


## REVIEW

# Impact of SARS-CoV-2 (COVID-19) pandemic on patients with lysosomal storage disorders and restoration of services: experience from a specialist centre

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## Key words

COVID-19, lysosomal storage disorder, outpatient, restoration, enzyme replacement therapy.

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## Abstract

This study aims to evaluate the impact of the COVID-19 pandemic on the lysosomal disorders unit (LSDU) at Royal Free London NHS Foundation Trust (RFL), a highly specialised national service for diagnosis and management of adults with lysosomal storage disorders (LSD). Review of home care enzyme replacement therapy (ERT) and emergency care, and COVID-19 shielding categories as per UK government guidance. New clinical pathways were developed to manage patients safely during the pandemic; staff well-being initiatives are described. LSDU staff were redeployed and/or had additional roles to support increased needs of hospitalised COVID-19 patients. During the first lockdown in March 2020, 286 of 602 LSD patients were shielding; 72 of 221 had home care ERT infusions interrupted up to 12 weeks. During the pandemic, there was a 3% reduction in home care nursing support required, with patients learning to self-cannulate or require support for cannulation only. There were no increased adverse clinical events during this period. Twenty-one contracted COVID-19 infection, with one hospitalised and no COVID-19 related deaths. In 2020, virtual clinics were increased by 88% (video and/or telephone) compared to 2019. RFL well-being initiatives supported all staff. We provide an overview of the impact of the COVID-19 pandemic on staff and patients attending a highly specialised rare disease service. As far as we are aware, this is the first detailed narrative on the challenges and subsequent rapid adaptations made, both as part of a large organisation and as a specialist centre. Lessons learnt could be translated to other rare disease services and ensure readiness for any future pandemic.

## Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus that first emerged in late December 2019 in Wuhan, Central China. It soon resulted in a global pandemic causing the most serious public health emergency due to a respiratory virus since the 1918 H1N1 influenza pandemic (Spanish Flu). In February 2020, the first symptomatic cases had been reported in several European (EU) countries including the United Kingdom (UK).<sup>1,2</sup>

According to Worldometer, a provider of global COVID-19 statistics, as of 15 April 2021, the COVID-19

pandemic has resulted in a total of 139 665, 313 confirmed cases and 2 999 215 deaths across 222 countries.<sup>3</sup>

The National Health Service (NHS) is a publicly funded healthcare system with guiding principles of care that is comprehensive, universal and free at the point of delivery care for all patients in the UK. During the pandemic, NHS staff and services had to radically adapt in response to the acute needs of people infected with SARS-CoV-2 while continuing to deliver urgent healthcare for conditions other than COVID-19.

The Lysosomal Disorders Unit (LSDU) at the Royal Free London NHS Foundation Trust (RFL) is one of eight Highly Specialised NHS England (NHSE) designated centres for the diagnosis and management of lysosomal storage disorders (LSD). In England, there are five adult

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and three paediatric centres. RFL LSDU has one-stop multidisciplinary clinics for patients from across the UK, providing comprehensive multidisciplinary life-long care for the diagnosis, management and follow up of patients and families. We describe our experience of managing patients safely during the COVID-19 pandemic.

## Aims

To evaluate the impact of the Covid-19 pandemic on patients and staff at the RFL LSDU, a highly specialised national service for diagnosis and management of adults with LSD. We describe organisational and specialist service responses and lessons learnt to ensure patient safety and staff well-being.

## Methods

All LSD patients were contacted, home care enzyme replacement therapy (ERT) and emergency care reviewed, patients were categorised to shielding groups as per UK government guidance. The impact of home care ERT interruption and/or COVID-19 infections were evaluated. New clinical pathways developed to manage LSD patients safely during the pandemic and staff well-being initiatives are described.

## Ethical approval

This is a narrative of the service delivery during the COVID-19 pandemic, restoration of services and lessons learnt with no patient identifiable information and does not require ethical approval.

## Results

### Covid-19 outbreak, lockdown and tiered restrictions

On 17 March 2020, in response to the first wave of COVID-19 outbreak, the UK government announced the first period of national lockdown for 12 weeks, which was extended for a further 4 weeks. Subsequently, the UK has had two further tiered lockdowns in early November 2020 and January 2020 due to rising COVID-19 infections.

During the pandemic, critical care and respiratory support needs trebled in some hospitals across the UK. This required hospital infrastructure changes to increase bed capacity for treating COVID-19 patients, whilst ensuring strict infection control measures to prevent the spread of the virus in hospitals. The pressure on hospitals was therefore very significant, as urgent medical care for non-COVID-19 conditions had to also be managed at the

same time as the increasing hospitalisations due to COVID-19. Non-urgent elective medical and surgical care were postponed. These changes also posed challenges for the management of patients with long-term, complex rare diseases.

### RFL LSD unit response to COVID-19 national lockdown in March 2020

LSD are rare monogenic inherited metabolic disorders resulting in progressive life-limiting multisystemic diseases in adults and children.<sup>4,5</sup> Development of new therapies, including ERT, substrate reduction therapies (SRT) and pharmacological chaperone therapy, has altered the natural history of many LSD.<sup>4,6–10</sup> In the UK, these high-cost disease-modifying therapies (DMT) are prescribed and managed in designated highly specialised services.<sup>11–14</sup>

