Proposal to conduct a long term cohort study of people with lysosomal storage disorders – version 5 (23.09.09)

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Proposal for long term cohort study of people with lysosomal storage disorders

Aim: To conduct a prospective cohort study of people in England with a lysosomal storage disorder to determine natural history and estimate effectiveness and cost-effectiveness of current and potential treatment strategies.

Objectives: Primary objectives:

(1) To determine the natural history of treated and untreated lysosomal storage disorders for those disorders where enzyme replacement therapy is currently available;

(2) To estimate the effectiveness of enzyme replacement therapy;

(3) To estimate the cost-effectiveness of enzyme replacement therapy for lysosomal storage disorders;

(4) To determine the natural history of lysosomal storage disorders where enzyme replacement therapy is likely to become available.

Secondary objectives include:

- To compare the effectiveness of *Replagal* and *Fabryzme* in children and adults with Fabry disease
- To estimate the life-time health care cost and other economic impacts on people with lysosomal storage disorders and their families

- To provide the basis for future research to develop treatment-responsive measures in adults and children.

Lay Summary

Lysosomal storage disorders are a group of rare, inherited diseases. In total they affect fewer than 1:7000 people. Traditionally, the therapeutic options for lysosomal storage disorders have focussed on managing the symptoms of the disease rather than treating the disease itself. However, in recent years, treatments which address the cause of the disease, the enzyme deficiency, are being developed for these disorders. Enzyme replacement therapies are now available for the treatment of Gaucher, Fabry and MPS I, and several more are being developed.

People with these disorders are treated at one of seven designated treatment centres in England. The Peninsula Medical School, in collaboration with the treatment centres and the support groups, would like to look at how effective and cost effective these therapies are. However, because these conditions are so rare, usual ways of testing how effective a treatment is, such as a randomised, controlled trial are much harder to conduct. Therefore, we hope to carry out a long term cohort study, whereby we collect data, at each centre, from all consenting adults and children with these conditions. By following people with these conditions over a period of time we will better understand how effective treatments are, when the best time to start giving these treatments is, what the appropriate dosing schedules are, and which symptoms led to the diagnosis of the disorder. Another aspect of the study will be to estimate the value for money of these treatments. In order to do this we will look at how frequently people use the NHS, the cost of their treatment, related costs to their family, and compare these for people who are receiving treatment with those people who are not, or for whom no treatment is currently available. This study is intended to last three years in the first instance and, in addition to addressing specific questions, will create a valuable research resource for patients and clinicians.

Background

Lysosomal storage disorders (LSDs) are a heterogeneous group of disorders with a combined prevalence of between 1:5,000 and 1:10,000. The prevalence of the more common individual lysosomal diseases is between 1:20,000 and 1:100,000 [1,2]. Higher prevalences of specific lysosomal storage diseases are encountered in some populations, for example Gaucher and Tay-Sachs disease among Ashkenazim Jews and aspartylglucosaminuria, and Salla disease and infantile neuronal ceroid lipofuscinosis in Finland [3]. The clinical picture of most lysosomal storage disorders is heterogeneous with age of onset, and type and progression of symptoms varying substantially among individual patients suffering from the same disorder. Within each condition, there is considerable variation in the underlying genetic mutation. There is a correlation between the specific mutation and the severity of the problems experienced by an individual but the genotype/phenotype relation is variable [4]. In general, a correlation exists between residual enzyme activity and severity of disease manifestation. In some lysosomal storage disorders external genetic or environmental factors markedly influence the flux through the defective pathway and therefore also have a major impact on disease manifestation.

There are more than 40 LSDs whose common feature is the deficiency of a lysosomal enzyme or transport protein. This deficiency results in a progressive intracellular accumulation of glycophospholipids, causing tissue damage and ultimately organ failure [4]. The likelihood that a particular cell type is involved in storage accumulation is determined by the flux of the substrate (the metabolic demand) and the residual capacity of that cell type to carry out the catabolic reaction. In general, the more severe the mutation the more cell types accumulate the storage material. For

patients with a missense lysosomal enzyme gene, and therefore showing a relatively high residual enzyme activity, storage is likely to occur in fewer cell types. It is the heterogeneity in individuals' residual degradative capacity which accounts for some lysosomal storage disorders manifesting as relatively benign non-neuropathic variants and others as devastating neuropathic variants. In the latter case storage is not restricted to cells in visceral tissues but also involves cells inside the brain. Many LSDs have traditionally been classified into subtypes, although it is increasingly recognised that most LSDs have a broad continuum of clinical severity and age of presentation [5] rather than falling into clinically discreet forms.

The symptoms arising from these disorders are generally progressive and clinical diagnosis becomes easier with time [6]. For the most part diagnosis relies on observation of clinical features raising a clinical suspicion resulting in formal testing.

The clinical course of these disorders is not easily predictable in an individual, especially in the later-onset disorders [7]. Although mutation analysis can predict the likelihood of neurological involvement for some LSDs, as mentioned, there is often variability in the genotype/phenotype relationships. The situation is further complicated by the large number of mutations identified, which, coupled with the fact that most patients are compound heterozygotes, makes phenotype prediction difficult. In addition, the relative frequency of different patterns of mutation varies between ethnic groups making comparisons between outcomes in different countries problematic.

