

Proposal to conduct a long term cohort study of people with lysosomal storage disorders – version 2 (19.12.06)

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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 *Fabryzyme* 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 in 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 Gauchers, Fabrys and MPS I, and several more are being developed.

People with these disorders are treated at one of six 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 glycopospholipids, 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 discrete 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 a 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 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 glucosylceramide 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 Gauchers, 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 Gaucher's 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, Gauchers 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 Fabrys 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, Fabrys 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 Gauchers Disease

Gauchers 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 (Connock et al. forthcoming). In this analysis, even assuming that ERT restores people with Gauchers 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 [18]. It is a clinically heterogeneous disease and is usually slowly

progressive with symptoms changing with age [19]. A substantial proportion of patients will develop cerebrovascular disease (transient ischaemic attacks and stroke). There are two ERT 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) [17]. 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 Fabryzyme 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 Gauchers 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 a 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 a milder 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 dose is 0.58mg/ kg body weight every week.

Effectiveness

The systematic review identified one placebo-controlled RCT and a phase I/II observational study provide 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 the treatment to be 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	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 evidence of effect, rather than evidence of no effect), cardiac disease
Gaucher	1:57,000	Initially Ceredase (licensed US 1994, Europe 1998) Imiglucerase - Cerenzyme licensed 2003 Miglustat 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)	Hepatosplenomegaly, decreased joint range of motion, restrictive pulmonary disease	Macrocephaly, hydrocephalus, Coarse facial features, bone deformities, mental retardation, cardiac disease, cornea clouding Aldurazyme has not 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	2.8 years (0.0 – 22.0)		
		Myozyme®		Cardiac	Lower motor neuron

Pompe's disease (Early and Late onset)	1:146,000	(alglucosidase alfa) – 4 infants in an open label study suggest that Rx should begin as early as possible – 15-40mg/kg. further study with 3 patients with late onset Pompe's showed good results.	0.5years (0.1 -55.0) early and late - onset	hypertrophy, heart failure, skeletal muscle weakness, respiratory failure	disease
<i>Late onset Tay-Sachs disease / Sandhoff disease</i>	1:201,000 1:384,000	Substrate reduction therapy shows some promise in mouse models Miglustat			
<i>Niemann-Pick type C</i>	1:211,000	Miglustat	9.3 years (0.1 -37.7)		

Patterns of treatment in England

Treatment Centres

For a period of two years, between April 2005 to March 2007, four centres, six hospitals have been nationally designated and funded, to provide a service for patients with lysosomal storage disorders (LSDs). Birmingham should become the seventh centre, in 2007. These services are commissioned by the National Specialist Commissioning Advisory Group.

Centres for children:

- Central Manchester and Manchester Children's University Hospitals NHS Trust (estimated 370 child patients)
- Great Ormond Street Hospital for Children NHS Trust (estimated 149 patients)

Centres for Adults

- Salford Royal Hospital NHS Trust (estimated 54 adult patients)
- Royal Free Hampstead NHS Trust (estimated 192 adult patients)
- University College London Hospitals NHS Foundation Trust, National Hospital for Nervous Diseases, Queen Square (Estimated 128 patients)

Centre for adults and children

- Addenbrooke's NHS Trust (estimated 234 patients; 189 adults 45 children)

From these figures there would appear to be 1127 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 Gauchers and Fabrys in adults and the mucopolysaccharidosis 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 Gauchers disease, Fabrys 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 lysosomal condition-specific databases for Gauchers, MPS I and Fabry which are held by the pharmaceutical companies, Genzyme and Shire/ TKT, the manufacturers of the enzyme replacement therapies as well as a registry for people with Gauchers who are receiving substrate reduction therapy. 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 Gauchers registry held at Addenbrookes which is part of the Gaucher's 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 treated within the six designated English treatment centres. 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

Data collection

Data will be collected on all consenting patients onto a condition-specific database. In the event that a possible participant is unable to provide consent, a professional outside of the research team will take the decision regarding non-capacity. 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. 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. All participants will be asked to complete yearly quality of life questionnaires.

There is already a well-developed system for capturing data for patients with Gauchers disease. The information which is collected has been agreed with all the treatment centres and is based on a Dendrite database, with the main server held at Addenbrookes. We plan to use a Dendrite based system for all conditions run via the web, accessed through the NHS system in keep data behind the firewall. Dendrite have developed local and national databases (for example, national cardiac database) and the systems are compatible with Hospital Information systems, thereby preventing duplicate data entry.

Data will be collected and updated six monthly.

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.

Analysis

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

1. 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.

2. 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) time series 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. Uncertainty will be addressed in

all analyses by a range of sensitivity analyses, including, where appropriate, stochastic and probabilistic methods.

3. 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 multi-variate model allowing for potential confounding variables. We will in addition compare recorded side-effects and frequency of switching treatments.

4. Costs of care

Data will be collected on health care resource use (e.g. numbers of hospitalisations, outpatient and GP appointments, medication use, other therapies) according to disorder, patient age and severity for a sample of patients with the less rare conditions

and on all patients with the rarer disorders. Additional data will be collected on associated family/carer costs and on family/carer related quality of life impacts on a sub-sample. These data will be used to estimate life-time health care costs according to disorder and severity.

5. 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 (20,21). 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.