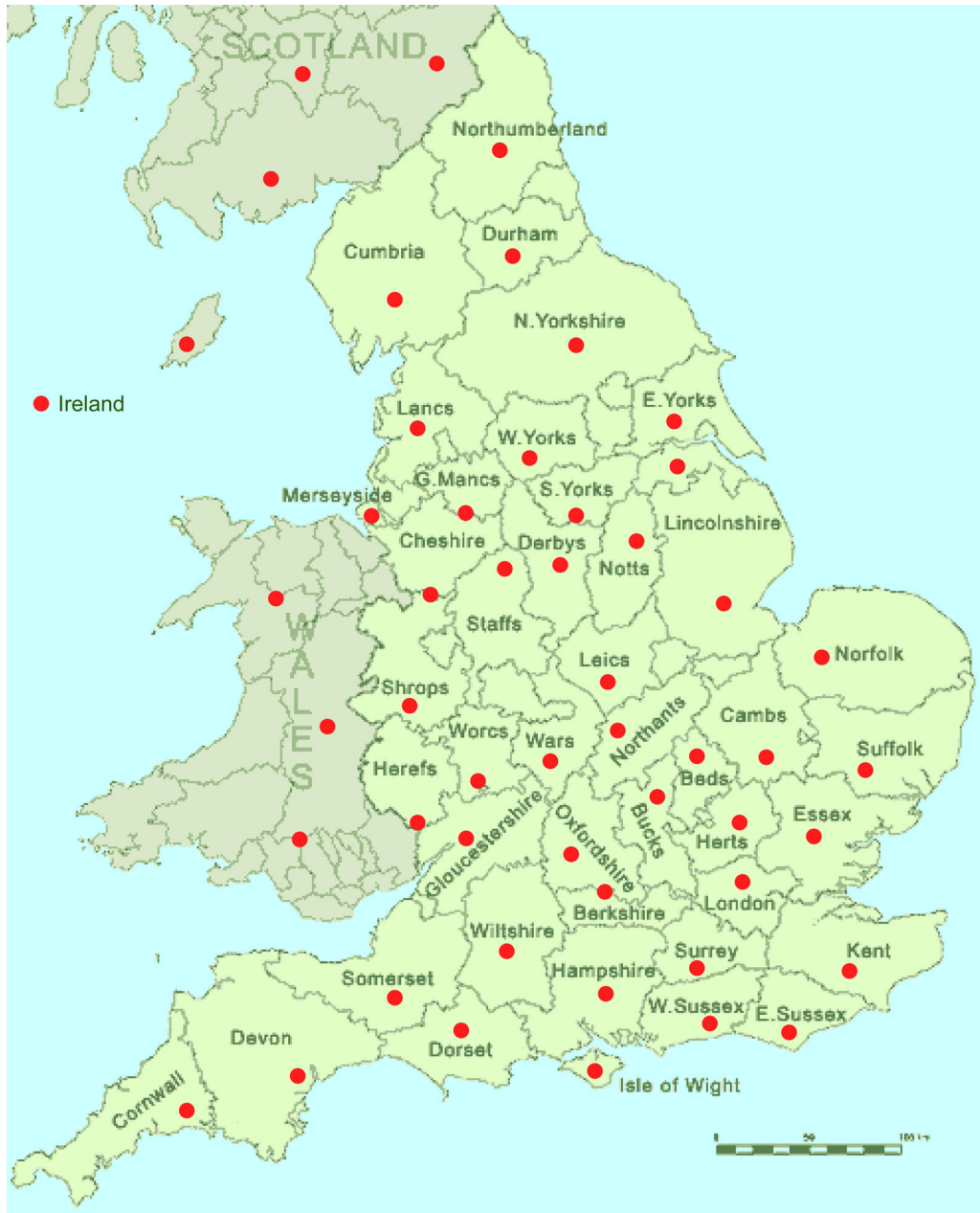
Patients attend one-stop clinics at the RFL LSDU from across the UK (Fig. 1) every 6 to 12 months as per NHS England standard operating policies and National Institute for Health and Care Excellence (NICE) guidance where available.<sup>11,15–17</sup>

Following a definitive diagnosis, baseline assessments and DMT initiation for eligible patients is completed within 3 months with simultaneous preparation for home care for both enzyme infusions and home care delivery of oral DMT. After an initial 6 months of home care nursing visits, training is also offered to patients to become independent with administering their infusions.

In March 2020, with numbers of COVID-19 infections rapidly increasing, in accordance with NHS England guidance, all non-urgent elective care was postponed for at least 3 months in order to increase inpatient and critical care capacity for patients suffering from COVID-19.<sup>18,19</sup> Ninety per cent of routine outpatient (OPD) appointments were switched to remote consultations, either through telephone or video consultations using NHS Attend Anywhere platform, a secure web-based platform for patients that was installed across NHS organisations in March 2020.<sup>20</sup> Only investigations deemed urgent were possible. In accordance with infection protection guidelines, aerosol-generating procedures such as lung function were suspended.

### Shielding patient list

On 23 March 2020, the UK Government advised all those considered to be clinically at increased risk of severe illness from COVID-19 (Table 1) to shield at home for a period of 12 weeks.<sup>21</sup> Shielding means protecting those people who are extremely vulnerable to COVID-19 due to certain existing health conditions.<sup>21</sup> The Health



**Figure 1** Royal Free London NHS Foundation Trust Lysosomal Disorders Unit (RFL-LSDU): patient demographics. Red circles depict each United Kingdom (UK) county from where patients travel from to attend Royal Free London NHS Foundation Trust Lysosomal Disorders Unit for clinical care. Map of the UK adapted from <https://www.picturesofengland.com/mapofengland/counties-map.html>.

Protection (Coronavirus, Restrictions) (England) Regulations 2020 ('Lockdown Regulations') came into effect on 26 March 2020 along with a more detailed guidance on shielding and protecting people who were considered clinically extremely vulnerable (CEV) from COVID-19.<sup>18,19,21</sup>

A further period of shielding was advised during the second national lockdown on 2 November 2020 with updated guidance for the CEV group (Table 2).

### Impact on LSD patients

LSD patients who fulfilled the CEV criteria were identified using the shielding patients list (SPL) algorithm, the tool developed by NHS digital under the direction of the Chief Medical Officer for England, with practical support being made available by the government for these patients.<sup>22</sup>

**Table 1** List of diseases and conditions considered to be very high risk

1. Solid organ transplant patients
2. People with specific cancers
  - People with cancer who are undergoing active chemotherapy or radical radiotherapy for lung cancer
  - People with cancers of the blood or bone marrow, such as leukaemia, lymphoma or myeloma who are at any stage of treatment
  - People having immunotherapy or other continuing antibody treatments for cancer
  - People having other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors
  - People who have had bone marrow or stem cell transplants in the last 6 months, or who are still taking immunosuppression drugs
3. People with severe respiratory conditions including all cystic fibrosis, severe asthma and severe chronic obstructive pulmonary disease (COPD)
4. People with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as severe combined immunodeficiency, homozygous sickle cell)
5. People on immunosuppression therapies sufficient to significantly increase risk of infection
6. People who are pregnant with significant heart disease, congenital or acquired

Source: COVID-19 – high risk shielded patient list identification methodology (<https://digital.nhs.uk/coronavirus/shielded-patient-list/methodology2020>).

The UK LSD centres and patient organisations also convened virtual meetings to discuss shielding categorisation and ERT interruption, with reports published through the British Inherited Metabolic Diseases Group (BIMDG).<sup>23</sup>

At RFL LSDU, we reviewed the medical records of 602 patients. Two hundred and twenty-eight of 418 patients with Fabry disease, 104 of 134 with Gaucher disease, 30 with mucopolysaccharidosis (MPS), 18 with Pompe disease and 8 of 12 patients with other LSD (including metachromatic leukodystrophy, Niemann-Pick Type C and alpha-mannosidosis) were categorised into the CEV groups: low risk, intermediate risk and high risk of developing severe complications from COVID-19 infection, which are summarised in Figure 2.