Treatments for lysosomal storage disorders

No definitive, curative treatment is yet available for any LSD. For most of the disorders, symptomatic treatment for specific problems is currently the only therapeutic option. For some LSDs it is possible to either augment the deficient enzyme (eg. by enzyme replacement therapy (ERT) or enzyme enhancement therapy - such as bone marrow transplant) or partially inhibit synthesis of the parent substrates by substrate reduction therapy. Treatment options are summarised in Table 1.

Bone marrow transplant

The first bone marrow transplants (hematopoietic stem cell transplant) were done on patients with Hurler's disease and reported in the early 1980s [8]. Since then bone marrow transplant [BMT] has been carried out for at least 20 different LSDs [9]. The results of BMT are variable but it appears that for the most part it is in the disorders which do not affect the central nervous system to any great extent where BMT has the greatest effect. [6] When carried out in individuals with CNS involvement, BMT is reported to be least effective in addressing the skeletal and neurological component of these disorders. For disorders which primarily affect the CNS, such as infantile Tay Sachs, Sandhoff or MPS III (Sanfilippo disease), BMT does not appear to be effective in slowing down the disease progression. Similarly, where there is significant skeletal impact on the disorder such as MPS IV (Morquio disease), BMT has not been reported to lead to an improvement in growth or other skeletal features [7]. In MPS I and VI (Maroteaux Lamy disease) a transplant early on in the course of the condition has been reported to be associated with some improvements although in MPS I, BMT after the onset of significant neurological signs does not lead to an improvement of

neurological function, and in most patients a steady loss of skills continues [7]. Furthermore, it appears that bone and cartilage cells remain MPS cells. [8,9]

Substrate reduction therapy

At present, Miglustat *(Zavesca),* is the only licensed substrate reduction therapy in the UK. Miglustat inhibits glucsylceramide synthetase which is the first step in the synthesis of most glycosphingolipids. It is currently licensed in the UK for treatment of mild to moderate type I Gaucher, in patients for whom enzyme replacement therapy is unsuitable.

A one year open label study involving 28 adults (seven with previous splenectomies) from four international Gauchers referral clinics, who were unable or unwilling to receive ERT reported reduced organomegaly and small haematological improvements after 12 months therapy [10]. An extension study to 36 months was conducted with 18 of the 22 eligible patients (14 completed the 36 month study) which reported a further reduction in liver and spleen volume, as well as haematological parameters with a reduction in the incidence of side effects (as experienced in the first 12 months) [11].

Other disorders where the effectiveness of Miglustat is currently being assessed are, Gaucher type III, Niemann- Pick type C and late onset Tay Sachs [9].

Enzyme replacement therapy (ERT)

There are currently four licensed enzyme replacement therapies in the UK for three LSDs; imiglucerase (*Cerezyme*®) for non neuropathic Gaucher disease (type I);

agalsidase beta (*Fabrazyme®)* and agalsidase alpha *(Replagal®)* for Fabry and laronidase (*Aldurazyme®)* for mucopolysaccharidosis (MPS) type I.

Other enzyme replacement therapies are currently being developed for Pompe [13], and MPS type II [14] and VI (Maroteaux -Lamy) [15]. Enzyme replacement therapy for Niemann – Pick Type B is at the pre-clinical stage [9].

Treatment and the blood brain barrier

Whereas substrate reduction therapies do appear to cross the blood brain barrier in small amounts (approx 10%), currently available enzyme replacement therapies do not appear to cross the blood brain barrier in sufficient amounts to be effective. This inevitably limits their potential effectiveness in those conditions in which CNS involvement is an important feature. There is some evidence that if patients are given sufficiently high doses of immunosuppressant drugs there may be better penetration of the enzyme into the CNS. It has been established that injecting the replacement therapy directly into the CNS is not an effective means of crossing the blood brain barrier [personal communication].

HTA commissioned reviews of effectiveness and cost-effectiveness.

An examination of the evidence for the effectiveness and cost effectiveness of enzyme replacement therapies for Gauchers, Fabry and MPS type I was commissioned by the HTA. For all three conditions the reports suggested on the basis of the limited data available that there are beneficial effects of ERT on symptom-related markers. [16, 17]. The following sections summarise key points from these reports.

ERT for Gaucher Disease

Gaucher disease is classified into three subtypes by clinical features. Type I can present at any age and has predominantly visceral symptoms without neurological effects. Type II presents in childhood and has neurological and visceral symptoms. It causes severe progressive brain disease and death occurs in infancy. Type III presents in early childhood with the presence of visceral and / or neurological symptoms. Imiglucerase is licensed for use in symptomatic Type I disease and to treat the visceral symptoms of Type III disease.

Effectiveness

The systematic review identified 63 studies (involving ten patients or more) [16]. These included one RCT which compared ERT to usual treatment and one RCT which compared two different derivations of ERT but provided only before and after data on the effectiveness of ERT. The other studies were considered to be of moderate quality at best and none had reliable comparator data.

