HSE Guidelines for the Treatment of Fabry Disease

This document is intended for use by healthcare professionals only.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgment or specialist consultation.

Guideline: HSE Guidelines for the Treatment of Fabry Disease		Published: February 2022 Review: February 2025	Version number: 1
Protocol Code: ERT001	Approved by: Dr Mike O'Connor National Clinical Advisor & Group Lead, Acute Hospitals	Contributors: Prof E Crushell, Dr J Hughes, Prof A Monavarii, Prof J O'Byrne, E Losty, H Byrne, F King, R ONeill	Page 1 of 16

Fabry Disease (FD) Guidelines

These FD guidelines have been adapted with permission from the UK Guideline for the treatment of FD. The guidelines have been reviewed by a group of prescribing physicians and healthcare professionals working in the treatment centres of excellence in Ireland. The guidelines are designed to standardise practice and support the implementation of treatment pathways for these patients in Ireland.

Lysosomal Storage Disorder (LSD) Advisory Group Position Statement:

Patient care for FD should be led by the centres of excellence with access to a multidisciplinary team with specialist interest in the management of patients with inherited LSDs.

Contents

Introduction

The enzyme replacement treatments (ERT) outlined in this guideline should be initiated in an appropriate setting for the management of FD. A specialist, consultant led, experienced multidisciplinary team who are part of the tertiary treatment centre at the Mater Misericordiae University or at The National Centre for Inherited Metabolic Disorders in CHI at Temple Street. Paediatricians will undertake to refer patients to the adult centre on reaching the age of 16-18 years. Adult and paediatric centres undertake to ensure as much as possible a seamless transfer of care.

Collaboration between the tertiary treatment centres and local primary and secondary care services is imperative to ensuring FD patients receive high standards of care. Local primary and secondary care clinicians will undertake to ensure all FD patients are referred to the specialist team in the tertiary centre for review/ input. They will endeavour to support local colleagues wherever necessary. Prior to commencing treatment there should be a full discussion regarding the expected outcomes of therapy and the possibility of treatment discontinuation should the disease continue to progress. As FD is a chronic, slowly progressive disorder and the aim of treatment is to delay/ reverse progression or to stabilise current parameters it is anticipated that treatment will be most effective when started early in the course of the disease. Treatment late in the course of the disease may have limited efficacy.

Audit

Clinical audit will be undertaken on a biannual basis. This audit will specifically review the patient cohort to ensure that clinical outcome targets (measure of efficacy) as listed in this document are reviewed and recorded. A recent EMA audit highlighted the need for disease specific registries for outcome evaluation and benefit-risk monitoring of medicinal products. Clinical research, to include outcome analysis and audit, should play a central role in Centres of Expertise. A top–down approach to support research for Centres of Expertise is recommended. Financial audit will be undertaken in relation to reimbursement of treatment reimbursed centrally. This will specifically monitor the claims made and compliance with eligibility criteria.

Funding of Treatment

FD patients within the public health system will be funded for their treatment by the Health Service Executive (HSE). Prior funding agreement will be sought before initiation of treatment for eligible patients. Once approval for funding has been received (co-ordinated via the Acute Hospitals Drugs Management Programme (AHDMP) ahdmp@hse.ie) treatment can be initiated. All new patients and dose increases for existing patients require prior approval via the Enzyme Replacement Therapy (ERT) committee. Funding approval applications can be made and sent to ahdmp@hse.ie.

Cost Saving Measures

For adult patients with an increased BMI the dose will be capped as for a BMI of 27kg/m^2

No drug should be wasted. Doses should be rounded to ensure whole vials are being used. Doses may alternate to facilitate this.

Part 1: HSE Adult Guideline for the Diagnosis and Treatment of Fabry Disease

1.1 FD diagnosis

A diagnosis of FD is only confirmed where

- α-galactosidase A (α-Gal A) deficiency is demonstrated
- A *GLA* gene variant of documented pathogenicity is present

Genotyping in female patients is essential as enzymatic levels of the female heterozygote may lie within the normal range even when patients are symptomatic.