During the period from 26 March to 31 July 2020, a total of 305 LSD patients (193 Fabry disease, 52 Gaucher disease, 18 Pompe disease, 30 MPS and 12 other LSD) attending the RFL LSDU were shielding.

### Interruption to home ERT infusions during the first lockdown in March 2020

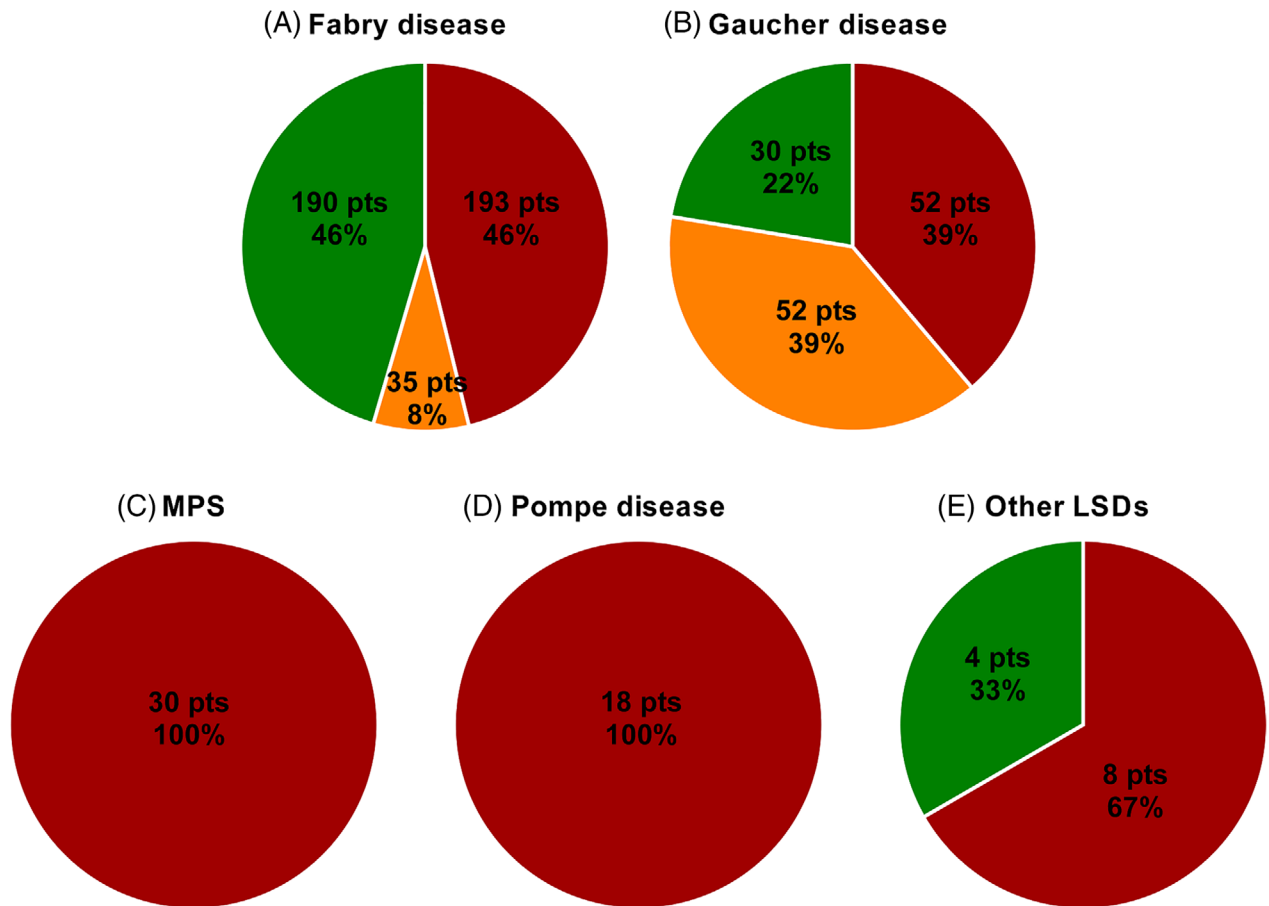
During the first lockdown, there was a lack of clarity on standard operating policies on Personal Protective Equipment (PPE) for home care nurses. We contacted all our patients through email and/or telephone or sent letters

**Table 2** People deemed clinically extremely vulnerable

1. Solid organ transplant patients
2. People with specific cancers:
  - People with cancer who are undergoing active chemotherapy
  - People with lung cancer who are undergoing radical radiotherapy
  - People with cancers of the blood or bone marrow, such as leukaemia, lymphoma or myeloma who are at any stage of treatment
  - People having immunotherapy or other continuing antibody treatments for cancer
  - People having other targeted cancer treatments that can affect the immune system, such as protein kinase inhibitors or PARP inhibitors
  - People who have had bone marrow or stem cell transplants in the last 6 months or who are still taking immunosuppression drugs
3. People with severe respiratory conditions including all cystic fibrosis, severe asthma and severe chronic obstructive pulmonary disease (COPD)
4. People with rare diseases that significantly increase the risk of infections (such as severe combined immunodeficiency (SCID), homozygous sickle cell disease)
5. People on immunosuppression therapies sufficient to significantly increase risk of infection
6. Problems with your spleen, for example splenectomy (having your spleen removed)
7. Adults with Down syndrome
8. Adults on dialysis or with chronic kidney disease (stage 5)
9. Women who are pregnant with significant heart disease, congenital or acquired
10. Other people who have also been classed as clinically extremely vulnerable, based on clinical judgement and an assessment of their needs. General practitioners and hospital clinicians have been provided with guidance to support these decisions.

Source: COVID-19 – high risk shielded patient list identification methodology (<https://digital.nhs.uk/coronavirus/shielded-patient-list/methodology2020>).

(for those without email/internet access). Early in the pandemic, with limited knowledge of the impact of SARS-CoV-2 infections on rare diseases, we considered the risk of contracting SARS-CoV-2 to outweigh the risk of treatment interruption. This decision for ERT interruption was also made possible with the previous experience of a worldwide supply shortage of Cerezyme and Fabrazyme in 2009, which resulted in an unpredicted treatment interruption/and or dose reductions over 1 year.<sup>24</sup> For those on ERT with home care nursing support, we offered treatment interruption during the 12 weeks of the first lockdown (Supporting Information Appendix S1: generic email sent to patients on home care during the first national lockdown, March 2020). Patients who were already self-infusing ERT at home, continued their treatment without interruption. Support for patients/carers to have training to become semi-independent/or fully independent in giving ERT infusions was offered by home care providers. Options to switch to oral DMT were considered and discussed with eligible



**Figure 2** Categorisation of lysosomal storage disorders patients (pts) into low, intermediate and high risk of severe COVID-19 infection. Fabry disease (A), Gaucher disease (B), mucopolysaccharidosis (MPS) (C), Pompe disease (D) and other lysosomal storage disorders (LSD) (E) according to the shielding patient list algorithm. (■), high risk (red); (■), intermediate risk (amber); (■), low risk (green).