All studies were suggestive of benefit from ERT. The RCT comparing ERT to usual treatment reported a potentially beneficial effect in haemoglobin and platelet levels and, to a lesser extent, on hepatomegaly. The other studies reported improvements in haematological parameters and in hepatomegaly and splenomegaly, with most parameters tending to return towards normal in the majority of patients after a year or more of treatment. For organomegaly and haemoglobin, the rates and extent of response are reported to have been greater the more abnormal the pre-ERT condition. Platelet levels are reported to improve more slowly. For most people liver size was reduced to near 1.2 times that expected for normal weight and the spleen was reduced by 5-10 fold. ERT was also reported to have a beneficial effect on bone crises and

fracture rate, as well as on pain, although the quantitative evidence for these benefits was described by the authors of the HTA report as being ‘extremely weak’.

The overall conclusion was that there was a paucity of high quality evidence and that it was therefore difficult to reliably estimate whether these reported effects translate into improved patient wellbeing and survival, or an altered need for health services.

Cost effectiveness

All published cost-effectiveness studies are over nine years old and conducted outside the UK. The authors of the report described above conducted a new cost-effectiveness analysis based on UK costs [17]. In this analysis, even assuming that ERT restores people with Gaucher to full health for their remaining lives, the incremental cost-effectiveness of ERT is more than ten times above the usually accepted threshold for what constitutes “good value for money” when using NHS resources to improve health. The authors emphasise that due to the weak research evidence base, extreme uncertainty surrounds these cost-effectiveness estimates. However, even with the most favourable possible assumptions the incremental cost-effectiveness of ERT appears prohibitive given current drug costs.

ERT in Fabry’s disease

Fabry's disease is an x-linked lysosomal storage disorder caused by a deficiency of the enzyme α-galactosidase A, an enzyme involved in the breakdown of lipids. As a result of this deficiency glycosphingolipids, accumulate in the body's tissues, particularly the heart, kidneys and nerve tissue. Symptoms usually appear during childhood and adolescence and affect many organ systems such as heart, CNS, kidney, bowel,

pancreas and lung [19]. It is a clinically heterogeneous disease and is usually slowly progressive with symptoms changing with age [20]. A substantial proportion of patients will develop cerebrovascular disease (transient ischaemic attacks and stroke). There are two ERTs licensed for use in the UK for Fabry's disease, agalsidase alpha *(Replagal®)* and agalsidase beta *(Fabryzyme®).* Both are given intravenously, with the recommended dose being 0.2mg and 1mg/ kg body weight bi-weekly, respectively.

Effectiveness

Considering studies of either form of ERT, the systematic review identified three randomised placebo-controlled trials (n=70, duration 5-6 months) and 11 uncontrolled before and after studies (n= 493, duration up to 24 months) [18]. Of the three controlled trials, 27 patients received Fabryzyme and 21 received Replagal. The studies are small, of short duration and use different outcome measures which made direct comparisons difficult. Overall their results suggest some beneficial effect of ERT on measures of pain and cardiovascular function, and an apparent stabilisation of renal function based on measures of creatinine clearance. The studies were unable to demonstrate any effect on neurological effects including the risk of transient ischaemic attacks or stroke. However, this is unsurprising given the lack of power to detect such effects as well as the short duration of treatment, and a beneficial effect cannot be excluded on the basis of current data.

There is currently a trial going on in Holland comparing Fabryzme and Replagal, however no results have been published as yet [personal communication].

Cost effectiveness

The authors of the report conducted a cost-effectiveness analysis of ERT in Fabry disease. The conclusions are similar to those reviewing ERT in Gaucher disease. The data are acknowledged to be poor, resulting in considerable uncertainty around all estimates. However, even where the model is based on the most favourable possible assumptions, applying conventional thresholds of societal willingness-to-pay for health gains for the UK NHS (£30,000 per QALY), and current treatment prices, the authors conclude that ERT (either Replagal® or Fabrazyme®) for Fabry's was highly unlikely to be cost-effective. These conclusions are crucially dependent on current drug costs.

ERT for MPS I

MPS I is an inherited autosomal recessive disorder caused by deficient activity of the enzyme α-L-iduronidase which results in an accumulation of glycoaminoglycans (GAGs) in many tissues including connective tissue, brain, heart and liver. This in turn leads to skeletal abnormalities, respiratory problems, joint problems, developmental delay and other issues such as corneal cloudiness, enlarged liver and spleen, recurrent hernias and heart disease. There are three subtypes: type IH (Hurlers disease) which presents in the first year of life, has severe neurological symptoms and a life expectancy of only one decade; MPS IHS (Hurler- Scheie disease) is an intermediate form with a life expectancy of only two to three decades and MPS IS (Scheie), is an attenuated form with later presentation and longer life expectancy than IH and IHS. Laronidase is licensed for IV administration for symptomatic MPS IS and HIS patients. The recommended does is 0.58mg/ kg body weight every week.