GLA gene variants of uncertain significance (VUS) in subjects with single organ involvement pose a diagnostic challenge. If the diagnosis remains uncertain, the following may provide supportive evidence of pathogenicity:

- biopsy of the affected organ (e.g. kidney or heart) to demonstrate the characteristic storage pattern by electron microscopy
- characteristic FD cardiomyopathy findings on cardiac magnetic resonance imaging (cMRI)
- evidence of Gb3 accumulation in urine
- plasma lyso-Gb3 levels ≥ 2.7 nM (diagnostic sensitivity and specificity of 100% in patients with "non-classic' *GLA* variants)

1.2 Treatment:

ERT for adults (≥ 16 years) with a confirmed diagnosis of FD and who meet the treatment starting criteria:

Agalsidase alfa (Replagal®) 0.2 mg/kg* in 100mls NaCl 0.9% IV over 40 minutes every other week
or
Agalsidase beta (Fabrazyme®) 0.3-1.0 mg/kg* in 500mls NaCl 0.9% IV over 4 hours (reducing to 90 minutes as tolerated) every other week

Oral therapy for adults (≥ 16 years) with a confirmed diagnosis of FD and who have an amenable pathogenic variant to meet the treatment starting criteria for migalastat:

Migalastat (Galafold®) 123 mg (1 capsule) once every other day by mouth at the same time of day.

1.3 Inclusion and Starting Criteria

Inclusion Criteria:

Patient must attend for medical appointments and investigations as determined by the clinical team.

Starting Criteria:

In males with "classical variants" (leucocyte enzyme activity <5% and a classical phenotype) Fabry - specific therapy should be considered at diagnosis.

In males with 'later onset' disease and in adult females, Fabry-specific therapy should commence when one of the following criteria are fulfilled:

Evidence of Fabry-related renal disease (one of):

- Chronic kidney disease (CKD) stage 3: at least 2 consistent estimates or measured GFR over a minimum of 6 months.
- CKD stage 2: at least 3 consistent estimates or measured GFR over at least 12 months with a GFR slope greater than age-related normal (0.8-1.0 ml/min/year)
- Persistent proteinuria:
    - In males Proteinuria >300 mg/24 hours *or*
    - Increased albumin:creatinine or protein:creatinine ratio for males
    - Females seldom progress to end stage renal failure (ESRF). In females, if proteinuria is the only presentation – anti-proteinuria medications (ACEi/ARB) should be tried in the first instance for a minimum period of 12 months.

Evidence of Fabry-related cardiac disease (one of):

- LV wall thickness >13 mm in males and >12 mm in females.
- LV mass index by 2D echo / cMRI above normal for age and sex.
- Late gadolinium enhancement on cMRI.

General symptoms of FD*:*

- Uncontrolled pain or gastrointestinal symptoms leading to a need to alter lifestyle or which significantly interferes with quality of life.

Comments:

- Patients whose sole eligibility criterion is gastrointestinal symptoms should have been assessed first by a gastrointestinal team, with a trial of conventional GI therapy.
- Patients whose sole eligibility criterion is pain should have been assessed first by a specialist pain team, with a trial of conventional pain therapy.
- If Fabry related symptoms are the only indication for consideration of Fabry-specific therapy a trial could be given for a year with pre-specified outcomes agreed as to what would constitute a positive effect for symptom control. Such outcomes may include:

- Reduction in the need for analgesia
- Reduction in time lost from work
- Significant Improvements in validated pain scores and / or quality of life measures.