**Table 3** Characteristics of patients with enzyme replacement therapy disruption

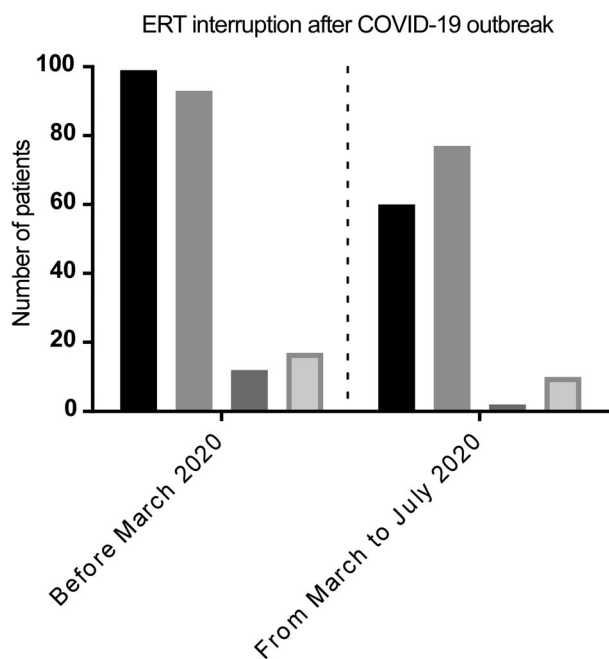
Disease	Sex, n (%)	Age Group, n (%)		
		20 to <40	40 to <60	60+
Fabry disease	Male 21 (54) Female 18 (46)	8 (21)	15 (38)	16 (41)
Gaucher disease	Male 11 (69) Female 5 (31)	4 (25)	4 (25)	8 (50)
Mucopolysaccharidosis	Male 2 (29) Female 5 (71)	7 (100)	—	—
Pompe disease	Male 2 (20) Female 8 (80)	2 (20)	5 (50)	3 (30)

Fabry and Gaucher disease patients. This included potential switch to migalastat – an oral, small molecule chaperone therapy in Fabry patients meeting the eligibility criteria (i.e. patients aged 16 years and older with an amenable mutation; and with a glomerular filtration rate (GFR) <30 mL/min/1.73 m<sup>2</sup>), and eliglustat – a SRT was

offered to adult type 1 Gaucher disease if we had information on cytochrome P450 2D6 (CYP2D6) metaboliser status, the presence of pre-existing cardiac disease or long QT syndrome and pregnancy.<sup>15,16</sup>

Prior to the COVID-19 outbreak, a total of 221 LSD patients at RFH were receiving ERT (99 Fabry disease,

93 Gaucher disease, 12 Pompe disease, 17 MPS), and a total of 124 patients were on SRT or chaperone therapy (24 Gaucher disease, 100 Fabry disease). During the first lockdown (from March to June 2020), 72 patients (39 Fabry disease, 16 Gaucher disease, 10 Pompe disease, 7 MPS: patients characteristics as shown in Table 3), interrupted ERT during shielding (Fig. 3), while



**Figure 3** Enzyme replacement treatment (ERT) interruption during the first phase of the COVID-19 pandemic. Prior to the COVID-19 outbreak, 221 patients (99 Fabry disease, 93 Gaucher disease, 12 Pompe disease, 17 mucopolysaccharidosis (MPS)) were receiving ERT. During the first phase of the emergency (from March to June 2020), 72 patients (39 Fabry disease, 16 Gaucher disease, 10 Pompe disease, 7 MPS) interrupted ERT during shielding. ERT was resumed in most patients at the end of the initial 12 weeks of shielding period, while 16 patients decided to continue ERT interruption for a further 4 weeks as per implementation of Government guidance on shielding until late July 2020. (■), Gaucher disease; (■), Fabry disease; (■), Pompe disease; (■), MPS. X-axis: disease types; Y-axis: percentage of patients on home care ERT.

6 Fabry patients were switched from ERT to oral treatment. No Gaucher patient chose to switch to oral therapy during this period.

ERT was resumed in most patients at the end of the initial 12 weeks of shielding, while 26 patients chose to continue treatment interruption for a further 4 weeks (Table 4).

### Restoration of services at the end of the first lockdown in June 2020

In June 2020, all NHS services were considering gradual restoration of their clinical services where possible and appropriate. To facilitate this transition, the NHSE London Clinical Advisory Group (CAG) published guidance for recommencing surgical and interventional medicine services in the London area.<sup>25,26</sup>

With existing NHS England LSD standard operating procedures (SOP) and the London CAG guidance, the RFL LSDU adapted its outpatients as detailed in Table 5, LSD pre-clinic triage ('Talk, Intervene, Walk' pathway), and Table 6, prioritisation of clinical urgency.

With the backlog of follow-up assessments and potential impact on staff and services, we identified resource requirements as shown in Table 7.

Figure 4 is a schematic representation of our planned restoration of OPD and details core sets of investigations for safe care of LSD patients.

### RFL LSDU response during the COVID-19 lockdowns in November 2020 and January 2021

With the lifting of the first lockdown in late June, routine clinical care face-to-face appointments gradually increased from August to October 2020. The UK had a second surge of cases in October and a further tiered lockdown on 2 November 2020.

During the second lockdown, only one Fabry patient decided to interrupt ERT.

