

Patient registries for orphan rare diseases

Scope and management

-meeting the demands of all involved stakeholders

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Patient Registries; The industry perspective

- Main objective: Ensure that the drug stays on the market!
- Provide data to:
 - Regulatory Agencies
 - Pricing and Reimbursement agencies

Patient Registries; The industry perspective

- Collect the needed data for the regulatory and reimbursement agencies
- Collect as much data as possible (accurate, complete, non biased)
- Provide credible output
- Systems used for data collection and statistical analysis needs to comply to FDA and EMA regulations (21CFRPart11, HIPAA, EU dir 95/46/EC)
- And the activity should NOT fall within European Clinical Trial directive 2001/20/EC

The Orphan Rare Disease (ORD)

- Restricted information from randomized clinical trials (RCT); often conditional regulatory and reimbursement approvals=> Need for real world data
 - Need to understand treatment long-term effectiveness and safety
 - Need to understand factors that are not normally accounted for within RCT
 - Adherence
 - Varied Patient populations (gender, age etc)
 - Concomitant medications and morbidity
- A need for clear evidence based assessments of treatment value clinical and HEOR

The Orphan Rare Disease (ORD)

- Restricted information from randomized clinical trials (RCT); often conditional regulatory and reimbursement approvals=> Need for real world data
- Low disease awareness, which affects referral and diagnosis
- Not optimal disease management

FOS - Fabry Outcome Survey

Patient Registry on Fabry disease established in 2001

Key aims

- To understand the natural history of Fabry disease
- To understand the long-term effectiveness and safety of agalsidase alfa on the clinical course of Fabry disease
- To provide high quality real-world clinical data, analyses and evidence to support improvements in the treatment and management of Fabry disease

March 2010:

22 Countries, 144 clinics, 1850 patients

HOS - Hunter Outcome Survey

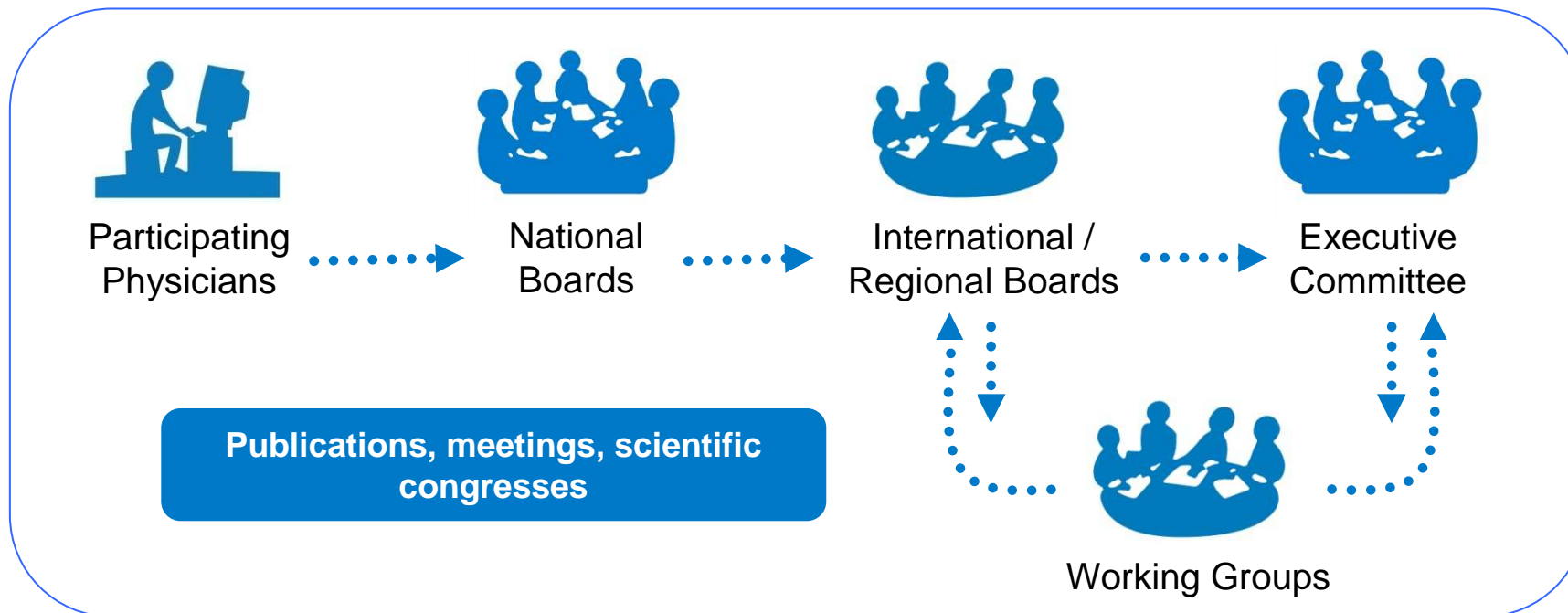
Patient Registry for Hunter syndrome established in 2005

