Orphan Regulation

The Academic View

Background

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  - Rare with small numbers of patients
  - Small number of centres
  - Very few clinicians
  - Natural history poorly documented
  - Clinical endpoints unclear

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NDC 58468-1083-1
Cerezyme
imiglucerase for injection
200 Units
For single use only
Rx only
For intravenous infusion only
genzyme


genzyme
NDC 58468-0070-1
ALDURAZYME
(LARONIDASE)
2.9 mg/5 mL
(0.58 mg/mL)
Concentrated Solution For
Intravenous Infusion Only
Rx Only
genzyme

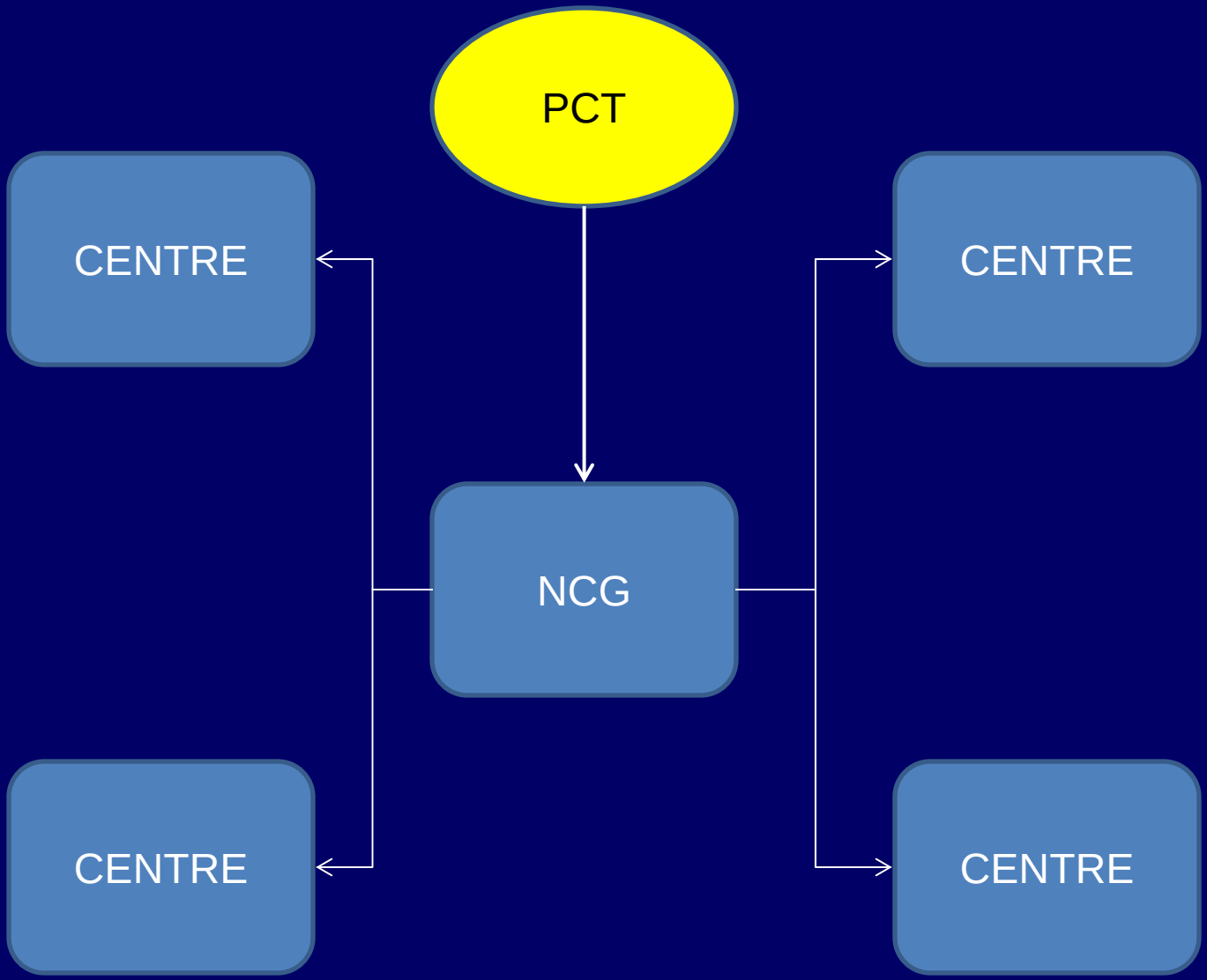

elaprase 2mg/ml
Shire


BIOMARIN

Lysosomal Storage Disorders

- Approximately 40 disorders
- Each characterised by deficiency of single enzyme

Clinical Services Centralised


PCT
CENTRE
CENTRE
NCG
CENTRE
CENTRE

NCG Designated Centres

- Only these centres are funded to administer the major therapies (enzyme replacement, substrate reduction)
- All patients needing these treatments therefore have to be seen at a designated centres
- Funding covers ERT (as well as cost of inpatient and outpatient care)
- It also covers the cost of home infusions