**Table 4** Length of enzyme replacement therapy interruption by disease type

Disease	Days of enzyme replacement therapy interruption, n (%)										
	15–24	25–34	35–44	45–54	55–64	65–74	75–84	85–94	95–104	105–114	>114
Fabry disease	1 (2.5)	—	1 (2.5)	1 (2.5)	5 (13)	6 (15)	7 (18)	8 (20.5)	3 (8)	—	7 (18)
Gaucher disease	1 (6)	—	2 (12.5)	—	4 (25)	3 (19)	3 (19)	—	—	1 (6)	2 (12.5)
Mucopolysaccharidosis	—	1 (14)	—	—	1 (14)	1 (14)	—	2 (29)	—	2 (29)	—
Pompe disease	1 (10)	3 (30)	1 (10)	—	—	4 (40)	—	—	—	—	1 (10)

**Table 5** Outpatient restoration of services pathway for lysosomal disorders patients**Talk, Intervene, Walk pathway**

- Talk
  - Triage (pre-clinic) including COVID-19 status 72 h before and on day of appointment (COVID-19 screening questionnaire)
  - Patient considerations: informed consent regarding risks
  - Agreement to comply to requirements (PPE)
  - Mental capacity
  - Transport and/or accommodation
- Intervene
  - Flow chart before and after re-opening of Institute of Immunity and Transplantation (IIT) clinic space or green zone elsewhere at Royal Free London NHS Foundation Trust
- Walk (to be in accordance with Royal Free London NHS Foundation Trust phase 2 guidance)
  - Appointment timings
  - Social distancing (phone on arrivals, wait in car, distancing in waiting room, patients in clinic rooms with clinicians moving between clinics, one-way traffic)
  - Enhanced cleaning

Source: Adapted from the Pan-London guidance on the principles for infection prevention and control 2020 to the Lysosomal Storage Disorders Unit Royal Free London NHS Foundation Trust.

### Impact of treatment interruption on clinical parameters

ERT for lysosomal disorders is administered weekly (e.g. laronidase for MPS 1; idursulfase for MPS 2; elosulfase alfa for MPS IVA; galsulfase for MPS VI) or biweekly (e.g. agalsidase beta and agalsidase alfa for Fabry disease; imiglucerase and velaglucerase alfa for Gaucher disease; alglucosidase alfa for Pompe disease) intravenous infusions. Disruptions in treatment, either intentional or forced by unavoidable events, can potentially lead to a deterioration of clinical parameters and quality of life and could lead to potential adverse outcomes, such as cardiac events and/or decline of renal function in Fabry patients, visceromegaly and bone crisis in Gaucher patients, worsening of respiratory function and walking capacity in Pompe and MPS patients.<sup>27–31</sup>

We therefore carefully monitored all patients during the drug holiday/ERT interruption and did not observe any increased frequency of disease-related complications, such as arrhythmias, strokes, decline of the kidney function or renal transplant in Fabry disease patients; bone crisis in Gaucher disease patients; new cranio-cervical episode in MPS patients; or deaths related to treatment interruption during the first or subsequent lockdown periods. Six Fabry patients had undergone cardiac device implantation between August 2020 and March 2021; however, only one of them had stopped treatment during the first lockdown. The occurrence of

**Table 6** Lysosomal disorders clinical urgency prioritisation during the restoration phase

Lysosomal disorders define the clinical urgency for stepping up services as follows:

Many lysosomal disorders have multi systemic involvement and it is recommended to liaise with the specialist LSD centre.

**1a – Emergency – within 24 h:**

To follow guidelines for multi system emergencies as defined by other specialist groups and liaising with specialist centre: cardiology, neurosurgical, renal, respiratory etc.

Patients will attend local Emergency Department (ED). For patients with complex spinal and airways (e.g. MPS – specialist centres to be contacted specialist input and/or transfer to centre as appropriate)

**1b – Urgent – within 72 h:**

To follow guidelines for multi system emergencies as defined by other specialist groups and liaising with specialist centre: cardiology, neurosurgical, renal, respiratory etc.

For patients with complex spinal and airways (e.g. mucopolysaccharidoses, MPS) – specialist centres to be contacted specialist input to discuss local care or transfer to specialist centre as appropriate

**2 Treatment can be deferred for up to 3 months (earlier treatment may be indicated for some patients)**

Enzyme replacement treatment (ERT): Gaucher, Pompe, portacath for ERT, non-invasive ventilation (NIV) – non-urgent

New patient appointments: Gaucher, Pompe, some MPS

**3 Treatment can be delayed for 3 months:**

ERT: Fabry, some MPS

New patient appointment: Fabry, MPS, other LSD without disease-modifying therapies

**4 Treatment delayed for more than 3 months: non-urgent elective procedures (e.g. ports, non-urgent surgical procedures)**

Source: Adapted from the Pan-London guidance on the principles for infection prevention and control 2020 to the Lysosomal Storage Disorders Unit Royal Free London NHS Foundation Trust.

pacemaker implantation was not considered a direct consequence of ERT interruption due to the pre-existing high burden of cardiac disease in these individuals. Routine clinical blood tests obtained by general practitioners (GP) or at local hospitals during the pandemic, when face-to-face appointments were not possible, did not show significant deteriorations of laboratory parameters (e.g. haematology, renal function etc.) compared to the previous years. However, GP were unable to measure disease-specific markers. The role of dried blood spots to monitor biomarkers needs further evaluation and is outside the scope of this manuscript. Treatment interruptions however had adversely impacted on subjective symptoms in some patients (33% of Pompe patients, 15% of Gaucher patients and 5% of MPS patients) and the most common complications reported were fatigue and low energy levels (50% of Pompe patients; 32% of Gaucher patients; 20% of Fabry patients; 14% of MPS patients), exacerbation of generalised pain in half of the

**Table 7** Resource requirements for restoration of LSD services during COVID-19 restrictions 2020/2021

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Most lysosomal storage disorder (LSD) patients are managed as Outpatient Department (OPD) and day case

Need for intensive/critical care: for some emergency and elective care (MPS, Pompe)

Personal protective equipment (PPE) requirement: as per UK guidance for OPD/Day case

Workforce: no additional workforce required

Equipment/diagnostics: phlebotomy; cardiac magnetic resonance (CMR)/echocardiogram, dual-energy X-ray absorptiometry (DXA); other imaging; lung function; physio; dietetics, psychology

LSD teams to discuss capacity with the relevant departments and prioritise essential investigations. For example: measured glomerular filtration rate (GFR) – if less than 30 mL/min, discuss with renal consultant before repeating it (continue to measure eGFR as per guidelines)

Where appropriate and possible, investigations such as MRI brain, lung function, DXA, audiology to be done locally and results/images sent to LSD centre

Bloods and phlebotomy: liaise with local shared care

Local availability for routine blood tests and some specialist tests

British Inherited Metabolic Disease Group (BIMDG) is discussing with National Metabolic Biochemistry Network (MetBioNet) for all metabolic centres currently (standardised pathway for all LSD centres to access to be confirmed)

Where appropriate, patients could have routine tests done locally or nearest LSD centre and follow-up with results by video consultation

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Source: Adapted from the Pan-London guidance on the principles for infection prevention and control 2020 to the Lysosomal Storage Disorders Unit Royal Free London NHS Foundation Trust.