Key aims

- To understand the natural history of Hunter syndrome
- To understand the long-term effectiveness and safety of idursulfase on Hunter syndrome
- To provide high quality real-world data, analyses and evidence to support improvements in the treatment and management of Hunter syndrome

March 2010:

24 Countries, 107 clinics, 756 patients



Data collection and storage



User-friendly application¹

Input of data to the Patient Registry
Clinic level patient management



Secure encrypted data communication

Secures access between the user application and database



Application and Database Server(s)

Managed by an independent external service provider



Data Quality

Data entry checks, clarification requests, complete audit trail

¹ The collection and processing of data (PC PAL Application Framework) complies with local and national requirements on the processing of personal data and the protection of privacy.

Challenges in collecting high quality global data on ORD

- Few patients affected, as many as possible to be included into the registry (global)
- Data collection to registry is not mandatory for the participating clinics
- Small clinics only follow few patients, registry is not on the top of their mind
- Patients do not come regularly to the clinic, the less severe, the fewer visits and follow up (Treated severe patients are more closely investigated)
- Rare chronic diseases are often multi systemic, followed up by different specialists with different management approaches, renal, cardiac, neurology...
- Parallel existing registries, other companies, HTA.

Application used for data capture;

In rare diseases clinics will not enter data every week;

Application must be user friendly (self explanatory)

- added value to the clinic in terms of support of patient management,
- direct access to own entered data as well as aggregated info on all patients in the registry

Hunter Outcome Survey - 1.00

Current data section: General Exam (BL) 2002-02-12

ENTERED

Submit

WELCOME

PATIENT

Select Patient

Patient Info

Addresses

Diagnosis

Medical History

VISITS

Examinations

Signs & Symptoms

Medication & Therapy

Laboratory Data

Investigations

Adverse Events

Local Data

QUESTIONNAIRES

HS-Focus

DATA CHECK SECTION

Overview

UTILITIES

Query

General exam | Neurological | Milestones | Infection | Surgery | Hospitalization | Photo / Video

General exam

Height / Length

Height / Length

Weight

BMI

BSA

Head circumference

Heart rate

BP Systolic

BP Diastolic

Respiratory rate

Oxygen dependent

Heart failure

NYHA grade

Spleen palpable

Liver palpable

In puberty

Pubic hair stage

Genital / Breast stage

Next scheduled visit

Follow up schedule

FOS Info

FOS

FOS Num: ES 17 1244 Initials: PCM Birthday: 12/06/1957

Family Num: 509 Sex: Female Age: 49.4 Yrs

RENAL

Creatinine in blood mg/dl

Date	Creatinine	Units	Status	Range
11/04/2002	112	0.5	mg/dl	Normal
11/04/2003	67	0.7	mg/dl	Normal
11/09/2004	75	0.8	mg/dl	Normal
08/11/2004	13.3	0.5	mg/dl	Normal
02/09/2005	8	0.8	mg/dl	Normal
11/17/2005	37.2	0.7	mg/dl	Normal
11/09/2006	37.9	0.8	mg/dl	Normal

eGFR

Date	Creatinine	eGFR	Range
11/04/2002	23.2	17.1	
11/04/2003	41.1	17.2	
11/09/2004	13.3	17.3	
08/11/2004	13.5	17.8	
11/09/2005	23	15.1	
11/09/2006	17.9	17.3	