Medical Advisory Group

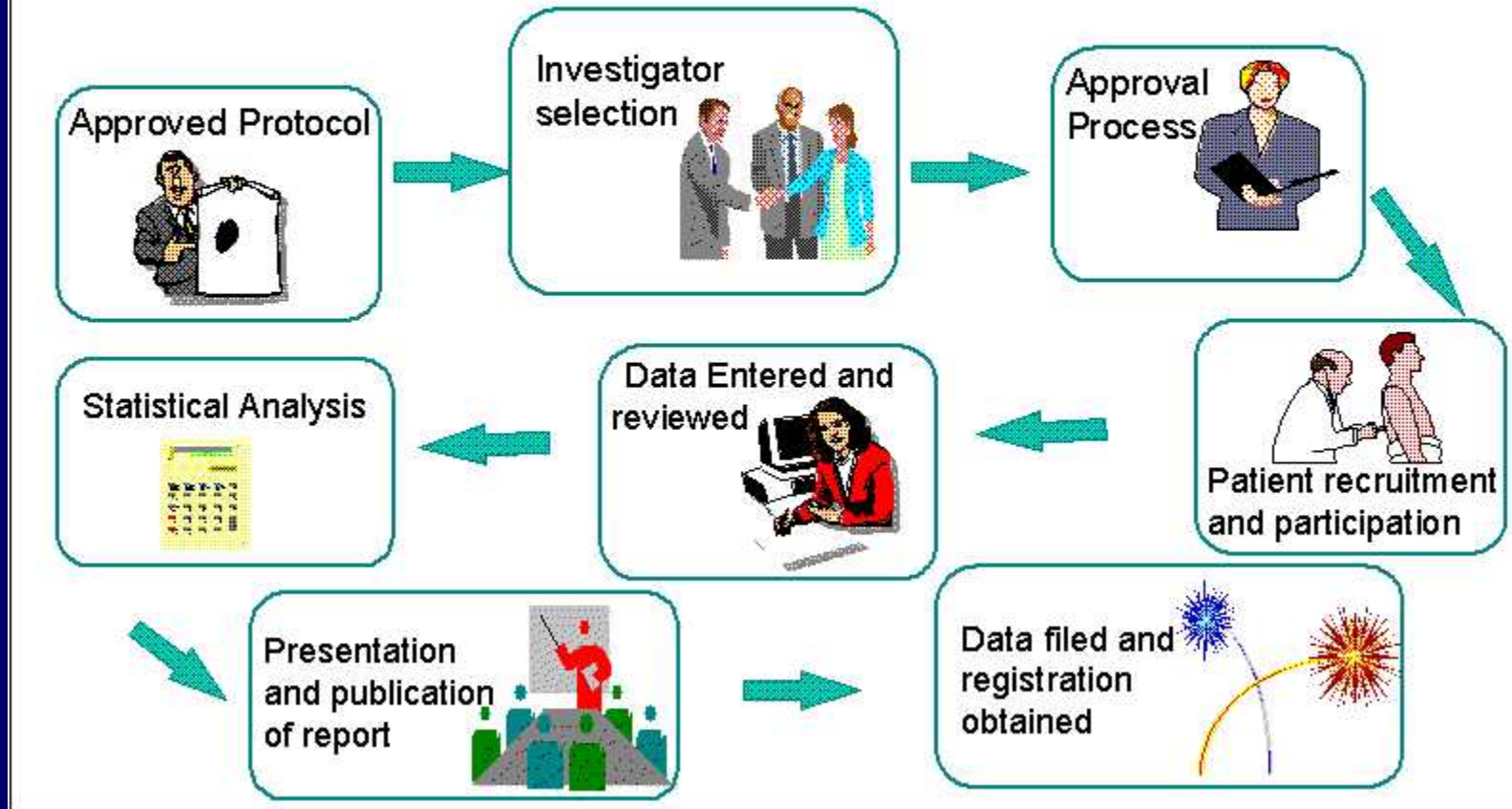
- Representatives from all centres
- Patient groups
- NCG (chair)
- Draws up guidelines and discusses difficult cases
- Advisory role only- final decisions made by NCG

Clinical Trials

Clinical Trials for LSD

- Almost exclusively trials of therapy sponsored by pharmaceutical companies
- Principal Investigators all full-time NHS clinicians with little time for active research
- Small numbers of patients means that multiple regulatory bodies are often involved

