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Patient centered outcome measurements in rare disease trials: Challenges and potential solutions

asterix

SEVENTH FRAMEWORK PROGRAMME

Different perspectives

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• Parent	Alex Johnson
• Methodological	Charlotte Gaasterland
• Statistical	Susanne Urach
• Regulatory	Kit Roes

Challenge 1: small populations

- Definition rare disease:

  Europe < 5 : 10 000

  US < 200 000

- More than 60 000 diseases are rare

- In Europe:

  30 000 000 patients with a rare disease

  5 – 245 000 patients per disease

Challenge 2: heterogeneity

- Heterogeneous phenotypes:

  different patients have different symptoms

- Progressive diseases:

  patients in different stages face different challenges

- Insufficient knowledge about disease variability and course

How to measure outcomes in trials?

- Generic outcome measures:

  Often not sensitive to change and/or

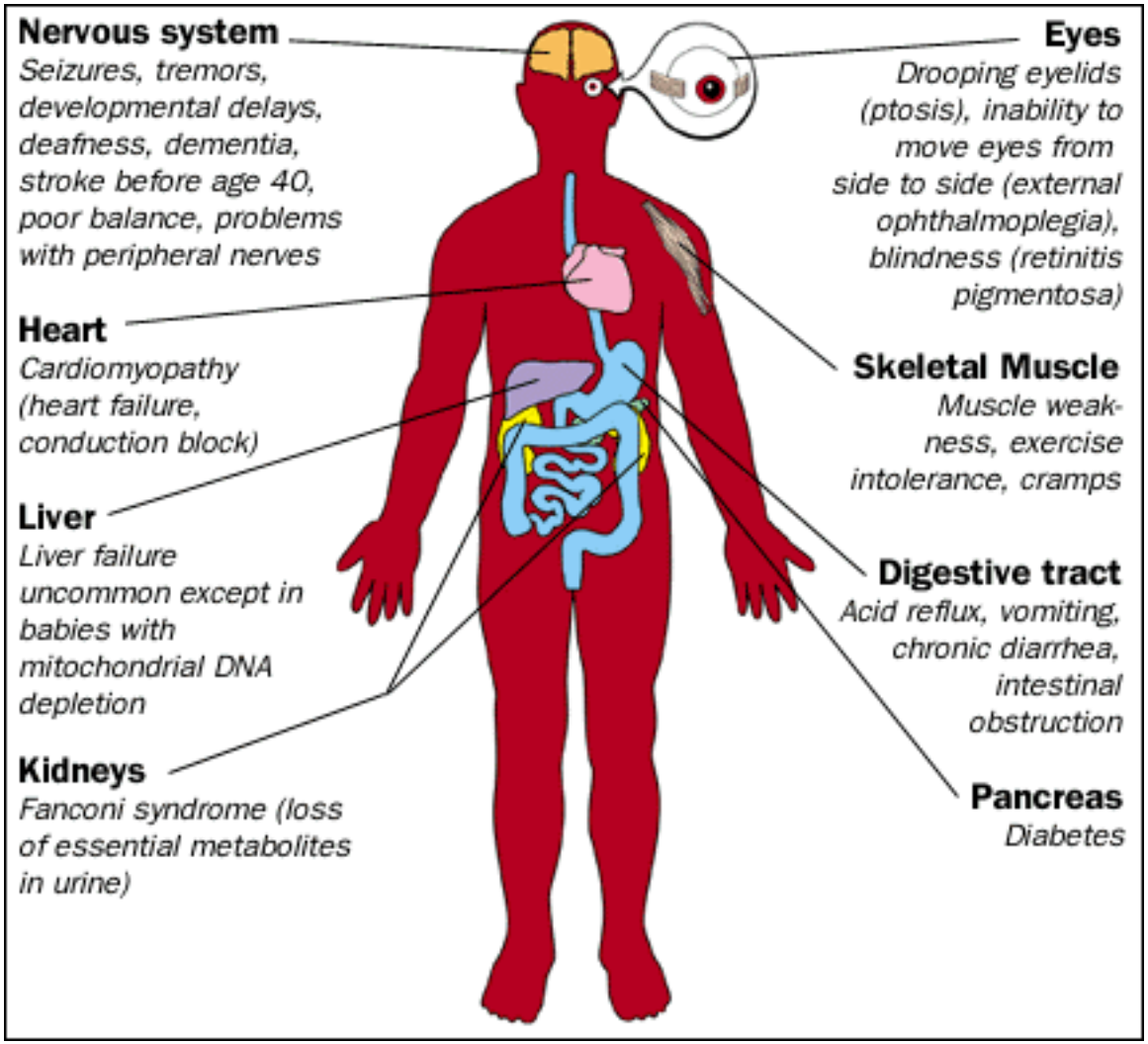
  only applicable to a subset of patients

- Disease-specific outcome measures:

  Virtually absent

  Development and validation require unrealistic patient numbers

Example 1: mitochondrial diseases



Example 1: mitochondrial diseases

- 1 in 5 000
- Different enzyme defects, unpredictable disease course
- Primary outcomes pivotal drug studies (EPAR): survival, ataxia scale, vision test
- Recent development:

International Paediatric Mitochondrial Scale tested in 17 subjects from 5 centres in 4 countries (Koene et al. J Inherit Metab Dis 2016)

Example 2: Mucopolysaccharidoses

Manifestations	**I-H**	**I-S**	**II**	**III**	**IV**	**VI**	**VII**
Mental deficiency	+	-	±	+	-	-	±
Coarse facial features	+	(+)	+	+	-	+	±
Corneal clouding	+	+	-	-	(+)	+	±
Visceromegaly	+	(+)	+	(+)	-	+	+
Short stature	+	(+)	+	-	+	+	+
Joint contractures	+	+	+	-	-	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leukocyte inclusions	+	(+)	+	+	-	+	+
Mucopolysaccharidoses	+	+	+	+	+	+	+

Example 2: Mucopolysaccharidoses

- 1 in 25 000
- Different enzyme defects, heterogeneity within each disease, all progressive
- Organs affected:

  brain, bones, heart, eyes, internal organs

- Primary outcomes pivotal drug studies (EPAR):

  6 Minute Walk Test, FVC
- No disease-specific measurement instrument

Example 3:
Duchenne Muscular Dystrophy

- 1 in 3 300 males
- Progressive muscle disease

- Primary outcome pivotal drug studies:

  6 Minute Walk Test

- Recent development:

  DMD Upper Limb PROM tested in 194 subjects from 8 centres in 6 countries

(Klingels et al. Dev Med Child Neurol 2017)