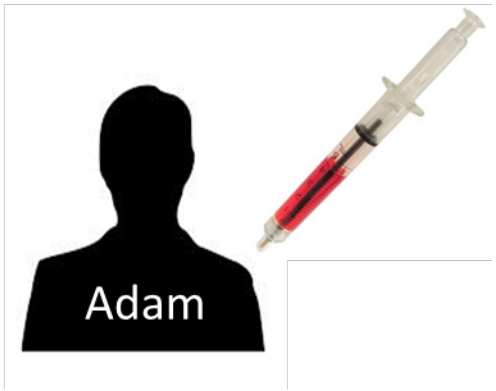
$$T = 50 + \frac{10\,\Sigma w_i x_i}{\sqrt{(1-\rho)\Sigma w_i^{\,2} + \rho(\Sigma w_i)^2}}$$

$$T = 50 + \frac{10 \sum w_i x_i}{\sqrt{(1-\rho)\sum w_i^2 + \rho(\sum w_i)^2}}$$

T	=	*GAS score*
x_i	=	*Original score*
w_i	=	*Weight given to the original score*
ρ	=	*Intercorrelation among goal scores (estimated at 0.3)*



1. What are your goals, defined in 5 levels of attainment?
2. Which goals are most important to you?
3. *Intervention*
4. Have you attained your goals?



Systematic Review

Is GAS useful in drug trials?

- *Is GAS used in drug trials?*
- *Has GAS been validated in drug trials?*
- *Has GAS been validated in other studies?*

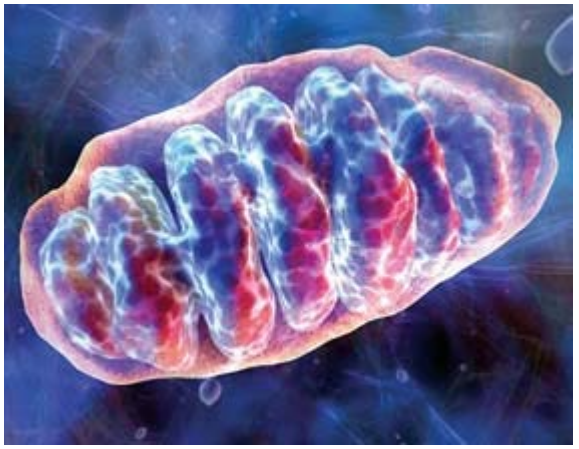
Systematic Review

Is GAS useful in drug trials?

- *Is GAS used in drug trials? YES*
- *Has GAS been validated in drug trials? HARDLY*
- *Has GAS been validated in other studies?*

  YES, BUT GENERALLY WITH LOW QUALITY

Next steps: GAS in mitochondrial disease



Under which statistical circumstances can we use GAS best?

What is the reliability, construct validity and responsivity of GAS?

Rare diseases – a field of problems

Do potential drugs for rare diseases need the same quality of evidence?

Who is responsible for setting up and maintaining a rare disease registry?

Is a Randomized Controlled Trial always the best possible solution?

Where do we find patients willing to participate in a rare disease trial?

Do we need as many patients in a rare disease trial as in a regular trial?

Should we collaborate on a larger (European) scale?

How much money are we willing to spend on rare disease drugs?

Thank you for your attention!