Pompe patients and of neuropathic pain in one-third of Fabry disease patients, worsening of musculoskeletal pain in 41% of MPS patients and of bone pain in 36% of patients with Gaucher disease, with no reported bone crisis. Low mood was observed in 23% of MPS patients, 22% of Pompe patients, 30% of Fabry patients and in a small number of Gaucher patients (9%). Most patients made a full recovery after restarting ERT.

The impact of the temporary home ERT interruption was also analysed through a survey carried out by the LSD Patient Collaborative group in July 2020. In a sample of 53 patients (15 Fabry disease, 13 Gaucher disease, 11 Pompe disease, 11 MPS, 3 other LSD) attending the RFL LSDU: 7 out of the 37 (i.e. 19%) who had ERT interruption reported worsening of pain, while 2 (5%) suffered from fatigue and psychological issues.

### Home care treatment and service provisions since March 2020

Where patients were willing to continue home ERT infusions during the lockdown periods, the home care

providers assisted in training shielding patients and/or their carers to become semi-independent (nurse assistance with cannulation/or portacath access or with drug preparation, shortening the period of nurse attendance to the patient's home) or fully independent (patient able to self-infuse).

Positively, there was a 3% reduction in home care dependency since the beginning of COVID-19 pandemic. Six patients switched to oral treatment from ERT, while no treatment interruption was required for patients receiving oral DMT.

### Face-to-face and virtual clinics

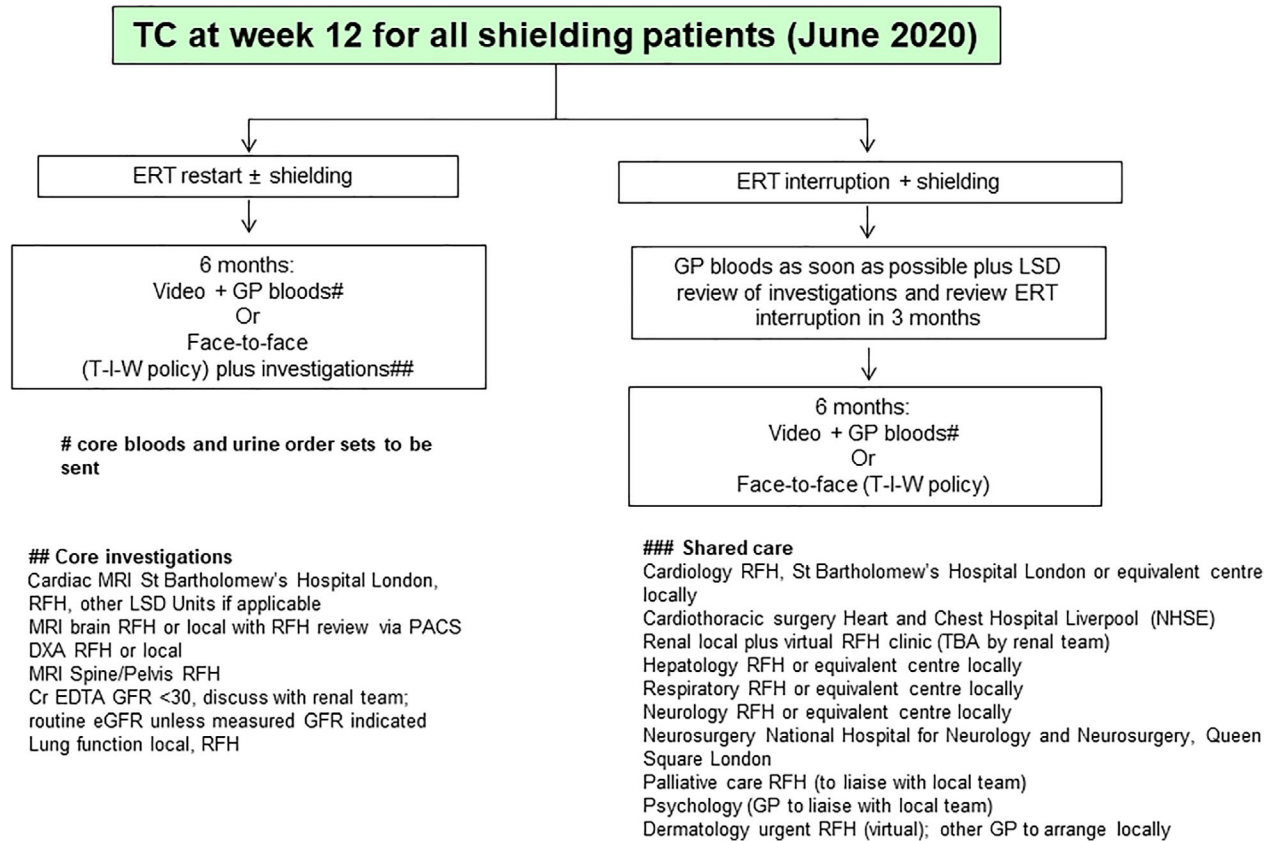
During the pandemic, there was a significant shift from face-to-face to virtual consultations. Twelve percent of appointments were held face to face from 16 March to October 2020, compared with 67% during the previous year from April 2019 to 15 March 2020. Conversely, remote consultations increased from 33% to 88% respectively from March to October 2020 (Appendix S2, RFL LSD OPD clinic attendances 2019 and 2020). Remote consultations for OPD appointments are delivered through telephone or video consultation depending on their individual care needs. Patients receive information about the date and time of their remote appointment and – for video consultations – the name of the waiting area they need to access. Visit preparation includes confirming that the patient has audiovisual resources and providing instructions on ideal setting. Virtual assessment is carried out by directly asking the patient and/or caregiver a set of questions as set out in a tailored clinical form and includes a patient-assisted virtual physical examination where possible. The virtual physical examinations where possible include inspection, range of motion, strength and neurological assessments, such as gait and to execute simple manoeuvres and/or mirror physician's motions in accordance with available guidelines.<sup>32,33</sup> Patients are asked to perform a self-assessment for identifying abnormalities (such as bruises, angiokeratomas, rashes, swelling etc.) and weigh themselves at home on the day of the appointment if possible. The RFL SOP for telephone consultation is provided as Appendix S3.

As a consequence of this switch to virtual appointments, several planned annual review investigations were cancelled in 2020: 198 measured GFR assessments, 70 magnetic resonance imaging scans (brain, hips, spine), 19 dual-energy X-ray absorptiometry, 22 lung function tests, 9 brain computed tomography scans and 3 echocardiograms.