Clinical Trials in a Nut Shell



Approved Protocol

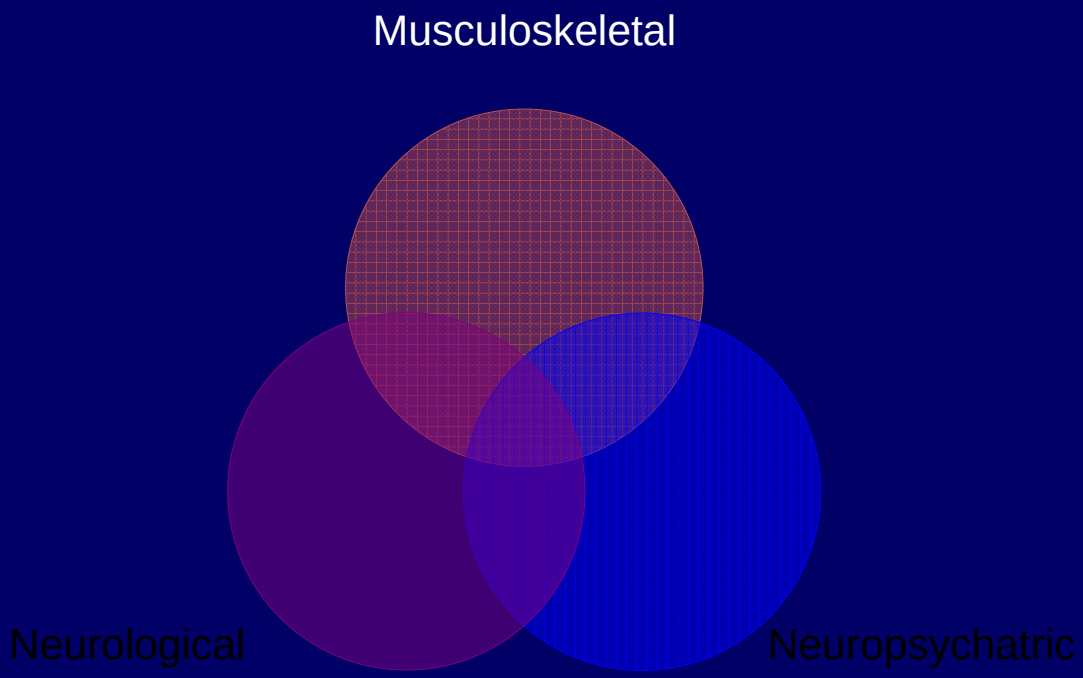
- Tend to be drawn up in consultation with EMEA
- Endpoints published but usually untested for that disease
- “Natural history” study

Developing Clinical Endpoints in LSD's

Endpoints in Mucopolysaccharidoses (MPS)

- MPS characterized by
  - Visceral disease esp musculoskeletal
  - Neurological
  - Psychiatric
  - Each may impact on the other
  - Relative preponderance of each may vary
  - This may render interpretation difficult

Endpoints



Musculoskeletal

- Six minute walk test (6MWT)
- Lung function
- Assessment of movement/function

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Six Minute Walk Test (6MWT)

- Developed in 2002*
- Primarily for patients with cardiac/respiratory disease

Am J Respir Crit Care Med 2002;166(1):111–117.

Indications for 6MWT

- *Before-and-After Treatment Comparisons*
  - Lung transplantation or lung resection
  - Lung volume reduction surgery
  - Pulmonary rehabilitation
  - Drug therapy for chronic obstructive pulmonary disease
  - Pulmonary hypertension
  - Heart failure
- *To Measure Functional Status*
  - Chronic obstructive pulmonary disease
  - Cystic fibrosis
  - Heart failure
  - Peripheral vascular disease
  - In elderly patients
- *To Predict Hospitalization and Death*
  - From heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension

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Indications for 6MWT

- Before-and-after treatment comparisons
- To measure functional status
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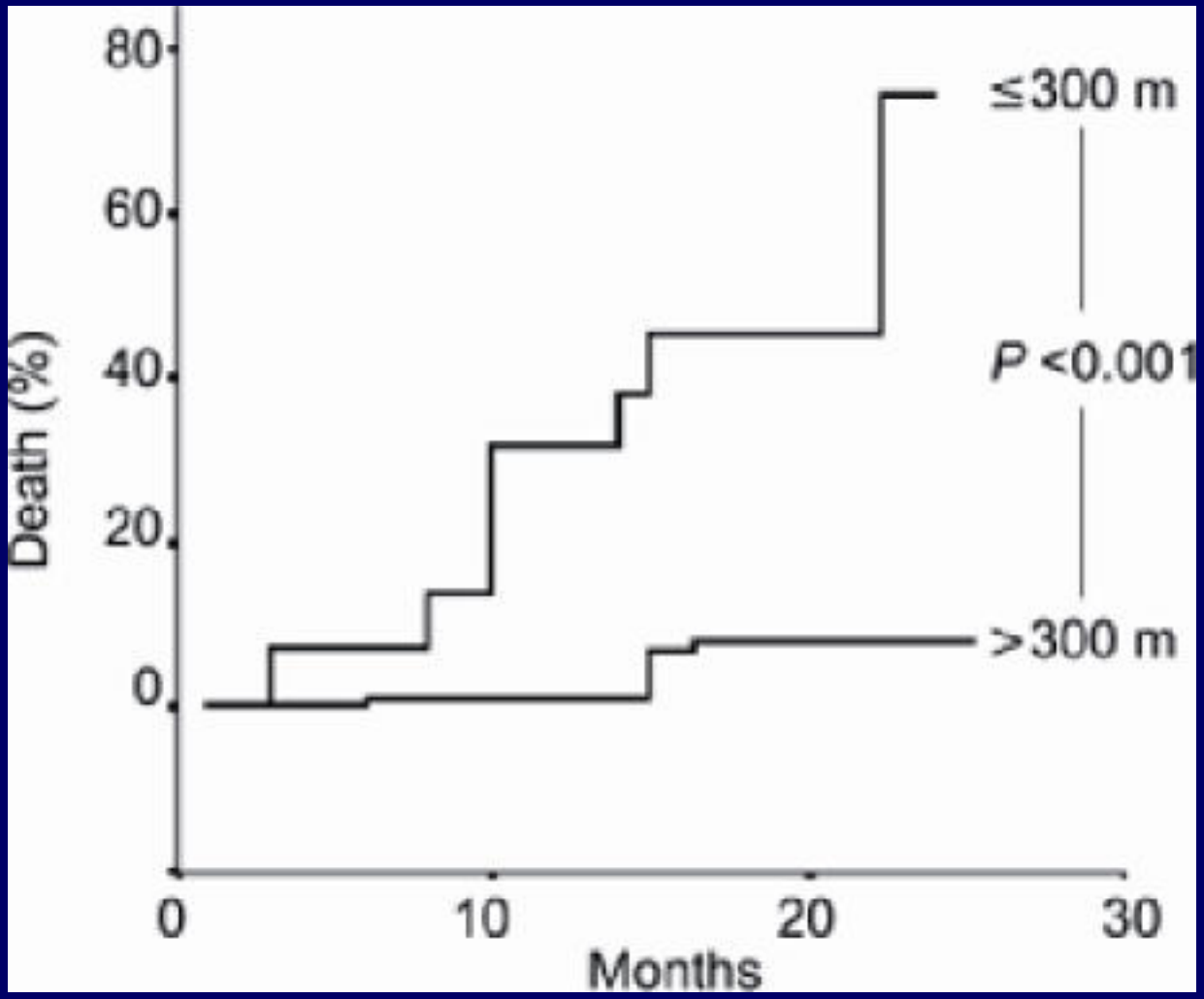
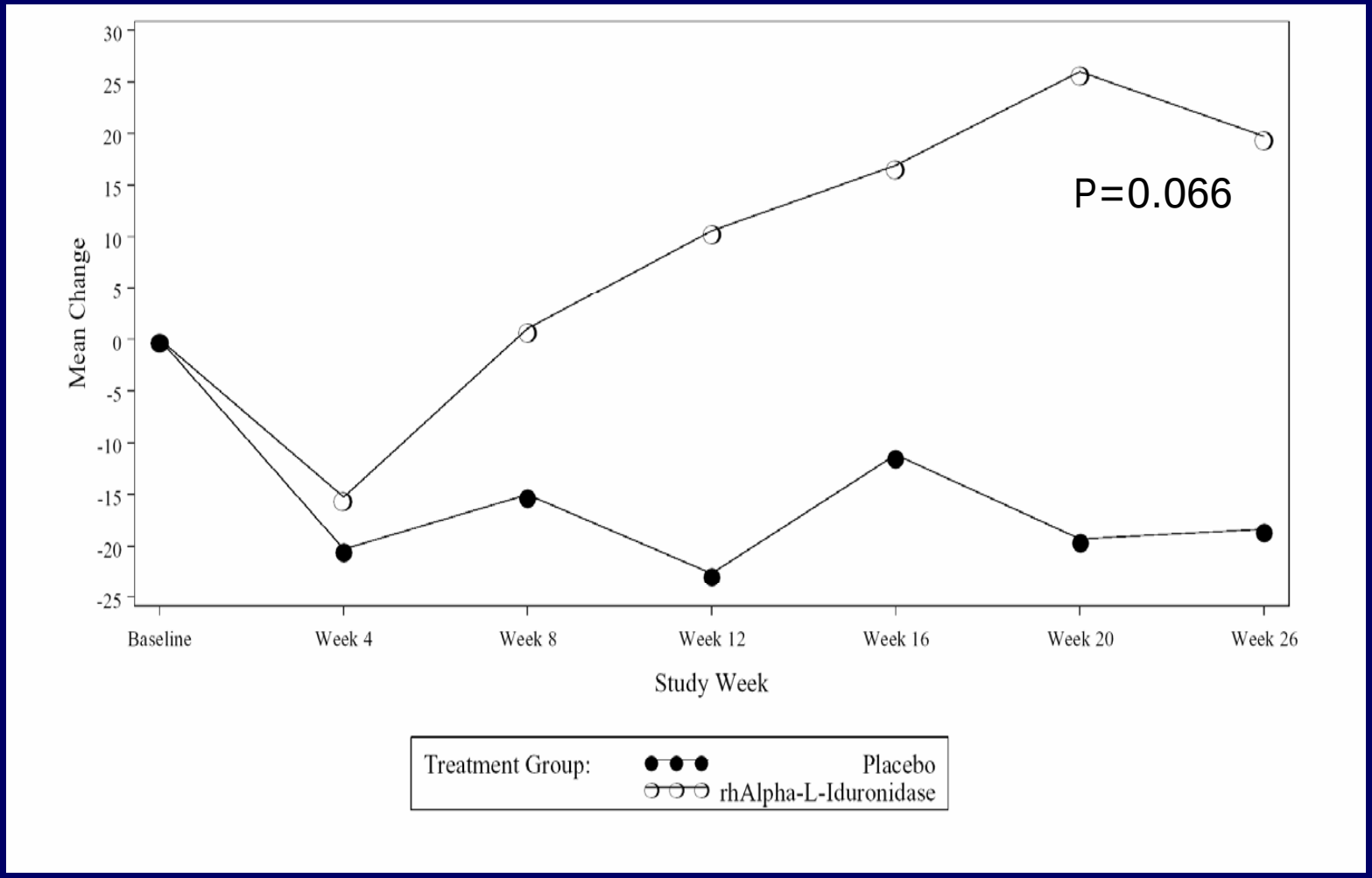
6 MWT in Heart Failure



