Post marketing surveillance: drugs in the real world

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Disclaimer

Opinions are not necessarily those of UK government or any other organisation

Drugs in the real world

- Pure >> real people
- Biomarker >> real life
- Short term >> long term

Experience in England
(Ultra orphan)

- Eculizumab for PNH
- Myozyme for Pompe
- ERT for Gaucher and Fabry
- Argus II for retinitis pigmentosum
- Managed access agreements

The NHS in England

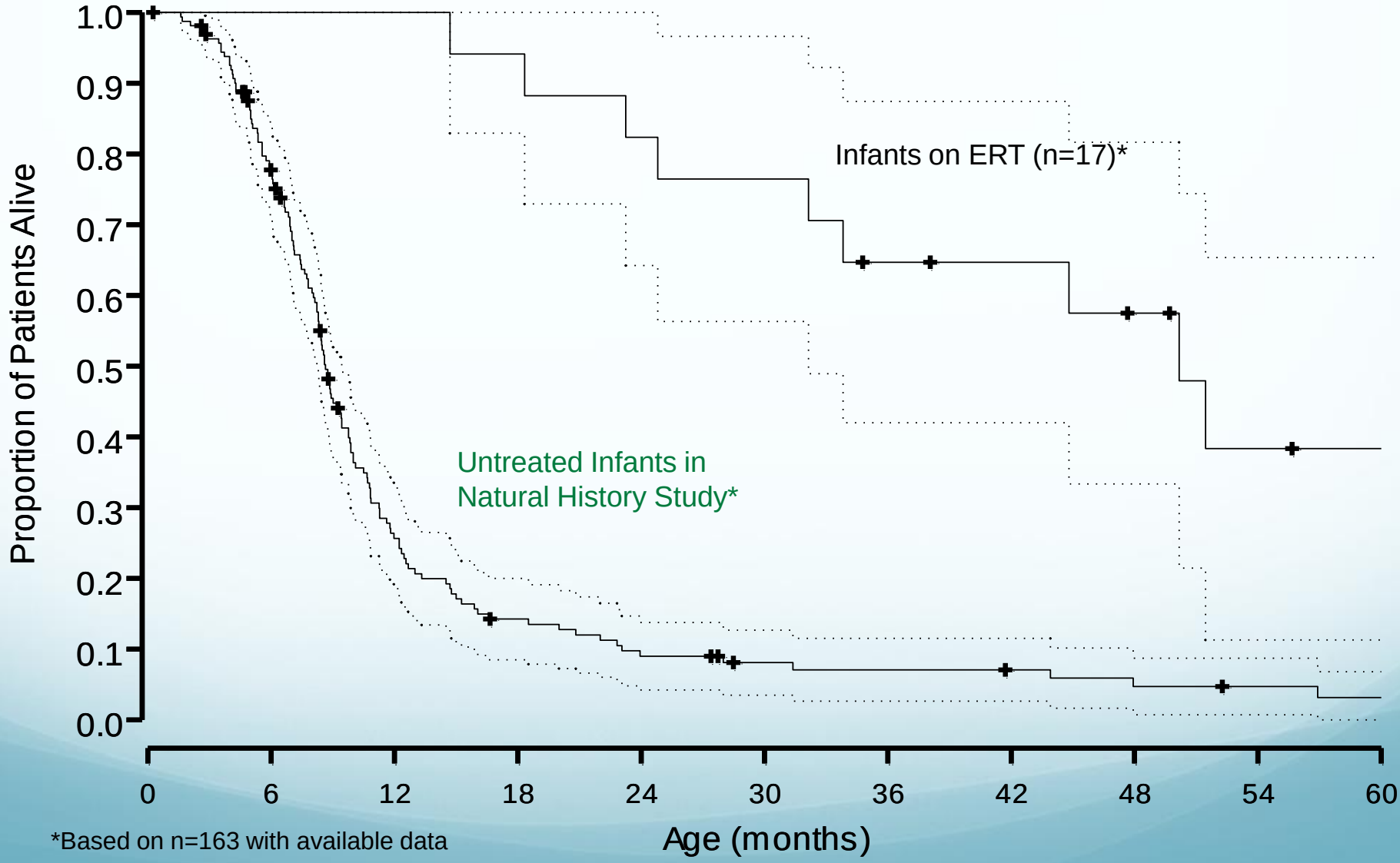
- Comprehensive coverage for 55m people
- ?Largest in the world
  - (too big??)
- A system not a single legal entity