Effectiveness

The systematic review identified one placebo-controlled RCT and a phase I/II observational study provides evidence of effectiveness. In the RCT 45 people with moderate to mild disease (predominantly HS) took part in a 26 week duration trial, with an open label extension for an additional 72 weeks. The Phase I/ II study included 10 patients (8 patients had the HS subtype with one patient each with H and S subtypes). The duration was 26 weeks with a subsequent extension to 52 weeks and beyond. Both studies reported positive effects on functional ability (specifically performance on the six-minute walking distance), markers of lysosomal storage and markers measuring change in specific disease symptoms.

Cost effectiveness

The authors of the review concluded that the lack of basic data related to natural history, in particular a lack of quality of life data, lack of efficacy data and the highly heterogeneous nature of the conditions meant that it would not be appropriate to attempt a cost-effectiveness analysis. They nonetheless argue that the extremely high costs of ERT in this condition mean that it is unlikely that, even if the treatment is highly effective, it would meet the current thresholds for cost-effectiveness. Again this argument is crucially dependent on current drug costs.

Table 1 shows the conditions for which there are treatments available. Please note the data on which symptoms are responsive and those which do not appear to respond to ERT are taken from a review article, publication date 2004 and are not taken from primary research studies.

Disease	**Approx. Prevalence (Australian data [5])**	**Enzyme Replacement Therapy**	**Substrate Reduction Therapy**	**Median Age of diagnosis* (range)**	**Symptoms responsive to ERT.**	**Symptoms which appear largely unresponsive to ERT (taken from [12]**
Fabry	**1:117,000**	**Fabrazyme** (agalsidase beta) 1mg/kg IV **Replagal** (agalsidase alfa) 0.2 mg/kg IV		28.6 years (0 – 55.7)	Hypohidrosis, neuropathic pain, decreased cold and warm sensing, GI disturbance	Progressive renal, cerebrovascular (stroke – no evide of effect, rather th evidence of no effect), cardiac disease
Gaucher	**1:57,000**	Initially Ceredase (licensed US 1994, Europe 1998) Imiglucerase - **Cerezyme** licensed 2003	**Miglustat (Zavesca)** licensed for patients in whom ERT is not appropriate.	9.5 years (0 -73.2)	Anaemia, thrombocytopenia, bone crises, bone fractures	Neurological abnormalities, interstitial lung disease
MPSI Hurler's disease/ Hurler-Scheie/	**1:88,000**	Iduronidase / **Aldurazyme –** 0.5mg/kg Prescribed for Hurler and Hurler-Scheie forms of MPS I and for people with the Scheie form who have moderate to severe symptoms. Risks and benefits of treating mildly affected patients with the Scheie form have not been established.		1.0 years (0.3 – 29.1)	Hepatospenomegal y, decreased joint range of motion, restrictive pulmornary disease	Macroephaly, hydrocephalus, Coarse facial features, bone deformities, menta retardation, cardia disease, cornea clouding Aldurazyme has n been evaluated for symptoms of the central nervous system.
MPS VI Maroteaux-Lamy Disease	**1:235,000**	**Naglazyme** (Galsulfase),		1.4 years (0 – 43.4)	Decreased joint range of motion, gait difficulties	Coarse facial features, bone deformities
MPS II Hunter syndrome	**1:136,000**	Iduronate-2-sulfatase **Idursulfase (Elaprase)**		2.8 years (0.0 – 22.0)		
Pompe's disease	**1:146,000**	**Myozyme®** (alglucosidase alfa) – 4 infants in an		0.5years (0.1 -55.0)	Cardiac hypertrophy, heart failure, skeletal	Lower motor neur disease

(Early and Late onset)		open label study suggest that Rx should begin as early as possible – **15-40mg/kg.** further study with 3 patients with late onset Pompe showed good results.		early and late - onset	muscle weakness, respiratory failure	
Late onset Tay-Sachs disease / Sandhoff disease	**1:201,000** **1:384,000**	Substrate reduction therapy shows some promise in mouse models	**Miglustat used in clinical trials**			
Niemann-Pick type C	**1:211,000**		**Miglustat used in clinical trials**	9.3 years (0.1 -37.7)		

Patterns of treatment in England

Treatment Centres

Services for patients with Lysosomal Storage Disorders (LSDs) including treatments such as Enzyme Replacement Therapy and Substrate Reduction Therapy are being nationally commissioned by the National Commissioning Group (NCG - formerly the National Specialist Commissioning Advisory Group, NSCAG) until March 2011. In England, seven hospitals have been nationally designated and funded, to provide a service for patients with lysosomal storage disorders (LSDs).

***Centres for children**:*

- Central Manchester and Manchester Children's University Hospitals NHS Trust (estimated 279 child patients)
- Great Ormond Street Hospital for Children NHS Trust (estimated 148 patients)
- Birmingham Children's Hospital NHS Foundation Trust (estimated 137 patients)

Centres for Adults

- Salford Royal Hospital NHS Trust (estimated 311 adult patients)
- Royal Free Hampstead NHS Trust (estimated 231 adult patients)
- University College London Hospitals NHS Foundation Trust, National Hospital for Nervous Diseases, Queen Square (Estimated 145 patients)

Centre for adults and children

- Addenbrooke's NHS Trust (estimated 204 patients; 159 adults 45 children)

From these figures there would appear to be 1455 patients with an LSD who are seen at one of the treatment centres.