1.4 Exclusion Criteria for starting Fabry-specific therapy

- The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy
- Patients with FD who are deemed too severely affected to benefit from enzyme replacement therapy (e.g. Severely incapacitated following stroke/ dementia)
- End stage renal failure requiring dialysis in the absence of other starting criteria
- Migalastat is not recommended for use in patients with severe renal insufficiency, defined as estimated GFR less than 30 mL/min/1.73m^2
- Pregnancy should be discussed prior to commencing any Fabry-specific therapy

1.5 Measures of Efficacy (including Goals)

Biochemical:

- Plasma lysoGb3 concentration (reduction from baseline by 20% after ≥ 12 months of therapy)

Renal function:

- eGFR change (decline by <4ml/min/1.73m^2/year)
- Initiation of renal replacement therapy or renal transplant (no requirement)

Cardiac Function:

- Left ventricular mass index (gain < 6gm/m^2 over the previous 3 year period)
- Cardiac rhythm monitoring (No requirement for therapeutic device insertion)
- Systolic and diastolic function (to prevent dysfunction with worsening of heart failure symptoms)

Other:

- Neurological endpoints (No new TIA/stroke)
- Brief pain inventory score (improvement)
- EQ5D Quality of life score (improvement)
- Composite clinical endpoint to include new renal end stage renal disease, arrhythmia requiring pacemaker or defibrillator, stroke or death (improvement)

1.6 Follow up and monitoring

Patients receiving Fabry-specific therapy should have at least a 12 monthly review in person at an LSD centre, with an additional review every 6 months (in person, or by telephone as clinically indicated) including the following assessments:

	Baseline	6 months	Yearly	Every 3-5 years
General				
Medical History (incl DHx)	X	X	X	
Clinical Examination	X	X[1]	X	
Family Pedigree	X			
Pain Score (BPI)	X		X	
QoL Score (EQ5D, Fabry specific)	X		X	
Investigations				
ECG	X		X	
24 hour ECG	X		X	
ECHO or Cardiac MRI	X		X[2]	
T2 MRI Brain	X			X[2]
Ophthalmology	X			X
Audiology	X			X
Laboratory Ix				
FBC	X		X	
U&E	X		X	
Spot urine albumin/ creatinine ratio or protein/ creatinine ratio	X	X[1]	X	
Other				
Lipid profile	X	X[1]	X	
Plasma Lyso-Gb3	X	X[2]	X	
Highly sensitive Troponin[2]	X	X[1]	X	

[1] **Unless virtual review** [2]**Clinical discretion**

Vital signs and adverse events should be recorded at each ERT infusion (unless patients are self-administering enzyme).

Efficacy measure follow up and monitoring to be carried out in collaboration between tertiary centres and local services.

1.7 Stopping Criteria

General

- Intolerable and unavoidable adverse effects
- Coexisting illness where either long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for FD
- At the request of the patient, or properly allocated guardian acting in the patient's best interests, if the patient is properly deemed not competent
- If the circumstances of the patient's lifestyle are such that sufficient compliance with treatment is not possible
- If the health and wellbeing of medical and / or nursing staff are placed under significant threat as a result of the actions or lifestyle of the patient
- Emigration of the patient outside the jurisdiction of the Republic of Ireland, when administration and funding of the treatment becomes the responsibility of Health Services in the new country of residence / domicile

Specific

Objective evidence of progression in measured clinical criteria which are not

- attributable to a secondary pathology
- commensurate with natural age-related decline
- remediable by changing product or institution or other simple therapeutic measure
- within the normal measured variation of that laboratory parameter
- out-weighed in clinical significance by stabilisation or improvement in one of the other criteria

  On the basis of current major criteria these might include:

  - Deterioration of eGFR by more than 4 ml/min/1.73m2/year and / or requiring renal replacement therapy
  - Progressive impairment of systolic or diastolic dysfunction resulting in worsening heart failure symptoms
  - Gain in LVMI > 6 gm / m2 over a three year period
  - Rhythm disturbance requiring therapeutic device insertion in the absence of other demonstrable benefit
  - New presentation of clinically significant neurovascular disease in the absence of other demonstrable benefit
  - Worsening of pain or gastrointestinal symptoms beyond baseline or no improvement if these are the only reasons to start treatment
  - Failure of reduction of plasma lysoGb3 or increase after initial response

Note:

In patients with a known cardiac variant form, without any other significant organ involvement then cardiac assessment alone is an appropriate tool for decision making.