Myozyme for Pompe

- Genetic disease: enzyme deficiency
- Muscle weakness

- TRIAL: Pure population, infant onset, early diagnosis
- REAL WORLD: Mixed population, later diagnosis?

ERT in Infantile-Onset Pompe Disease: Survival Comparison by Kaplan Meier Analysis



*Based on n=163 with available data

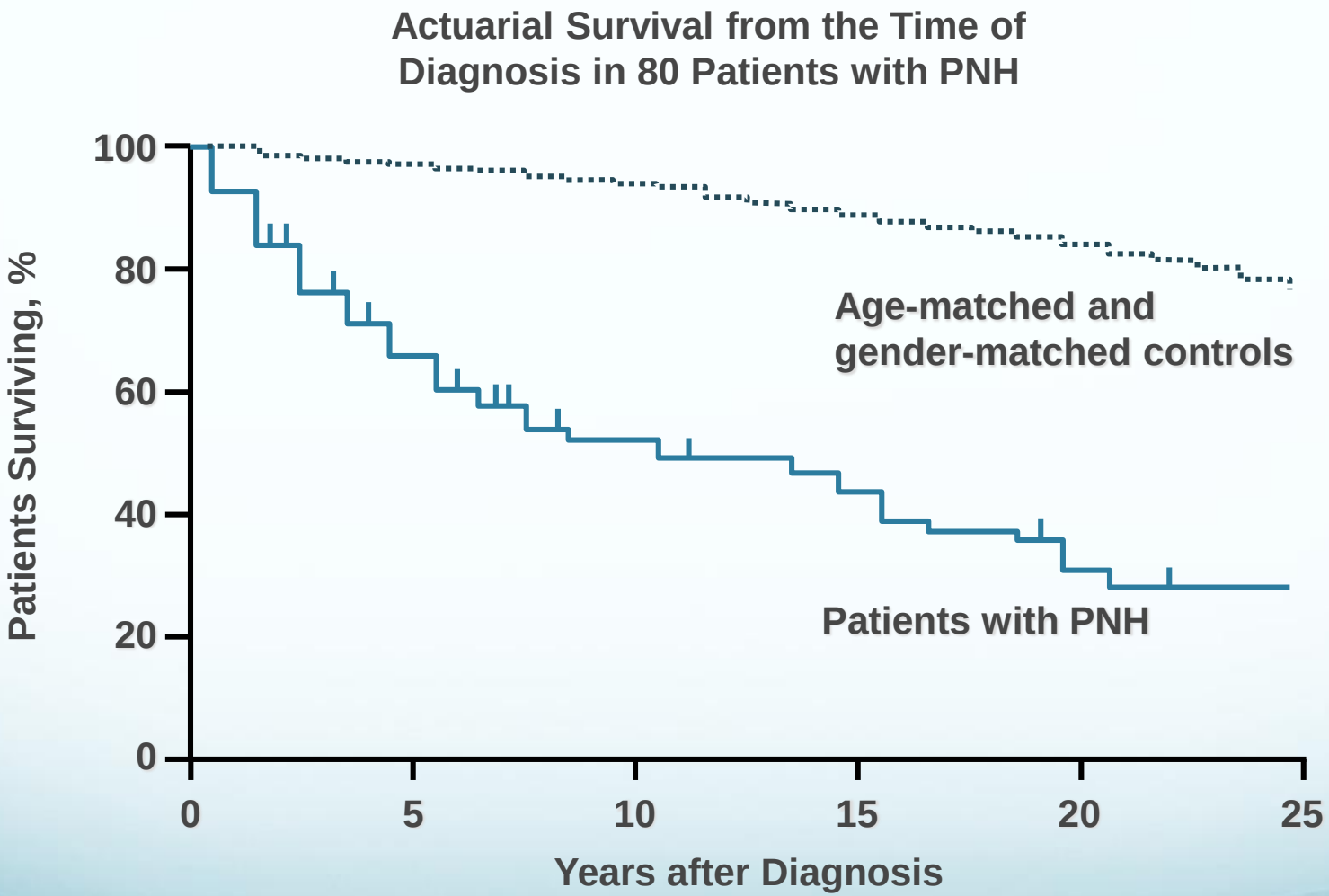
PNH

- Paroxysmal nocturnal haemoglobinuria
- Abnormal red cell clone
- Intra vascular haemolysis
- Complement mediated

Eculizumab (Soliris)

- Complement blocker
- Clear biological effect
  - Stops haemolysis
- Real world?