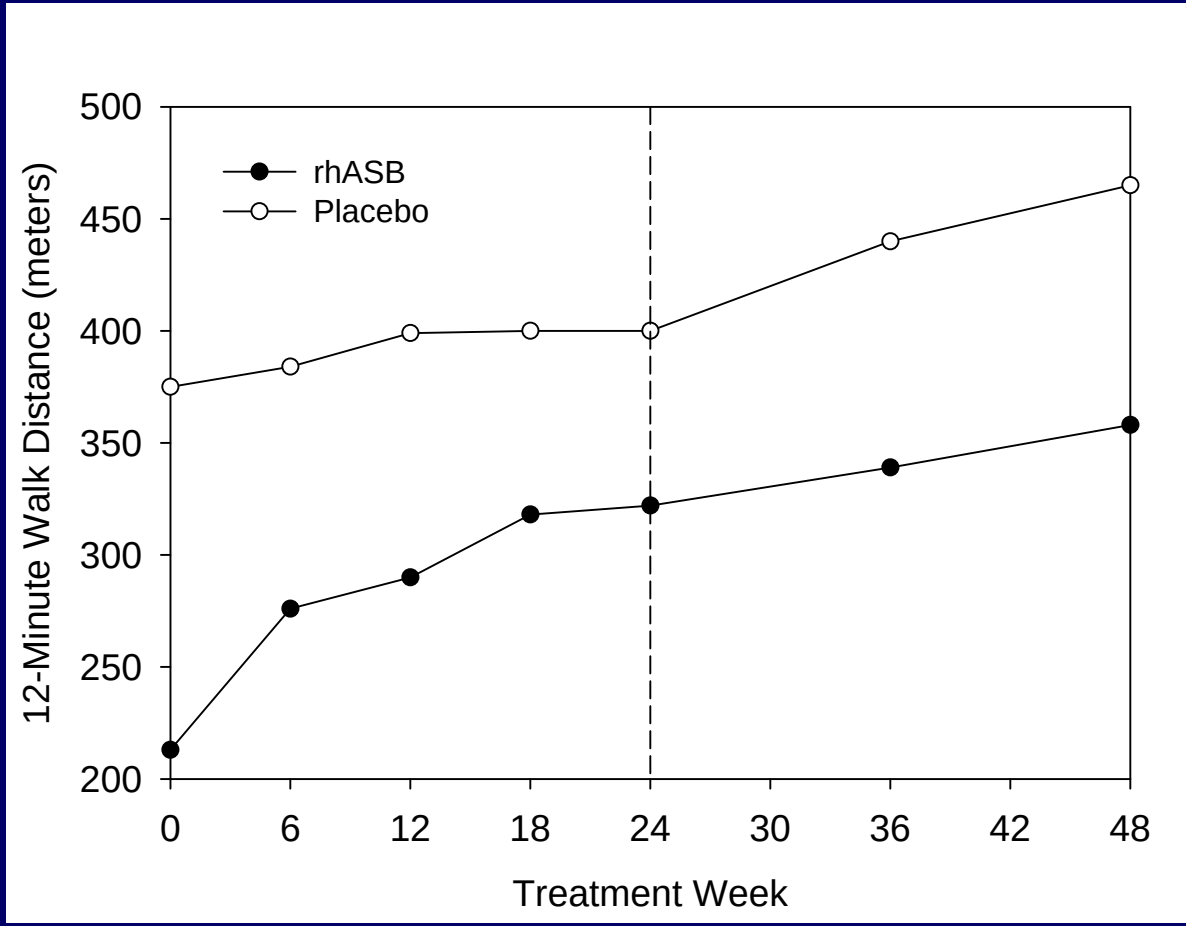
Arslan et al. Tex Heart Inst J. 2007; 34(2): 166–169.