Part 2 HSE Paediatric Guideline for the Diagnosis and Treatment of Fabry Disease

2.1 Diagnosis

A diagnosis of FD is only confirmed where

- α-galactosidase A (α-Gal A) deficiency is demonstrated
- A *GLA* gene variant of documented pathogenicity is present

Genotyping in female patients is essential as enzymatic levels of the female heterozygote may lie within the normal range even when patients are symptomatic.
GLA gene variants of uncertain significance (VUS) in subjects with single organ involvement pose a diagnostic challenge. If the diagnosis remains uncertain, the following may provide supportive evidence of pathogenicity:

- biopsy of the affected organ (e.g. kidney or heart) to demonstrate the characteristic storage pattern by electron microscopy
- characteristic FD cardiomyopathy findings on cardiac magnetic resonance imaging (cMRI)
- evidence of Gb3 accumulation in urine
- plasma lyso-Gb3 levels ≥ 2.7 nM (diagnostic sensitivity and specificity of 100% in patients with "non-classic' *GLA* variants)

2.2 Treatment:

ERT for children < 16 years with a confirmed diagnosis of FD and who meet the treatment starting criteria:

Agalsidase alfa (Replagal®) 0.2 mg/kg in 100 mls of NaCl 0.9% IV over 40 minutes every other week
OR
Agalsidase beta (Fabrazyme®) 0.3-1.0 mg/kg in 500 mls of NaCl 0.9% IV over 4 hours (reducing to 90minutes as tolerated) every other week

Oral therapy for children ≥12 years and ≥45kg with a confirmed diagnosis of FD and who have an amenable pathogenic variant to meet the treatment starting criteria for migalastat:

Migalastat (Galafold®) 123 mg (1 capsule) once every other day by mouth at the same time of day.

2.3 Inclusion and Starting Criteria

Inclusion Criteria:

Patient must attend for medical appointments and investigations as determined by the clinical team.

Starting Criteria (one or more of the following)

Disease-modifying therapies should be considered when there are documented FD related clinical manifestations. There is no evidence currently that treating asymptomatic children prevents disease progression in classical and later onset variants.

FD related renal disease (one of):

- Persistent microalbuminuria (3 consecutive early morning urine samples or 3 random early morning urine samples over a period of six months)
- Reduction in estimated / measured GFR (after a review by nephrologist and other causes have been excluded).

FD related cardiac disease (one of):

- LV mass index by 2D echo / cMRI above normal for age or increased by 2SD over a 12 to 24 month period
- ECG: arrhythmias, shortening or prolonged PR interval on age appropriate ECG analyses

Evidence of general symptoms of FD:

- Isolated neuropathic pain:

  Acroparesthesia confirmed by the LSD physician to be Fabry specific and not responding to basic analgesia may be sufficient to consider ERT.

  Comments:

  Whilst analgesia for acroparesthesia must be considered for a minimum period of 6 months in a child less than ten years of age, neuropathic pain is frequently the first Fabry symptom in children and hence defines a more severe cohort. This occurs in approximately 60% of children with "classic" *GLA* gene variants.

- Unexplained gastrointestinal (GI) symptoms affecting quality of life (following exclusion of other GI pathology)

  Comments:

  Common causes for childhood GI symptoms such as food allergies, coeliac disease, or infections must be excluded first; prior to considering ERT for GI symptoms in children. Review by a gastroenterologist to ensure all common causes for GI symptoms are excluded with / without GI endoscopy is recommended.

2.4 Exclusion criteria

- The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy.
- Situations where the burden of treatment is deemed by the patient and MDT (including family) to outweigh benefits

2.5 Measures of Efficacy (including goals)

An improvement in or a prevention of deterioration in:

- Age appropriate paediatric pain scores/ devices (improvement)
- School attendance (improvement)
- Analgesia (Reduction)
- Age appropriate Quality of Life score (improvement)
- Growth and development (improvement/ or stabilisation if normal)
    - Growth and development are infrequently affected in FD children. If there are concerns than other causes should be explored without delay

Comment

CKD /ESRD are very rare in children with AFD. A paediatric nephrologist should evaluate children with these manifestations and exclude other causes.