## LSD patients follow-up June 2020

LSD Telephone clinics until end of June 2020 unless urgent (TBA case by case)



**Figure 4** Lysosomal storage disorder patient clinical follow-up pathway. Schematic representation of the proposed framework developed by the Royal Free London NHS Foundation Trust Lysosomal Storage Disorders Unit. BIMDG, British Inherited Metabolic Disease Group; CAG, Clinical Advisory Group; CEV, clinically extremely vulnerable; Cr EDTA GFR, glomerular filtration rate using chromium-51-labelled ethylenediamine tetraacetic acid; DMT, disease-modifying therapies; ERT, enzyme replacement therapy; GP, general practitioner; JCVI, Joint Committee on Vaccination and Immunisation; LSD, lysosomal storage disorders; LSDU, Lysosomal Storage Disorders Unit; MPS, mucopolysaccharidosis; NHSE, National Health Service England; OPD, outpatient; PPE, Personal Protective Equipment; REST, resilience and emotional support team; RFL, Royal Free London NHS Foundation Trust; RFLE, Royal Free London NHS Foundation Trust Executive; SOP, standard operating procedure; SPL, shielding patients list; SRT, substrate reduction therapy; UK, United Kingdom.

### New patient referrals

During the period from March 2020 to January 21, there were 38 new referrals (27 Fabry disease, 7 Gaucher disease and 4 patients transition from the children's hospital). Twenty of these first appointments were conducted remotely, while the remaining 18 were held face to face. Transition clinics were conducted through secure hospital patient video platforms and organised by the referring children's hospital.

For those patients unable to attend face-to-face appointments, a core set of blood tests and other urgent investigations were organised in the community (Fig. 4).

Urgent reviews and in-patient assessments (e.g. urgent portacath insertion, in-patient management of acute

colitis, etc.) continued throughout the pandemic, in accordance with infection protection guidance.

Frequent dialogue was maintained with the UK LSD Patient Collaborative Group to provide regular updates and address patient queries. The LSD clinical team remained in constant contact with shielding patients and carers by regular telephone calls and/or email.

### LSD clinical trials during the pandemic

For patients with a life-limiting LSD for whom no disease-modifying treatments are yet available, a trial represents a source of hope, giving the opportunity to receive a treatment that would otherwise not be

available. Therefore, we endeavoured to minimise disruptions to clinical trials of novel DMT, while strictly adhering to Good Clinical Practice and infection control guidance, with the trial participant safety being of paramount importance.

Before the COVID-19 outbreak, 18 LSD patients were enrolled in clinical trials. Since March 2020, 26 remote and 36 on-site patient visits were organised. Fifteen hospital study visits were switched to home visits, with infusion of investigational medicinal product undertaken by the LSDU clinical nurse specialists in patients' homes.

Working closely with the study sponsors, clinical research associates, data manager, research nurses, and RFL Research and Development, 39 remote study monitoring visits allowed timely completion of study data queries/data locks.

### Redeployment of LSD staff during the pandemic

During the first phase of the COVID-19 pandemic, two clinical nurse specialists were redeployed to the intensive care unit for 4 days per week from April to June 2020.

The lead nurse was redeployed 4 days a week to the hospital COVID-19 Incident Room, and continued to support the LSD home care providers, pharmacy, commissioning teams, monitoring of ERT interruptions and restart of therapies, and supervision of OPD for specialist services. During their redeployment, the LSD nursing team ensured uninterrupted clinical and research cover for LSD patients.

One consultant was actively involved with the well-being team and paediatrics and developed an app to monitor staff well-being; one consultant supported cancer services and one part-time consultant remained within the service. Two consultants continued to provide a 1 in 2 cover for LSD out of hours.

Effective communication was key to ensuring a safe service and was achieved with daily patient hand over sheets through team emails, telephone communication for urgent patient queries, daily nursing huddles and weekly multidisciplinary team meetings.

### COVID-19 infection prevention and control guidance

RFL had published new COVID-19 guidance for restarting services, infection prevention and control, and testing.<sup>34</sup> Staff have daily screening and temperature checks for COVID-19 symptoms, twice weekly SARS-CoV-2 lateral flow tests with mandatory reporting of results through a secure online portal and COVID-19 reverse transcription polymerase chain reaction tests for

symptomatic staff, with occupational health protocols for positive results. Mandatory infection protection policies remain in place for all staff including the wearing of surgical grade facemasks.

Patient screening (including COVID-19 symptoms, contacts and travel history) and triage was undertaken prior to any hospital encounter as per the Trust's infection control guidance.

### LSD patients and COVID-19 infections

SARS-CoV-2 infection has resulted in hyper-inflammatory multi-organ dysfunction requiring intensive care admissions.<sup>35–38</sup> This had raised concerns regarding potential complications in LSD patients: for example exacerbation of myopathy and respiratory compromise in Pompe Disease, worsening of upper airway and cardiomyopathy in MPS, macrophage activation and worsening immune compromise in splenectomised patients with Gaucher disease patients, worsening of Fabry cardiomyopathy, arrhythmias, end-stage renal disease, etc.

However, to the best of our knowledge, no serious cases of COVID-19 infections have been reported worldwide in any patient cohorts with LSD.

At the RFL LSDU, 21 patients (15 Fabry disease, 5 Gaucher disease and 1 with Pompe disease) had symptomatic COVID-19 infections. Of these, one Fabry patient with pre-existing comorbidities (obstructive sleep apnoea and non-invasive ventilation) required hospitalisation. All patients have recovered since.

There were two non-COVID-19 related deaths in 2020; one male and one female with Fabry disease died of fatal arrhythmias that were disease-related and both patients had received uninterrupted ERT treatment during the pandemic.

Of the 21 patients who contracted COVID-19 infection, only 2 patients (1 Fabry disease and 1 Gaucher disease) contracted COVID-19 before October 2020. The relaxation of restrictions in the summer of 2020 and the emergence of a highly transmissible new variant of SARS-CoV-2 in the UK in November 2020 were plausible reasons for the increase in COVID-19 infections since October 2020. However, reassuringly, only one patient required hospitalisation and there have been no COVID-19 related deaths.

### Staff well-being initiatives

The RFL Executive (RFLE) team set up many staff well-being initiatives. All staff had free access to well-being apps and the clinical psychology team set up a resilience and emotional support team (REST) for staff. Free accommodation, car parking, meals, and an in-house free supermarket were offered to all staff during the first

12 weeks of the lockdown. The chaplaincy and other religious support groups also provided continued support to patients, families and staff. There continue to be weekly COVID-19 updates through the hospital intranet.

With the support of the RFLE and funding from Royal Free charities, the lead author led the development of a COVID-19 opt-in digital app. It is voluntary and facilitates self-monitoring of generalised anxiety, personal burnout and mental well-being scales. The staff well-being steering group is provided with regular anonymised data updates.