MPS I Phase III Study: Six-Minute Walk Change Over Time

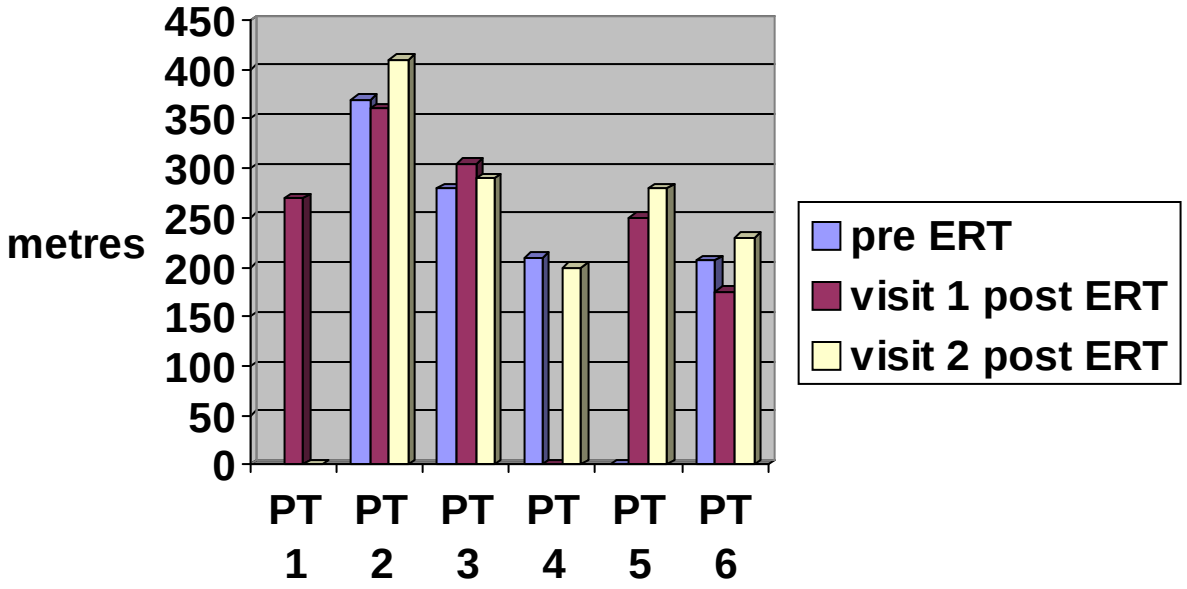


MPS VI Phase III Study

12-Minute Walk: Primary Efficacy Variable



MPS II: 6MWT Pre- and Post- ERT*



* Wood M et al 2009

Musculoskeletal

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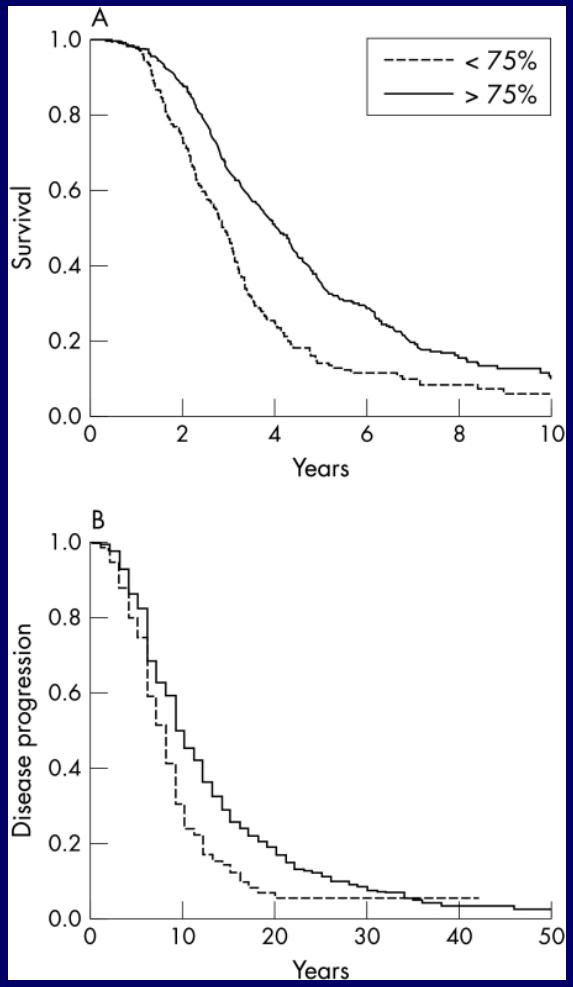
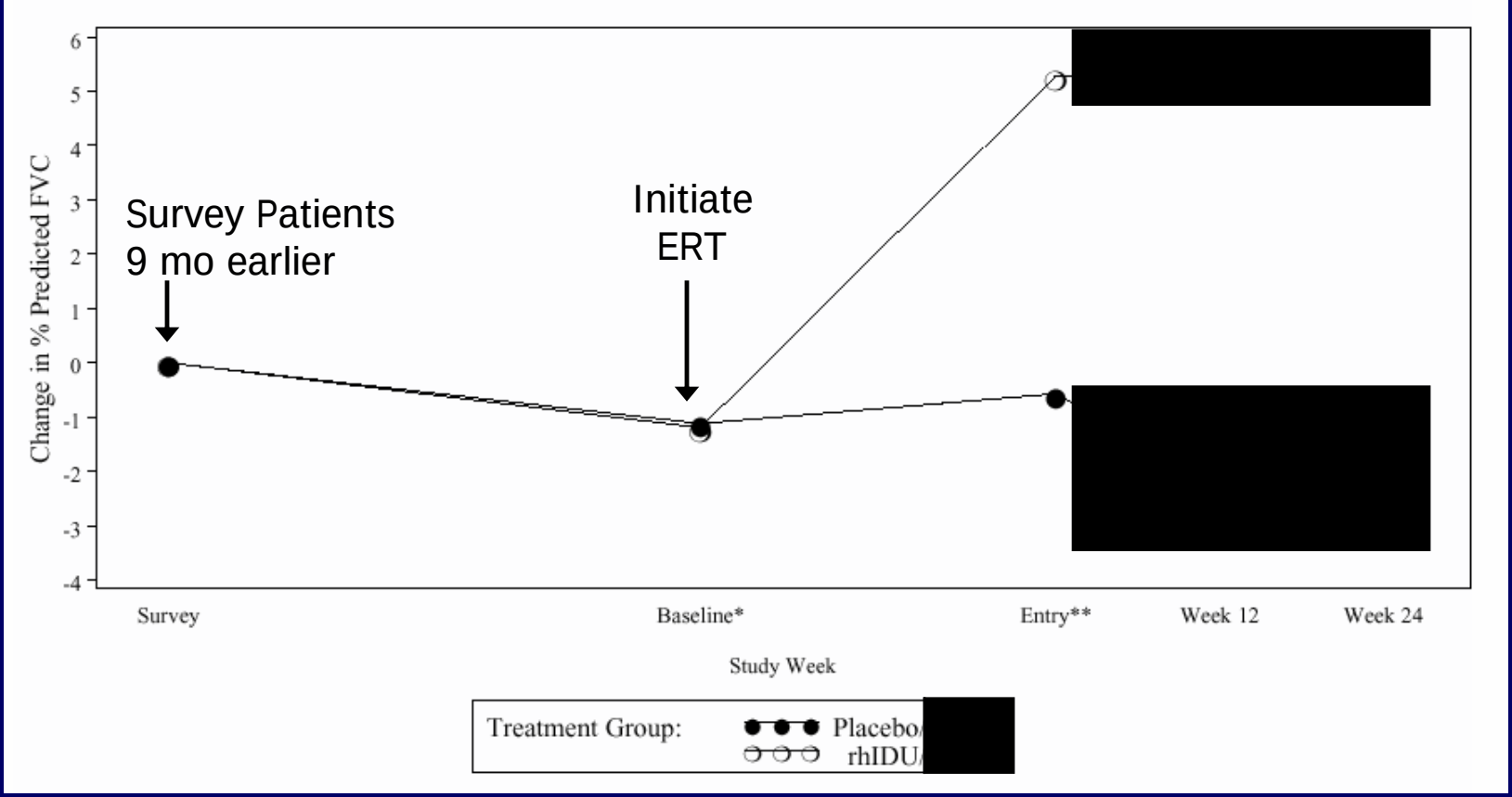
FVC in Amyotrophic Lateral Sclerosis (ALS)