2.6 Follow up & monitoring (See also appendix 2.0 below)

- Clinical review
- School attendance
- Growth and development
- Pain and QoL questionnaires
- Urine albumin/creatinine ratio (spot urine; 3 x consecutive urine samples if random early morning spot urine abnormal)
- Urine protein/creatinine ratio (random spot urine)
- Plasma lyso-Gb3
- ECG; cardiac ECHO (baseline and thereafter as indicated)
- Ophthalmology with slit lamp examination (baseline and thereafter as indicated)
- Age specific audiology (baseline and thereafter as indicated)

Boys and girls < 5 years:

- Arrange clinical review if indicated.

Boys and girls ≥ 5 years and < 10 years:

Boys with classic pathogenic variants:

- Frequency of review as clinically indicated by the treating clinician eg. 12 to 24 monthly.

Girls and boys with late-onset variants:

- Frequency of review as clinically indicated by the treating clinician eg. 24 to 36 monthly.

Boys and girls ≥ 10 and < 14 years:

Monitor as above (every 12 months) and include:

- Calculated GFR (Counahan-Barratt [CB] method or Schwartz)
- MRI brain if clinically indicated only (stroke/symptoms of TIA/other neurological symptoms. Arrange review by a paediatric neurologist and other causes excluded)

Boys and girls ≥ 14 and <16 years with classic variants:

Monitor as above (every 12 months) and include:

- Cardiac MRI (optional but preferred)
- Measured GFR once every 3 years, with calculated GFR (CB method) annually
- Baseline MRI brain only if clinically indicated
- Audiology at 14 years and thereafter as clinically indicated

Patients on ERT will be reviewed every 6 months by the paediatric metabolic team

2.7 Stopping Criteria

- Severe life threatening infusion associated reactions that cannot be managed by standard protocols, including desensitisation
- Other life threatening / life limiting illness
- Poor compliance – consider a safe-guarding referral if deemed appropriate
- End stage renal failure due to other causes that cannot be treated, or that is not suitable for renal transplant when there are no other Fabry specific symptoms.
- Situations where the burden of treatment is deemed by the patient and MDT (including family) to outweigh benefits

Appendix 1.0 Adult check list for efficacy measure follow up and monitoring to be carried out in collaboration between tertiary centres and local services. This form should be saved in the patient's medical record. Additional forms may be used to record on-going 6 monthly and yearly reviews.

Patient Details									***Affix patient Addressograph if available**
MRN				**Surname**					
First name				**Gender**					
DOB				**Address**					
	Baseline		**6 monthly**		**Yearly**		**Every 3-5 years**		
General		**Date Completed**		**Date Completed**		**Date Completed**		**Date Completed**	
Medical History (incl DHx)	**X**		**X**		**X**				
Clinical Examination	**X**		**X[1]**		**X**				
Family Pedigree	**X**								
Pain Score (BPI)	**X**				**X**				
QoL Score (EQ5D, Fabry specific)	**X**				**X**				
Investigations									
ECG	**X**				**X**				
24 hour ECG	**X**				**X**				
ECHO or Cardiac MRI	**X**				**X[2]**				
T2 MRI Brain	**X**						**X[2]**		
Ophthalmology	**X**						**X**		
Audiology	**X**						**X**		
Laboratory Ix									
FBC	**X**				**X**				
U&E	**X**				**X**				
Spot urine albumin/ creatinine ratio or protein/ creatinine ratio	**X**		**X[1]**		**X**				
Other									
Lipid profile	**X**		**X[1]**		**X**				
Plasma Lyso-Gb3	**X**		**X[2]**		**X**				
Highly sensitive Troponin[2]	**X**		**X[1]**		**X**				

Unless virtual review **[2]Clinical discretion**

Appendix 2.0

Paediatric check list for efficacy measure follow up and monitoring to be carried out in collaboration between tertiary centres and local services. This form should be saved in the patient's medical record. Additional forms may be used to record on-going 6 monthly and yearly reviews.