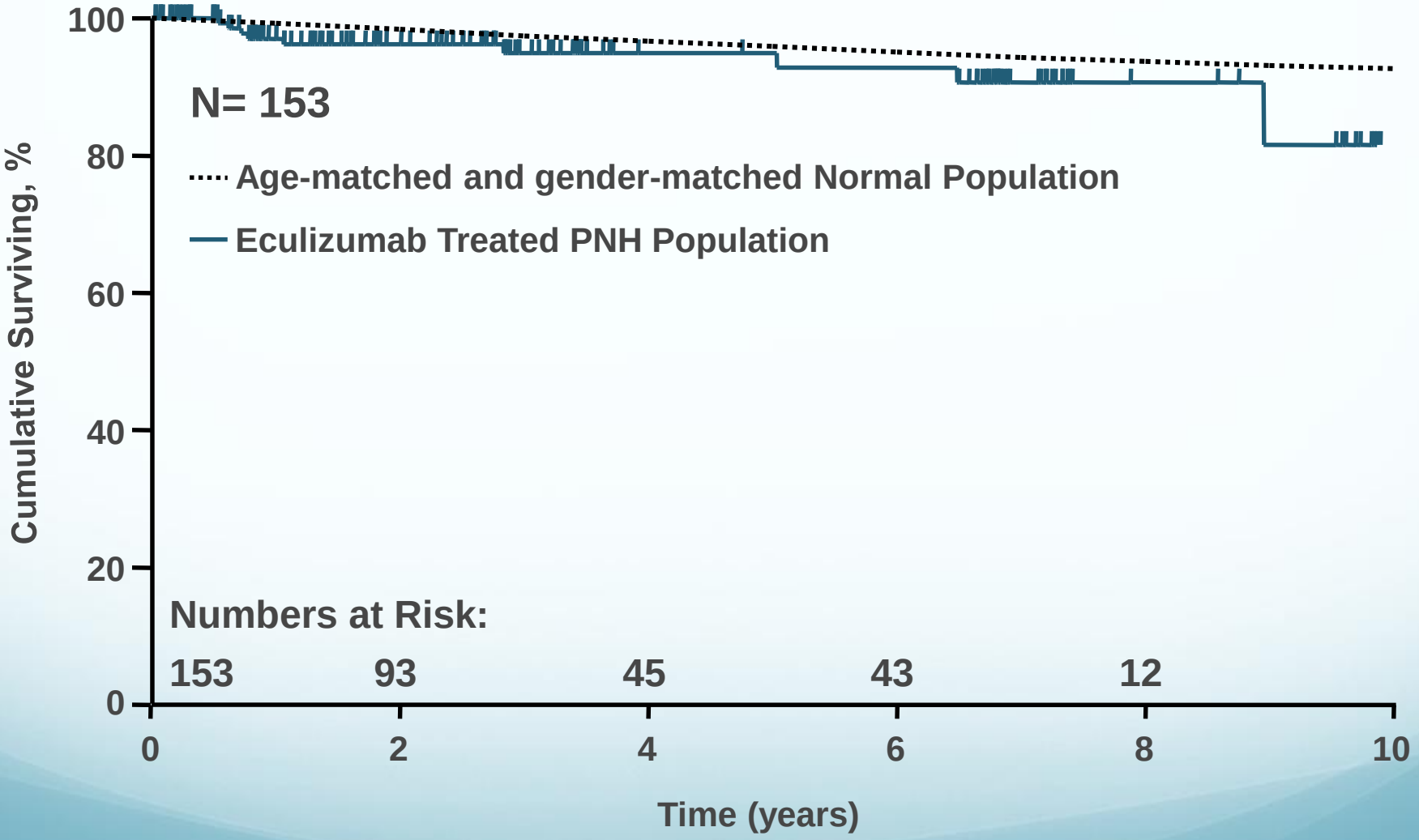
Mortality with Best Supportive Care



5 year mortality of 35% recently confirmed[2]

Hillmen P, et al. *N Engl J Med.* 1995;333(19):1253-1258

Overall Survival of UK PNH Patients Treated With Eculizumab Compared With the Normal Population in 2012



Hill A. ASH 2012.

Fabry disease

- Genetic disease
- Enzyme deficiency
- X linked – males
- Substrate accumulation over many years
- Many mutations

ERT for Fabry: classical phenotype

- X linked – males
  - Pain
  - Renal failure

  - Heart - cardiomyopathy
  - Stroke
  - Gut

ERT for Fabry

- Licensing trials (2001)
  - clearance of lysosomal deposits (blood vessels, heart, kidney) (n=58)
  - reduced pain (n=26)
- Real world?

15 years later…

- ‘The long term influence of enzyme replacement therapy on mortality and morbidity related to Anderson Fabry disease remains to be established’