As would be expected from prevalence data the most common LSDs amongst patients seen in these centres are Gaucher and Fabry in adults and the mucoploysaccharidosis disorders (in particular MPS I and MPS III), in children [Treatment Centres, personal communication].

At present, Wales, Scotland and Northern Ireland have separate prescribing arrangements and there is no precise data as to the numbers of patients with lysosomal storage disorders living in these regions, although some do receive care at the designated centres.

Rationale for proposed study

It has been argued [16, 17] that there is currently little point in conducting further studies of effectiveness or cost-effectiveness of ERT in Gaucher disease, Fabry disease or MPSI. This is based on the argument that the costs of the drugs are currently so high that however effective these treatments are there is no possibility that they can cross currently accepted thresholds for willingness to pay. The authors of these reviews argue that, if society has decided that because of the particular rarity and severity of these conditions it is willing to pay for therapy, then further information is not required while, if society is to apply the thresholds generally used to make such decisions, no amount of information will move the decision across this threshold.

In our view this stance, while arguable, is mistaken. Better estimates of the effectiveness of the interventions, of the relative effectiveness of treatment depending on when in the course of the condition treatment begins and of different treatment regimens are important for patients and their families as well as for clinicians. The costs of the drugs may well change substantially in the future with changes in technology and the possible entry into the market of other providers. In these circumstances evidence of effectiveness will be needed to underpin decisions on cost effectiveness. The proposed study will provide at least partial answers to these questions in addition to providing better data on NHS costs to inform future estimates of cost effectiveness.

In addition, the proposed study offers the opportunity to assemble a cohort of patients with other LSDs for which ERT may become available in the future. We anticipate that the same difficulty in carrying out long term randomised controlled trials will apply in these conditions and that better estimates of the natural history of untreated UK patients will make possible later estimates of cost-effectiveness of therapy based on observational data.

Currently there are several lysosomal condition-specific databases which are held by the pharmaceutical companies which manufacture the enzyme replacement therapies and the substrate reduction therapy currently licenced in the UK. This has led to the development of two registries for Fabry's, which do not appear to be compatible with each other, hindering comparison treatment efficacy. The MPS society (UK) also has a registry of all UK people diagnosed with an MPS disorder since 1981. In addition

there is a national Gaucher registry held at Addenbrookes which is part of the Gauchers Disease – diagnosis and management advice service.

It was felt to be necessary to establish this UK cohort study independent of the pharmaceutical industry, not least because the intention is to collect data on all lysosomal storage disorders and not solely ones where there are treatments. In addition, given that there are currently three pharmaceutical companies that manufacture these treatments, to conduct the study with any one of the companies might lead to potential conflicts of interest.

Proposed study

We aim to conduct a longitudinal, prospective cohort study involving all adults and children with lysosomal storage disorders, living in the UK who are treated within the seven designated treatment centres in England. As new therapies and treatment modalities are being proposed and developed for these disorders, issues around diagnosis, when to start treatment, and valid and reliable outcome measures to assess treatment effectiveness are raised. With lysosomal storage disorders, early diagnosis is important to allow treatment before irreversible organ damage occurs.
Furthermore, it is possible that given the progressive nature of these disorders, there might be clinical markers within each condition which indicate the optimum point at which enzyme replacement therapy should initiated.

The study will initially collect data on conditions for which ERT is currently available or being developed, although it is intended that eventually all children and adults diagnosed with an LSD will form part of the study. We believe that the majority of people with lysosomal storage disorders will be referred to these centres, regardless of whether there is a specific treatment available; where there is no specific treatment, people receive palliative care from these centres.

Methods

Identification / Recruitment of Eligible Patients

All patients with lysosomal storage disorders, living in the UK and attending the treatment centres will be identified and consent will be sought for their participation in the study.

1 Identification

The research assistant/nurse will identify eligible patients from the department database, or department patient lists and will enter the patient's initials and date of birth into an 'Initial table for Recruiting' spreadsheet and assign a study ID. There will be one spreadsheet per condition.

The LSD consultant will be asked to confirm the patient's eligibility to take part in the study i.e. that they will not be distressed by being approached to take part. Eligibility status will be entered into the spreadsheet and eligible patients and / or their carer will be sent an introductory letter (Appendix 1, 2, 2b or 2c).

To ensure patients / patients' carers have sufficient time to read and absorb the information and have the time and opportunity to discuss the study with relatives, GPs, research staff etc, an invitation letter and patient information sheet will be posted to the patient / patient's carer at least one month before they are due at their clinical review appointment (Appendices 3-6).

It is anticipated that some patients will be missed by the researcher and / or the LSD consultant at their first clinical review appointment after receiving their invitation to participate in the study. This might be due to the patient not attending the clinic, or due to other commitments for the researcher and/or consultant on the day of their attendance. In such cases, the patient will be sent an additional invitation letter and patient information sheet one month before they are next due at their clinical review appointment (Appendices 3-6).

2. Explanation of the Trial

The LSD consultant or research nurse will meet patients when they attend their clinical review appointment. The study will be verbally explained to the patient / patient's carer using the appropriate Information Sheet and the use and timing of the questionnaires will be explained to the patient/patient's carer. Sufficient time will be allocated for the patient / patient's carer to ask questions and have them answered to their satisfaction.