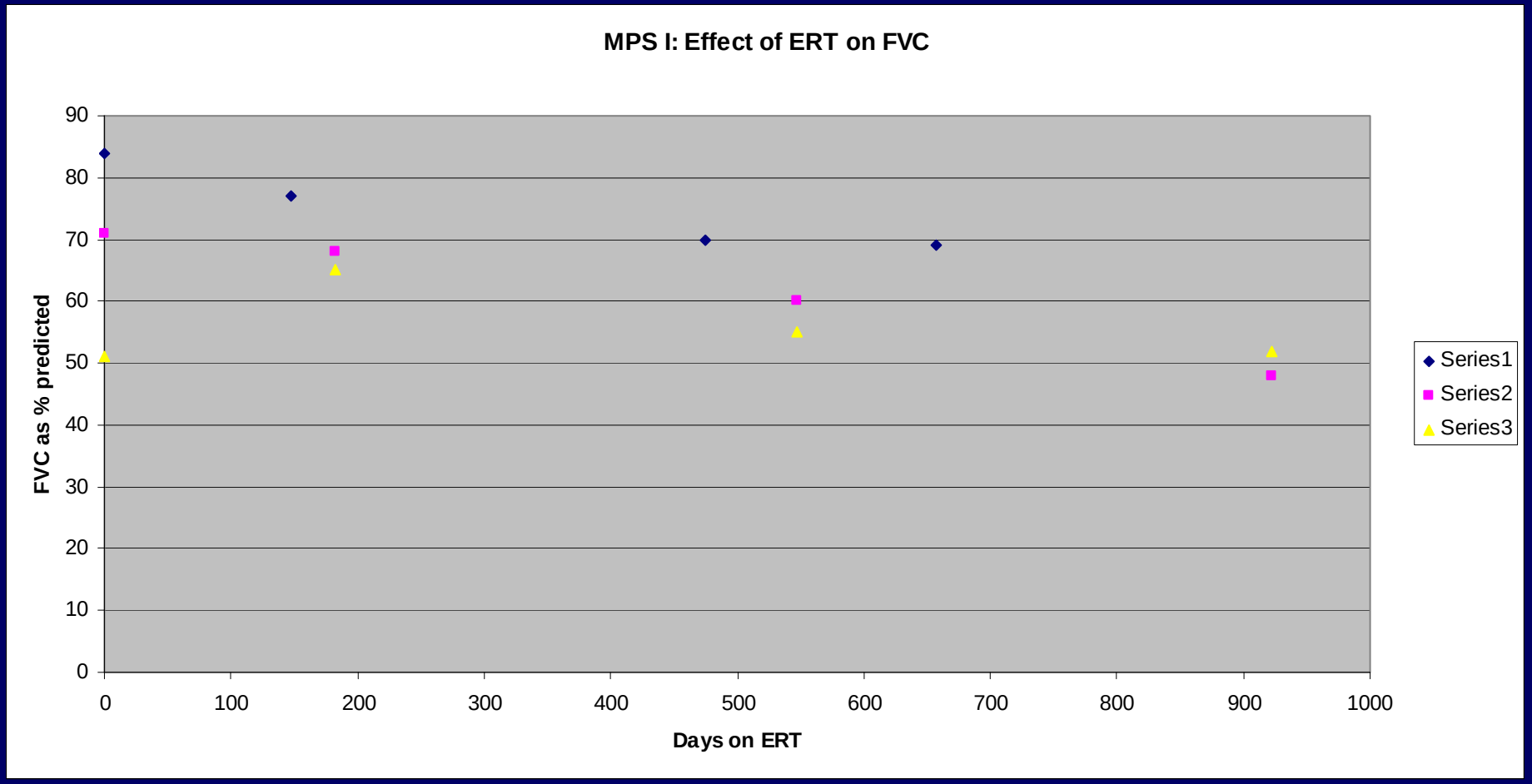


A Czaplinski et al *J Neurol Neurosurg Psychiatry.* 2006 77(3): 390–392

MPS I: FVC change in survey patients before and after Phase III trial



Effect of ERT on FVC in MPS I (GOSH)