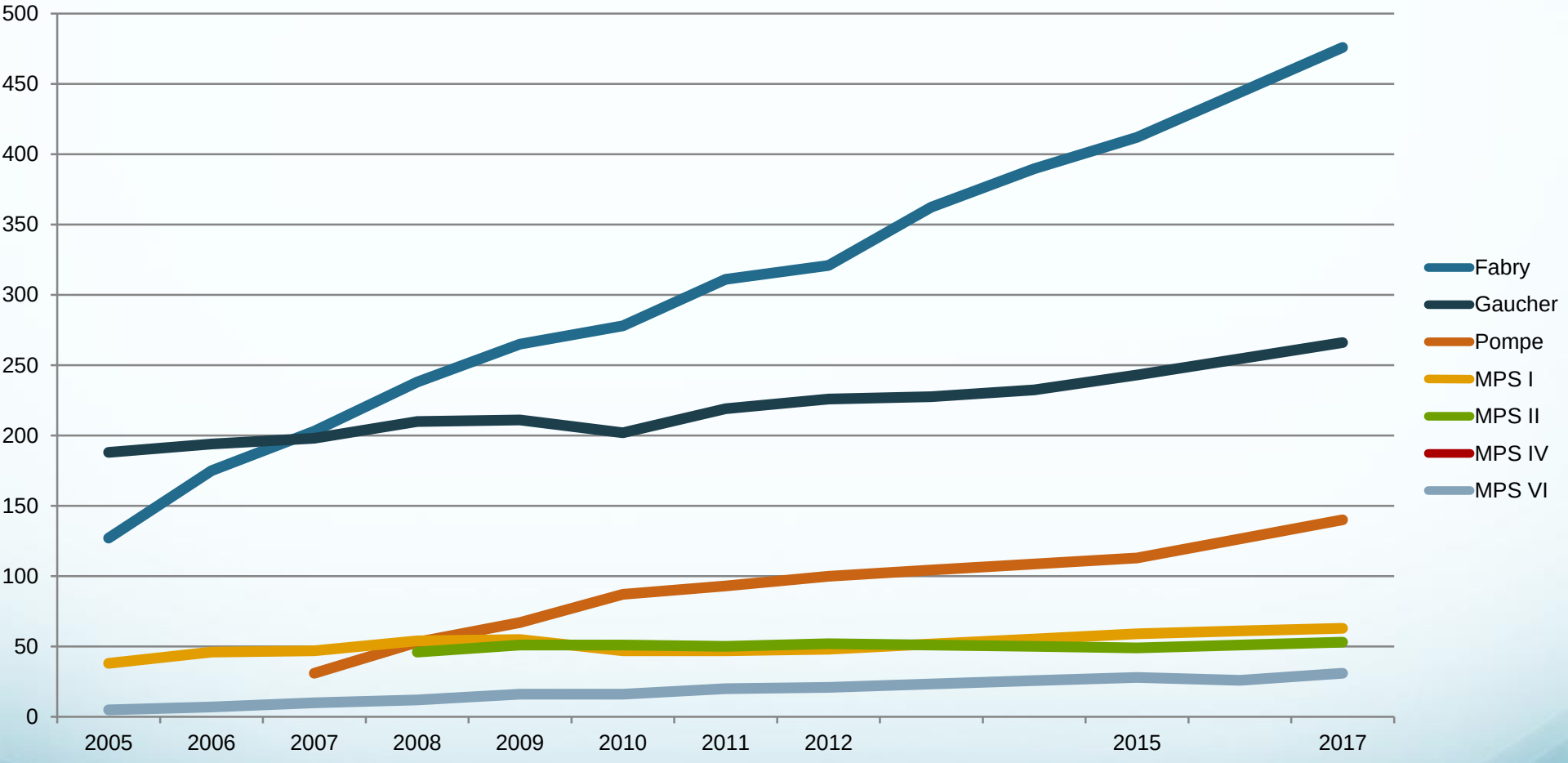
- ElDib et al 2016 Cochrane database of systematic reviews

HTA study
(Anderson LJ et al JIMD 2014)

- 289 adults, 22 children
- Medical records study
- Time on ERT – up to 10 yrs adults; up to 5 yrs children
- LVMI, eGFR, proteinuria, Stroke

Trial vs real world

- Wider phenotype
  - (Gaucher:Israel vs UK)


500
450
400
350
300
250
200
150
100
50
0
2005
2006
2007
2008
2009
2010
2011
2012
2015
2017
Fabry
Gaucher
Pompe
MPS I
MPS II
MPS IV
MPS VI

ERT for Fabry – current proposal

- Avoidable events:
  - Stroke
  - Renal replacement therapy
  - Cardiac device implant
- Real world, whole country cohort

Three claims

- ‘No patient with Fabry disease has developed end stage renal failure’
- ‘No patient with Behcets has gone blind’
- ‘No patient with CAPS has developed amyloid’

Retinitis pigmentosum

- Argus II device – but gene therapy will raise similar issues
- Functional tests but ?real life
- EQ5D does not work well for blindness (Brazier)
  - (Cf also GBD study)

Managed access agreements (*NOT managed entry agreement)

- Elosulfase
  - Individual targets – 5 domains
  - Uptake
- Ataluren
  - NSAA decline, group
- Asfotase alfa
  - Quality of life measure

And…

- Alkaptonuria!

Conclusion

- Acute diseases – possible
  - PNH, aHUS, SCID
- Chronic disease – very difficult
  - ?10 – 20 year perspective (haemophilia, multiple sclerosis)
  - ?No disease events

NB – all for ULTRA RARE disease