<18 Years: Schwartz method
>=18 Years: MDRD method

Start of Replagal 18/04/2003 Time 42 Months Stop of Replagal

FOS has contributed to increased understanding of Fabry disease

Males – FOS has provided details of the natural progression and range of signs and symptoms experienced.²

Females – FOS has confirmed that women are not simply ‘carriers’ of Fabry and that some women experience the full range of symptoms experience by men.^{2,3}

Children – FOS has shown that neurological, gastrointestinal and dermatological symptoms are experienced by children, impacting on their quality of life.^{2,4}

1. *Fabry disease: Perspectives from 5 years of FOS*. Mehta A, Beck M, Sunder-Plassmann G (Eds) 2006. Oxford PharmaGenesis,
2. Mehta A, et al. *Eur J Clin Invest*. 2004; 34: 236-242.
3. Deegan PB, et al. *J Med Genet*. 2006; 43: 347-352.
4. Ramaswami, U, et al. *Acta Paediat*. 2006; 95: 86-92.

HOS has contributed to increased understanding about Hunter syndrome

-By six years of age \approx 50% of patients show cardiovascular abnormality, increasing to \approx 90% by 15 years of age¹

-Median age at onset of symptoms is 1.5 years²

-Median age at diagnosis is 3.5 years²

-Otitis media and abdominal hernia are earliest presenting Symptoms²

-Most patients demonstrate characteristic facial features (95%) and enlarged liver/spleen (89%)²

-Stunted growth has been commonly observed in Hunter syndrome.

HOS has described that patients experience normal growth until 9 or 10 and thereafter fall below the 3rd percentile

¹ Wraith JE et al. *Clinical characteristics of patients with mucopolysaccharidosis type II: the Hunter Outcome Survey (HOS)*. Abstract ASHG Oct 23-27, 2007.

² Wraith JE et al; *Initial report from the Hunter Outcome Survey*. *Genetics in Medicine*. 10(7):508-516, July 2008