3. Consent

Written informed consent (Appendix 7 or 8) will be obtained from each participant. For people under 16, written parental or guardian consent will be obtained (Appendix 8).

3.1 Two-tier consent

The study will operate a two-tier consent process whereby if a patient or their carer does not wish to complete the quality of life or resource-use questionnaires, they will be asked if they agree to their data being extracted from their medical notes for the purposes of the study (Appendix 7B or 8B).

3.2 Consenting patients who lack capacity

The research team will initially assume that each patient has capacity and every effort will be made to support them to help them make their own decision regarding participation in the study. Information about the study will be provided to each

individual in a way that is most appropriate to help them understand the study and make their own decision.

If the treating clinician or another member of the healthcare team believes *on the balance of probabilities*, that the individual lacks capacity to give informed consent, then they must take reasonable steps to identify someone to consult, before they are included in the research. That person (the consultee) must be involved in the person's care, interested in their welfare and must be willing to help. They must not be a professional or paid care worker.

Where there is no willing "personal consultee", the researcher will identify an appropriate adult (such as a psychologist or social worker) involved in their care but unconnected to the study and ask them to assist in explaining the study.

The consultee will be given information about the research project and be asked:

- for advice about whether the person who lacks capacity should take part in the study, and
- what they think the person's feelings and wishes would be, if they had capacity to decide whether to take part.

Once a willing consultee has been identified, they will be asked to provide written informed consent on behalf of the patient (Appendix 25 or 25B).

3.3 Re-consenting 16 year olds

When a patient who is in the study turns 16 they must be approached for re-consenting. They will be consented using adult forms.

- When the parent/carer has not given any consent for their child's participation in the study, the researcher can approach the patient directly for consent when the patient turns 16.
- When the parent/carer has given 'notes only' consent for their child's participation in the study, the researcher can approach the patient directly for full consent when the patient turns 16.
- Patients can only be re-consented when the LSD consultant has confirmed their eligibility to take part in the study. That is, that they will not be distressed by being approached to take part.

4. Informing the patient's GP of participation in study

Once consent has been received from the patient or their carer, a letter will be sent to the patient's GP (Appendices 23 – 24) notifying them of the patient's involvement in the study, along with a Patient Information Sheet.

Data collection

Data will be collected on all consenting patients onto a condition-specific database. Each database will follow the same structure with a set of data common to all conditions and condition-specific data. Data collected will include both prospective data and limited historical data. Historical data is available for a number of conditions contained within the variety of existing registers and in the patients' notes. Data fields will be agreed within the group but will be guided by the principle that only data which will clearly contribute to answering a specific question will be included.

Identification of data fields

Procedures and data collection will be piloted on the following three disorders – Gaucher, Pompe and MPS I. Clinicians from the seven sites have identified, individually and in working groups, which data fields are important to collect for these disorders. Initially, the team determined basic information relating to which key organs are affected in each disorder, and then the primary tests which demonstrate the functioning of that organ. Further communications within the working groups clarified the data fields to be collected for each disorder.

Questionnaires

Questionnaires are to be handed out to patients (or carer/parent) consenting to have the additional questionnaires at their annual check up appointment with their clinician. They may also be asked to complete additional questionnaires at any additional monitoring appointment they attend. The patient will obviously have the right to refuse to complete the questionnaires at all times. Ideally questionnaires will be completed during the hospital visit, but if this is not possible the patient/carer will be given a Stamped Addressed Envelope and asked to return the questionnaires to the Research Nurse. The patient ID will be written on the top of each sheet in the pack either before or after completion. When the questionnaires are taken home, this will be done before they are removed from the treating centre. The Patient/Carer will be contacted up to a maximum of three times at two week intervals to chase if the questionnaires have not been returned. A brief record of the conversation/message left each time will be made on the notes page (Appendix 25) and kept in the study file. Dates will be recorded in the database.

Once returned the questionnaire answers will be entered into the database and the paper copies will be kept in study folders.

The age-appropriate questionnaires to be given to the patient and carer (if applicable) are detailed in Table 2.

For those conditions where the senses are impaired the HUI (Health Utilities Index) will also be given to patients over 5 years of age.

- Pompe – where there is cardiomyopathy
- Gaucher – Type III
- MPS I – all
- MPS II – all
- Fabry – all
- Niemann Pick C – all

Table 2: Questionnaires

Age	Senses affected by condition?	Questionnaires
0-1	Not applicable	Service use and cost – child proxy (app 16B) Caregiver Strain Index (app 18)
2-4	Not applicable	PedsQL toddler– parent (app 20) Service use and cost – child proxy (app 16B) Caregiver Strain Index (app 18)
5-7	No	PedsQL 5-7 – child (app 12) PedsQL 5-7 – parent (app 11) Service use and cost – child proxy (app 16B) Caregiver Strain Index (app 18)
	Yes	As above plus: HUI - proxy (app 19B)
8-12	No	PedsQL 8-12 – child (app14) PedsQL 8-12 – parent (app13) Service use and cost – child proxy (app 16B) Caregiver Strain Index (app 18)
	Yes	As above plus: HUI – proxy (app 19B)
13-15	No	PedsQL 13-18 – child (app 21) PedsQL 13-18 – parent (app 22) Service use and cost – Child proxy (app 16B) EQ5D (app 10) Caregiver Strain Index (app 18)
	Yes	As above plus: HUI – proxy (app 19B)
16-or over	No	EQ5D (app 10) SF-36 (app 9) Service use and cost – adult (app 16) Caregiver Strain Index (if applicable) (app 18)
	Yes	As above plus: HUI – self (app 19)