Patient Details							*Affix patient Addressograph if available
MRN			**Surname**				
First name			**Gender**				
DOB			**Address**				
	Baseline		**6 monthly**		**Yearly**		**Intervals at Clinical discretion**
General		**Date Completed**		**Date Completed**		**Date Completed**	**Date Completed**
Medical History (incl DHx)	X		X		X		
Clinical Examination	X		X[1]		X		
Family Pedigree	X						
Pain Score (BPI)	X				X		
QoL Score	X				X		
Investigations							
ECG	X				X		
ECHO	X						
Ophthalmology	X						
Audiology	X						
Laboratory Ix							
FBC	X				X		
U&E	X				X		
Spot urine albumin/ creatinine ratio or protein/ creatinine ratio	X		X[1]		X		
Other							
Lipid profile	X		X[1]		X		
Plasma Lyso-Gb3	X		X[2]		X		

[1] **Unless virtual review** [2]**Clinical discretion**

Appendix 3.0 Membership of the Lysosomal Storage Disorders Clinical Advisory Group (February 2022)

- Chair: Ms Helen Byrne, Assistant National Director, Acute Operations
- Ms Fionnuala King, Chief Pharmacist, AHDMP.
- Ms Rhona O'Neill, Chief II Pharmacist, AHDMP.

Representation from Paediatric Centre

- Prof Ellen Crushell, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Dr Joanne Hughes, Consultant Paediatrician, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Prof. Ahmad Monavari, Consultant Metabolic Paediatrician, Clinical Director, National Centre for Inherited Metabolic Disorders, CHI at Temple Street.
- Ms Eithne Losty, Lysosomal Storage Disorders Clinical Nurse Specialist.

Representation from Adult Centre

- Prof. James O'Byrne Consultant Physician, National Centre for Inherited Metabolic Disorders, Mater Misericordiae University Hospital, Dublin

Appendix 4.0 Revision History

Revision number	Revision date	Summary of changes

References:

1. HSE National Clinical Programme for Rare Diseases. 2019. Model of Care for Rare Diseases. Available at: https://www.hse.ie/eng/about/who/cspd/ncps/rare-diseases/resources/model-of-care-for-rare-diseases.pdf [Accessed December 2021]
2. Jonker, C.J., *et al. Registries Supporting New Drug Application.* Pharmacoepidemiology and Drug Safety 2017; 26(12): p.1451-1457.
3. Highly Specialist LSD Service. 2020. *Guidelines for the treatment of Fabry Disease.* [Edition 2]. United Kingdom: British Inherited Metabolic Disease Group.
4. Ortiz A, Germain DP, et al. *Fabry disease revisited: Management and treatment recommendations for adult patients.* Molecular Genetics and Metabolism 2018; 123: 416-427
5. Germain, D.P., et al., *Use of a rare disease registry for establishing phenotypic classification of previously unassigned GLA variants: a consensus classification system by a multispecialty Fabry disease genotype-phenotype workgroup.* J Med Genet, 2020. **57**(8): p. 542-551.
6. Caputo, F., et al., *Gastrointestinal Involvement in Anderson-Fabry Disease: A Narrative Review.* Int J Environ Res Public Health, 2021. **18**(6).
7. Arends, M., et al., *Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study.* J Am Soc Nephrol, 2017. **28**(5): p. 1631-1641.
8. Azevedo, O., et al., *Fabry Disease Therapy: State-of-the-Art and Current Challenges.* Int J Mol Sci, 2020. **22**(1).
9. Felis, A., et al., *Current and Investigational Therapeutics for Fabry Disease.* Kidney Int Rep, 2020. **5**(4): p. 407-413