6 MWT/Lung Function

- Useful endpoints in clinical trials
- Not quite so useful in clinical practice
  - Combination of cardiac and musculoskeletal disease
  - Lack of close supervision
  - Selection of patients

- Discrepancy between value of endpoints in clinical trials and clinical practice
- May be multifactorial
- Different/additional approaches may be needed in clinical practice

Endpoints

- Primary endpoints may be different for different sponsors (eg Fabry)

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- Somatic endpoints may be affected by neurological endpoints
- Biomarkers may or may not correlate to clinical enpoints
- Little or no progress has been made in neurological/neuropsychiatric endpoints

Natural History Study

- Regulatory requirement prior to clinical trials
- Usually cross-sectional
- Provide little or no information about natural history
- Time-consuming and laborius
- Potentially confusing for patients

Investigator Selection

- Very few specialists
- Same ones tend to be involved every time
  - Experience of clinical trials
  - Trial “fatigue”
  - Resource heavy
    - Beds
    - Personnel esp labs and pharmacy
  - Clinical Research Facilities

Patient Recruitment and Participation

- Small numbers
- Very few new patients/year
- Same patients tend to be approached every time
  - Trial fatigue
  - Consent issues in growing children

Data Entered and Reviewed

- Trial nurses usually expected to enter data
- Usually no separate funding for data manager
- Inappropriate use of skilled personnel

Statistical Analysis

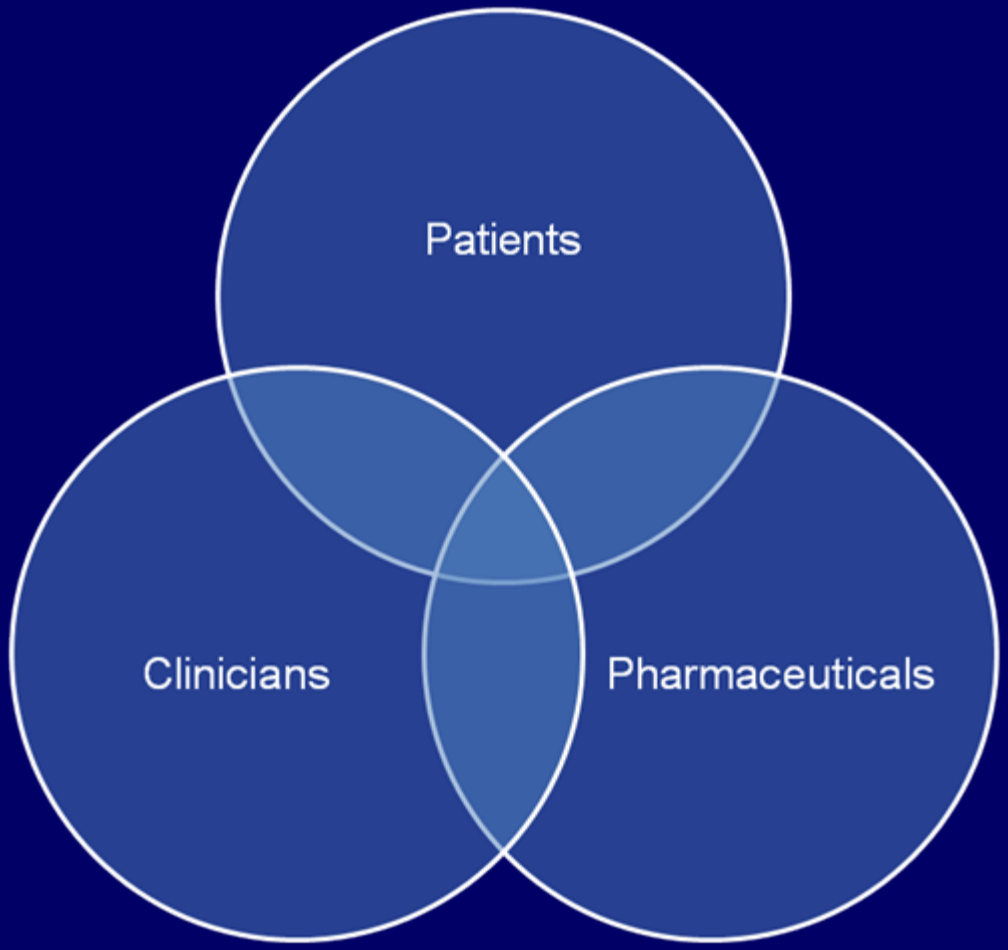
- Often performed by the sponsor
- Not independent

Presentation and Publication

- Use of “ghost” writers

Data filed/Registration obtained

- Closer cooperation between regulatory agencies is needed


Patients
Clinicians
Pharmaceuticals

Suggestions

- Spend more time developing endpoints
- Reduce the paperwork required
- Remember that most clinicians working in clinical trials have clinical priorities
- Encourage the development of CRF