Database

We will use MACRO, a web-based electronic data collection system from InferMed. A secure, condition-specific database will be designed for all conditions. Data will be collected at the patients' annual or six-monthly review and entered onto the database by the Research Nurse / Analyst at each study site.

Data quality assurance

Data accuracy is a requirement under the Data Protection Act, and together with data completeness is essential for maximising validity and reliability research outputs. To ensure data consistency between centres a data code-book or definitions manual will be developed. Data checks (valid ranges, filter checks, logical checks) will also be conducted as part of data entry processes and will be built into the database system. Key data will be "double entered" using source data verification.

Analysis

The database will contain longitudinal individual-level patient data for all consenting patients attending the participating treatment centres.

Natural History

Data will be analysed to describe the natural history of treated and untreated LSDs. Key outcome measures relevant to each disorder will be analysed by genotype where this information is available and where there are sufficient numbers of patients with a specific genotype. Exploratory analysis of patient trajectories will be conducted using graphical methods. For conditions where sufficient data are available, formal statistical modelling which exploits the longitudinal nature of the data (both

prospective and retrospective) will be used to study individual dynamics. Important issues to be addressed will include accounting for non-linearity in the rate of disease progression, and patient heterogeneity in age of presentation and clinical severity. This will be achieved by exploring dynamic linear growth curve models in a Bayesian framework with patient-specific random effects, and random walk priors for the mean and slope parameters [21]. Such models can be extended to allow for dependency amongst the set of outcome measures for each condition by inclusion of patient-specific latent variables [22]. The latent variables represent unobserved constructs and provide a means of identifying the main elements of the underlying structure of the disease process. The flexible framework makes it possible to combine patient characteristics measured on different scales and to make adjustments for outcome-specific measurement errors. Given the likely sparsity of data for individual LSDs, careful attention will need to be given to specification of prior distributions to ensure model identification.

Effectiveness of treatment

For each condition, different approaches will be needed to estimate the effectiveness of ERT. The approach will depend largely on the amount of data available on untreated patients. Where data are not available for significant numbers of untreated patients, treatment efficacy will be estimated by taking advantage of the fact that the age and stage of their condition at which patients have begun taking ERT was dependent on the time when the treatment first became available. Historical data are available for many of these patients on their clinical condition at the time of beginning

treatment while for others we will have data only on current clinical situation. The analysis of the available data will require (a) longitudinal analyses of changes in outcome measures and resource use before and after treatment, taking account of a range of covariates (e.g. baseline severity, demographic characteristics) and (b) extrapolation of pre- and post-treatment data to estimate the likely lifetime costs and effects in untreated and treated cohorts of patients.

Given the rare nature of these disorders and the corresponding modest sample sizes, conventional analyses may not have the power to detect or exclude clinically worthwhile treatment benefits. Consequently, we propose making assessments of treatment efficacy in a Bayesian framework to supplement analyses using classical methods. Although definitive answers may not always be possible, with frequentist confidence limits unlikely to exclude a null result, taking a Bayesian approach can provide a clearer guide by quantifying the probabilities that clinical effects lie in a particular range [23]. These probabilities, calculated by combining study data with a prior distribution, apply directly to future patients and can be used explicitly in formal decision analysis. A key component of our approach will be obtaining credible data on priors through incorporation of information from previous trials and elicitation of opinions from clinicians. We will conduct extensive sensitivity analyses to assess the effect of uncertainty in the choice of model specification and prior assumptions.

Comparison of the effectiveness of agalsidase alpha and agalsidase beta in Fabry disease.

Both agalsidase alpha and agalsidase beta are licensed for use in the UK for the treatment of Fabry disease. Both treatments received their license in 2002. There is a five fold difference in the licensed dosing regimen although costs per patient are broadly similar. It appears that, although all centres use both drugs, there has been tendency for each centre to use one or other as their initial drug of choice. This it appears has been determined mainly by historical reasons based partly upon which drugs trials they were involved in. Some patients subsequently switch to the alternative treatment, for clinical reasons, and it has been suggested that more recently there may be more variety in initial drug choice. There are national guidelines for the initiation of therapy to which all centres adhere which suggests that the populations receiving either treatment are likely to be broadly similar. There are currently approximately 185 adults and 45 children with Fabry disease receiving treatment with one or other of these drugs.

We will compare the outcome of treatment depending on which of the two drugs patients were initially assigned (the equivalent of an intention to treat analysis) in a multivariate model allowing for potential confounding variables. We will in addition compare recorded side-effects and frequency of switching treatments.