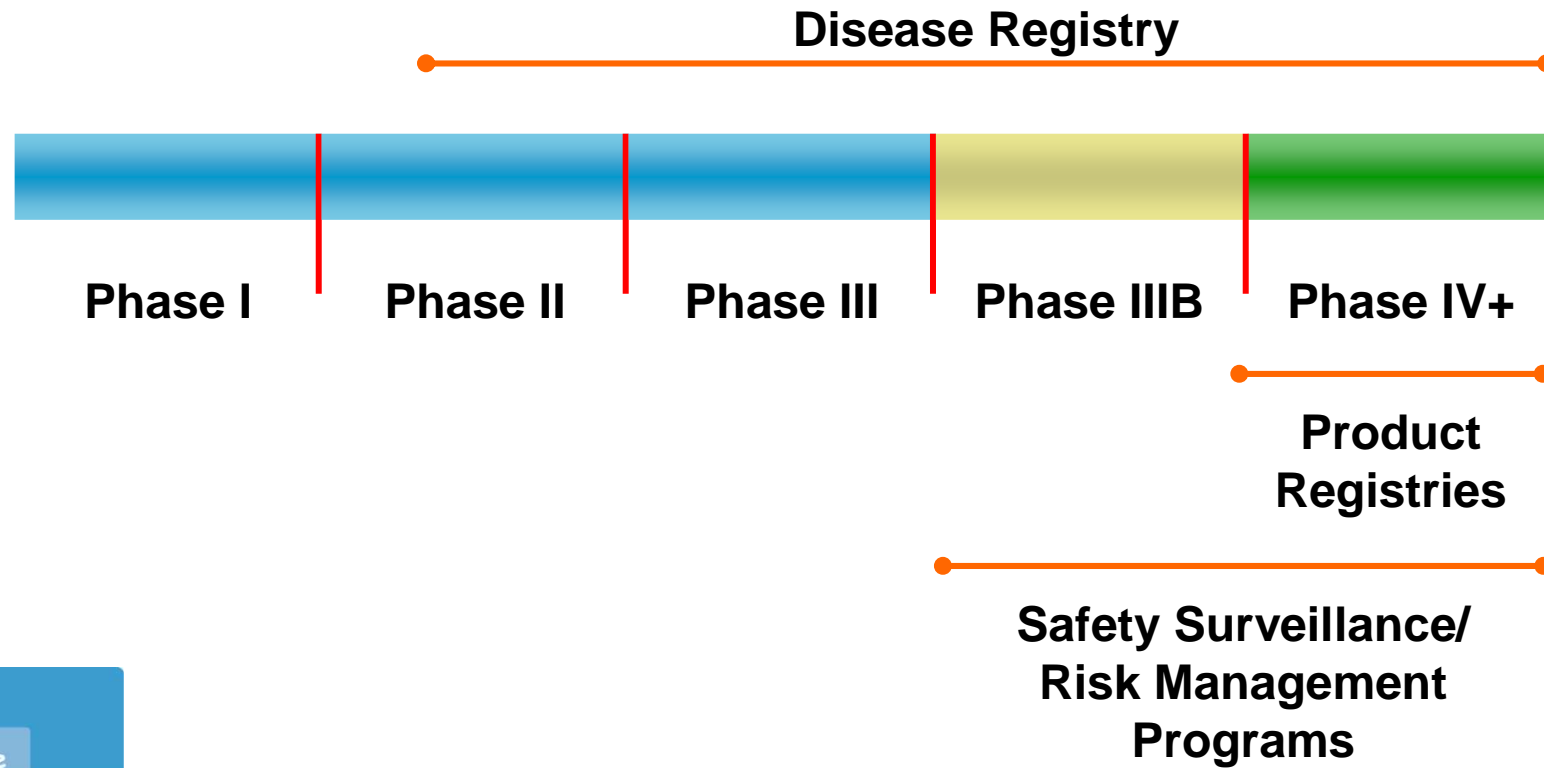
ORD Issues moving forward

- Price and reimbursement
- The lack of available Natural History data
- Linking patient registries; need for standards

ORD Issues moving forward

- The pressure from payers will increase, they need to be assured about treatment outcome (in many countries continuous reevaluations)
 - What is acceptable treatment outcome in a progressive disease?
 - Slower progression?
 - Stabilization?
 - Regression to normal?
 - Prevention?
 - What to compare with? Often limited natural history data available
- Start to collect data before treatment is available
 - Develop sensitive Disease Severity Index
 - Genotype/phenotype