## Discussion and lessons learnt

The World Health Organisation published on significant disruption caused by the COVID-19 pandemic on the management of chronic diseases, and describes the catastrophic mental health, social and economic impact caused as a consequence.<sup>39–41</sup> Scechi *et al.*, using a telephone questionnaire in a small cohort of patients, had evaluated the direct and indirect effects of the COVID-19 pandemic on Italian patients with LSD.<sup>42</sup> Similar to our observations, there was no evidence of increased acute COVID-19 infections in LSD patients compared to the general population. Forty-nine per cent of patients receiving ERT in hospitals experienced treatment disruptions versus 6% of those receiving ERT at home. The reasons for treatment interruption included reluctance of patients wanting to attend hospitals for infusions and/or issues with re-organisation of infusion centres.

In the UK, the vast majority of patients have ERT infusions at home which is mostly administered by home care nurses. During the first lock down in March 2020, there was limited knowledge of the impact of COVID-19 on patients with rare diseases. We had to therefore weigh the risk of our patients contracting COVID-19 and temporary treatment interruptions risk. After careful consideration, for patients who had home care nursing support, we offered the choice of treatment interruption for up to 12 weeks.

In 2011, the Dutch published safety of interrupting ERT for up to 12 weeks in Fabry disease during the global shortage of Fabrazyme in June 2009 due to viral contamination of Genzyme's production facility of agalsidase beta. In 35 male patients who either had a reduced dose of Fabrazyme or switched to an alternative ERT, the authors found no increase in adverse clinical events.<sup>43</sup> In 2013, Deroma and colleagues had published the effects of ERT dosage reduction due to the temporary shortage of Cerezyme in 2009 in 34 Gaucher patients followed up for 1 year. The authors did not observe substantial changes in the laboratory parameters – except

for an increase of the chitotriosidase activity.<sup>44</sup> During the pandemic, we also noted that whilst there was a mild increase in subjective symptoms, such as neuropathic pain in Fabry patients, fatigue and bone pain in Gaucher patients, they generally improved/resolved following recommencement of ERT. The majority of our patients have remained stable during the lockdown and shielding periods. There were two non-COVID-19 related deaths due to disease progression and both had not interrupted ERT during the pandemic.

At RFL LSDU, one-stop clinic assessments have not been possible during the pandemic. As a national centre with over 90% of our patients from outside London (Fig. 1), an SOP for telephone consultations was developed in 2017 to review clinically stable LSD patients and improve patient experience (Appendix S3). This existing policy had immediately given us an advantage, enabling us to switch face-to-face visits to virtual clinics during the first lockdown.

Our experience at RFL LSDU provides an opportunity to ensure lessons learned during the pandemic are incorporated into managing LSD patients beyond the pandemic.

## Telemedicine: pros and cons

Telemedicine improved patient compliance and reduced the rate of clinic non-attendance, whilst ensuring consistent, safe and high-quality care. During the pandemic there has been improved collaboration with the patient's GP and local hospitals for regular monitoring – for example routine blood tests and imaging done closer to patients' homes. This collaboration has improved patient experience, especially for those with limited mobility, reducing the need to travel long distances to access specialist LSD services.

Face-to-face patient interactions are an essential part of the healthcare professional – patient/carer relationship. Nuances in the patient's clinical, mental and social care changes are not always possible to ascertain over the phone or through video consultations. Patients with hearing and visual impairment, learning disabilities and mental health issues are disadvantaged without regular face-to-face meetings with the wider team. The value of the multidisciplinary interactions with the metabolic clinician, nurse specialists, psychology and multidisciplinary team assessments done as part of the one-stop clinic is also missed with virtual clinics.

## The future

We anticipate that a hybrid model with face-to-face clinics, virtual nurse and doctor-led clinics and increasing

engagement with local services will continue for the foreseeable future, whilst the NHS sets to restore its routine and non-urgent care post-pandemic.

The UK COVID-19 vaccination programme was launched on 8 December 2020. Pfizer BioNTech mRNA COVID-19 vaccine, AstraZeneca Oxford and Moderna vaccines have been approved and rolled out in accordance with the Joint Committee on Vaccination and Immunisation (JCVI) vaccine prioritisation guidance.<sup>45–48</sup> The lead author and three nurse specialists are COVID-19 vaccinators at RFL.

All LSD patients are encouraged to have the vaccination in accordance with JCVI guidance. Thus far, our patients have reported no serious reactions or deaths related to the vaccine.

The next steps include assessments of the long-term psychological impact of the pandemic affecting our patients, carers and families.

## Conclusion

The SARS-CoV-2 pandemic has led to an unprecedented global health care crisis that has also resulted in catastrophic economic and social disruptions. Many healthcare systems globally, including the NHS, had to rapidly adapt and manage the rising mortality and the resulting morbidity caused by this new pathogen.

At the RFL LSDU, we created a different model of safe and effective care, being proactive and responsive to the ever-changing situation with three lockdowns and three surges in COVID-19 infections in the UK. Frequent and regular contact with our patients, meticulously categorising patients requiring shielding, optimising patient and staff communications ensured that we encountered no excess patient mortality or morbidity, either directly due to SARS-CoV-2 infections or due to disease progression as a consequence of treatment disruption.

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Up to 12 weeks interruption of ERT did not appear to increase adverse clinical events and this is in keeping with previously published reports during the Fabrazyme and Cerezyme shortage in 2009.<sup>43,44</sup> In contrast, some patients experienced an increase in subjective symptoms, such as fatigue during treatment interruption. The lessons learnt as a consequence would be to minimise ERT interruptions by ensuring there is a Standard Operating Policy (SOP) in place for continuing home care infusions. The SOP should include home care and use of appropriate PPE to minimise the risk for home infusions; early engagement with patients to consider self-infusing and/or be semi-independent whenever possible. To ensure both medical and mental health well-being of our patients and continuity of safe care, we suggest regular and frequent contact with patients through virtual clinics during unexpected treatment interruptions.

Early and effective collaboration with other national LSD centres and patient organisations were key to providing a standardised approach to patient communications and management.

In 2021, with the rollout of vaccines, we are optimistic to resume one-stop clinics for routine clinical care.

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## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

**Appendix S1.** Generic letter emailed or posted to all lysosomal storage disorders patients at Royal Free London NHS Foundation Trust during the first UK national lockdown in March 2020.

**Appendix S2.** Lysosomal storage disorders patients' outpatient appointments: face-to-face and telemedicine 2019 and 2020.

**Appendix S3.** Standard operating procedure policy for telephone consultation.