Costs of care

Data will be collected on health care resource use using the Service Use and Cost Questionnaire (Appendix 16). Information such as numbers of hospitalisations, outpatient and GP appointments, medication use, and other therapies will be collected

according to disorder, patient age and severity for all patients. Additional data will be collected on associated family/carer costs and on family/carer related quality of life impacts using the Caregiver Strain Index (App 18). These data will be used to estimate life-time health care costs according to disorder and severity.

Cost-effectiveness.

These data will be used to help develop and populate a number of decision-modelling based cost-utility analyses for the main policy comparisons that might be relevant and feasible. Wherever possible these analyses will make use of the models previously developed by the West Midlands Health Technology Assessment Collaboration.

Given that the numbers involved will be relatively small (relative to typical epidemiological cohort studies) and also, for evidence relating both to treatment effects and economic impacts, subject to considerable uncertainty it will be essential to investigate the cost-effectiveness through modelling. Decision modelling in particular provides an explicit framework for integrating (a) disease natural history data (b) evidence and/or assumptions about treatment effectiveness and cost, (c) extrapolating these data over time, and (d) quantifying uncertainty surrounding all of the model inputs, so that a wide range of policy scenarios can be explored (23,24). The models will be used to establish the level at which the costs of the ERT would meet conventional thresholds of cost effectiveness taking account of NHS and societal costs.

Development of condition-specific rating scales

Currently there are condition-specific rating scales for Gauchers (the Severity Score Index [26, 27]) and Fabry (the Mainz severity Score Index [28]). There is no condition-specific severity scoring system for MPS I (although such a scale is under development [26]). However these scales have been developed from adult data and their relevance to children has not been established, nor do they appear to be particularly sensitive to treatment [personal communication]. There is an urgent need for the development of better severity scoring systems. The development of such scales is not part of the current application, however, the natural history data and the carer/family data collected as part of this study can be used to inform the development of such disorder-specific treatment responsive measures. The availability of a whole population sample for these conditions will provide the basis for further development and testing of such systems.

Ethical considerations

Multi-centre ethics agreement has been obtained from the South West Research Ethics Committee, and site-specific ethics approval has been granted by the relevant local ethics committee for each site. Research Governance approval has also been granted for the data collection and analysis of this data for the seven treatment centres to collect the data and for the Peninsula Medical School to undertake data analysis with the centres.

Benefits to the NHS

A longitudinal cohort study collecting individual patient data from people with lysosomal storage disorders will provide benefits to the NHS, designated treatment

centres and patients. As suggested by the HTA-commissioned assessments of enzyme replacement therapy for Gaucher, Fabry and MPS I [16,18], in order for an evaluation of the clinical and cost-effectiveness of emerging enzyme replacement therapies to be conducted, comprehensive and valid data of sufficient quality needs to be collected, prior to the therapy being licensed. This study proposes to collect data from all people with lysosomal storage disorders in the UK who attend the seven treatment centres in England, thereby minimising selection bias. A similar type of study, which established a Cystic Fibrosis database, has reported benefits to clinicians and patients [30]. Similar to LSDs, many patients with CF are seen at specialised clinics, where care is tailored to the individual. Their data capture and reporting system has been customised to allow for individual patient reports regarding their disorder. The system also allows the participating clinicians to compare care programmes between centres.

Staffing implications

Professor Stuart Logan will have overall responsibility for the project. Dr Katrina Wyatt and Professor Logan will have day to day responsibility for the project which will be coordinated by Sheena Oxer. Dr Rob Anderson and Dr Ken Stein will supervise the data modelling and health economic analyses and Dr William Henley will manage the statistical analyses. The clinical applicants will ensure appropriate design of data gathering and clinical relevance of analyses. The patient support groups will provide input to ensure that appropriate account is taken of patient and family views.

Data collection will require considerable clinical expertise. There are in total 1127 patients with LSDs seen at the participating centres and we anticipate very high rates of agreement to participate. We estimate that initial data entry will take approximately

2 hours per patient and each follow-up visit approximately half an hour per patient. We are currently funding a full time research analyst in Cambridge, two 0.75WTE research analysts in Manchester, three 0.7WTE research analysts in London, and one 0.5WTE research analyst in Birmingham. Given the amount of data which will also need to be collected retrospectively we propose to fund a data entry research assistant at each site for 12 months. The study also requires a fulltime research fellow with modelling experience to develop and analyse the models, with additional support from the Peninsula Technology Assessment Group (PenTAG).

Additional support has been requested to allow for travel between the sites, conference attendance, computers and printers (for all sites for data collection) and recruitment.

NHS support and Treatment costs:

Following extensive discussion with each of the treatment centres regarding additional treatment and NHS costs, it has been agreed that whilst there are *no* additional treatment costs (ie drug costs or investigations) associated with this study there are time implications for the consultants who manage patients with LSDs. In order to collect the necessary information from each patient, it will be necessary to spend additional time with each patient to explain the study, gain consent and collect and record additional information, more frequently than would otherwise be required in a routine consultation. As each patient is seen by a consultant for their management and treatment, this will does carry a time implication for each treatment centre. Two hours consultant time has been agreed per week per treatment centre for the duration of the study.

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