Start earlier than today to collect Natural History data

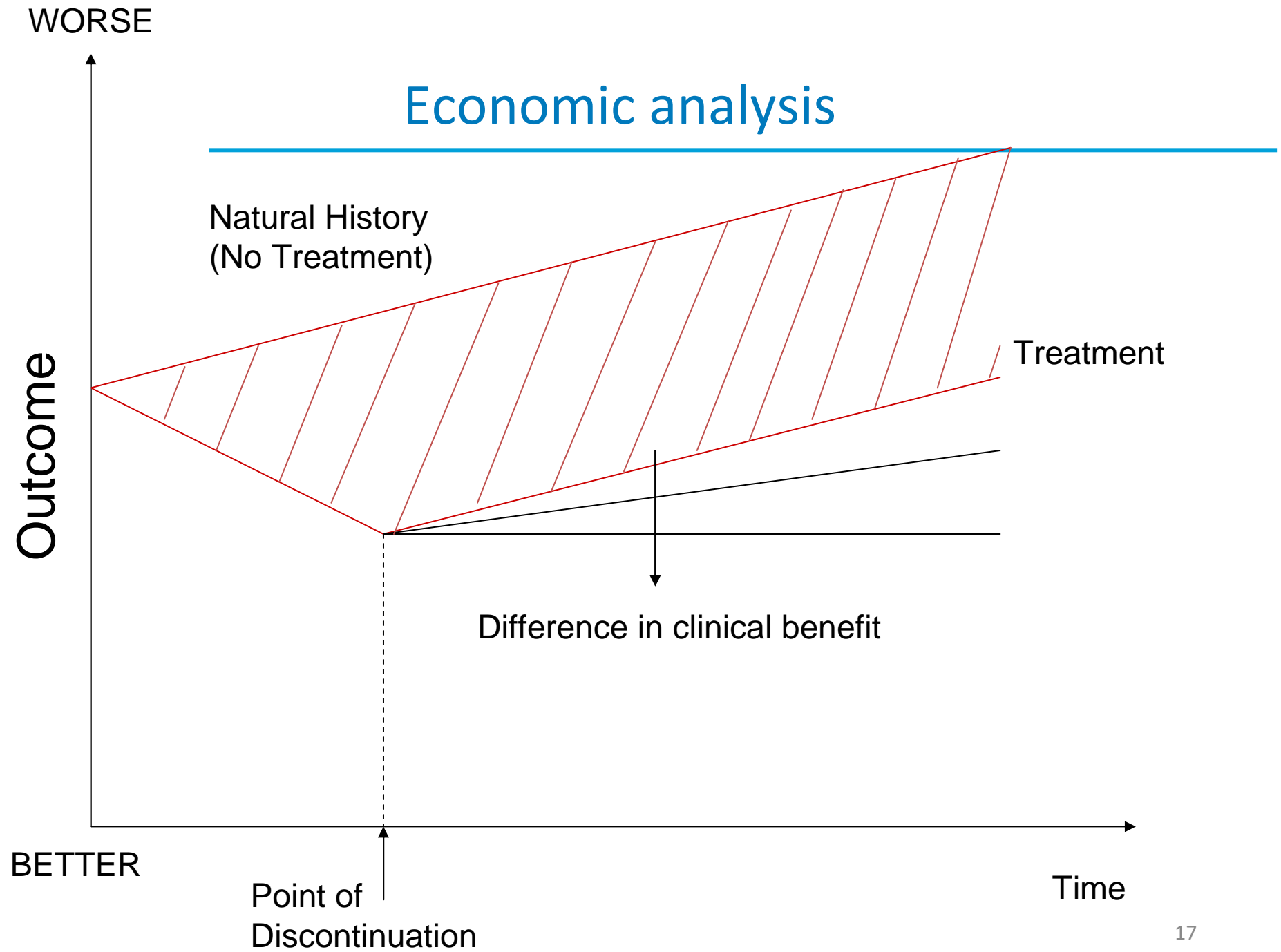


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 - What to compare with? Often limited natural history data available
- Data should also be collected directly from patients (PRO)
 - How does the treatment affect their lives?
 - Impact on direct and indirect costs
 - Resource utilization data

ORD Issues moving forward

- The pressure from payers will increase, they need to be assured about treatment outcome (in many countries continuous reevaluations)
 - What is acceptable treatment outcome in a progressive disease?
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 - Regression to normal?
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 - What to compare with? Often limited natural history data available
- Data should also be collected directly from patients (PRO)
- Available Health Economic models do not work for ORD, risk patients will not continue on treatment
 - Other ways on how to look upon the data needs to be evaluated



ORD Issues moving forward cont

- In many countries there are several parallel initiatives on data collection (HTA, Industry, National Registries etc)
 - Avoid double/triple data entry
 - A need to be able to access all collected information on a disease
 - Evidence based patient treatment
 - Develop prediction models
 - Apply personalized health care

Linking data from different sources

Generic Standards;

CDISC/CDASH

HL7

etc

Lysosomal Storage Disorders (LSD) as an example

- >40 diseases classified as LSD
- Enzyme replacement therapy (ERT) available for 5
- Additional ERT current in Clinical Trial Programs
- More than one treatment available for some of them
- Clinics are dealing with several patient registries/ disease
- Over the years one particular patient may be treated with different approaches
 - Different pharma needs "their" data on safety, effectiveness and HEOR
 - Treating physician wants all info in one place for their patients

LSD “Red Flag” Symptoms*

Develop Standards for LSD?

- Coarse facial features
- Corneal clouding
- Angiokeratoma
- Umbilical/inguinal hernias
- Short stature
- Skeletal deformities
- Organomegaly
- Muscle weakness
- Neurologic failure/decline

Severity grading needed using preferably one standard

Yes, No not enough

Summary Issues moving forward

- Price and reimbursement
- The lack of available Natural History data
- Linking patient registries
 - A common standard (EU) for data collection on ORD would facilitate linking between registries and avoid several data entry on the same data