6. Development of condition-specific rating scales:

Currently there are condition-specific rating scales for Gaucher's (the Severity Score Index [22, 23]) and Fabry's (the Mainz severity Score Index ([24]). There is no condition-specific severity scoring system for MPS I (although such a scale is under development [25]). 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 and research governance approval will be sought for the data collection and analysis of this data for the six treatment centres to collect the data as well as for the Peninsula Medical School to undertake data analysis with the centres. All patients with lysosomal storage disorders attending these centres will be approached and asked whether they would consider allowing their information to be stored on a dedicated database. Written informed consent will be obtained from each participant. For people under 16, written parental or guardian consent will be obtained. For people with severe neurological involvement who are unable to give 'informed' consent, as determined by the carer or treating clinician, the guardian or carer will be approached.

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 Gauchers, Fabrys and MPS I [16,17], 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 England, thereby minimising selection bias. A similar type of study, which established a Cystic Fibrosis database, has reported benefits to clinicians and patients [26]. 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. Dr Rob Anderson and Dr Ken Stein will supervise the data modelling and health economic analyses. The clinical applicants will ensure appropriate design of data gathering and clinical relevance of analyses. It is anticipated that 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 propose to fund a full time research nurse in Cambridge, two, 0.75WTE research nurses in Manchester and two full time research nurses in London (as there are three sites and approximately 500 patients). As it is proposed that Birmingham will be an NSCAG Centre in 2007, funding for a part time (0.5) research nurse has been requested to establish the data collection and entry system. Centres will be able to interpret this resource flexibly allowing integration of the research nurses with the clinical teams. Given the amount of data which will also need to be collected retrospectively we propose to fund a data entry research assistant (part time at Cambridge and Manchester and fulltime in London) for the first 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 requested per week per treatment centre for the duration of the study.

References

- [1] B.J.H.M. Poorthuis *et al.*, The frequency of lysosomal storage diseases in The Netherlands, *Hum. Genet.* **105** (1999), pp. 151–156.
- [2] P.F. Meikle, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders, *JAMA* **281** (1999), pp. 249–254.
- [3] L. Peltonen, Molecular background of Finnish disease heritage, *Ann. Med.* **29** (1997), pp. 553–556.
- [4] *Acta Paediatrica* 2005; 94 (suppl 447): 79
- [5] Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of Lysosomal Storage Disorders. *JAMA* 1999 281(3) 249-254
- [6] Wraith JE. The management of lysosomal storage disorders. *Current Paediatrics* 2004; 14; 389-393
- [7] Wenger DA, Coppola S, Liu S-L. Insights into the diagnosis and treatment of lysosomal storage disease. *Arch Neurol* 2003; 60; 322-328
- [8] Hobbs JR, Hugh-Jones K, Barrett AJ, Byrom N, Chambers D, Henry K, James DC, Lucas CF, Rogers TR, Benson PF, Tansley LR, Patrick AD, Mossman J, Young EP. Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. *Lancet.* 1981 Oct 3;2(8249):709-12
- [9] Vellodi A. Lysosomal Storage Disorders. *Br. J. Haem.* 2004 128; 413-431

- [10] [Cox T](#), [Lachmann R](#), [Hollak C](#), [Aerts J](#), [van Weely S](#), [Hrebicek M](#), [Platt F](#), [Butters T](#), [Dwek R](#), [Moyses C](#), [Gow I](#), [Elstein D](#), [Zimran A](#). Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. *Lancet* 2000 355(9214):1481-5.
- [11] Elstein D, Hollak C, Aerts JM, van Weely S, Maas M, Cox TM, Lachmann RH, Hrebicek M, Platt FM, Butters TD, Dwek RA, Zimran A. Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT 918) in type I Gaucher disease *J Inherit Metab Dis*. 2004; 27(6): 757-66.
- [12] Brady R, Schiffmann R. Enzyme-replacement therapy for metabolic storage disorders *The Lancet* 2004; **3**: 752-56
- [13] L. Klinge, V. Straub, U. Neudorf, J. Schaper, T. Bosbach, K. Görlinger, M. Wallot, S. Richards and T. Voit. 2005 Safety and efficacy of recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease: results of a phase II clinical trial. *Neuromuscular disorders* 15 (1) 24-32
- [14] [Muenzer J](#), [Lamsa JC](#), [Garcia A](#), [Dacosta J](#), [Garcia J](#), [Treco DA](#) 2002 Enzyme replacement therapy in mucopolysaccharidosis type II (Hunter syndrome): a preliminary report. . *Acta Paediatr Suppl*. 2002;91(439):98-9.
- [15] Harmatz, P, Whitley CB, Waber L, *et al* 2004. Enzyme replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome). *J Pediatrics* 144(5) 574-580

[16]] Connock M, Burls A, Frew E *et al* The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease NICE Technology Assessment Report 2005

[17] Connock M, Frew E, Juarez- Garcia A *et al*. The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Fabry's disease and MPS I. NICE Technology Assessment Report 2005

[18] Peters FPJ, Vermeulen A, Kho TL. Anderson- Fabry's disease: α – galactosidase deficiency. *Lancet* 2001; 357: 138-40

[19] Mehta A, Ricci R, Widner U *et al*. On behalf of the FOS investigators. Fabry disease defined: baseline clinical manifestations of 366 patients in FOS – the Fabry Outcome Survey. *Eur J Clin Invest* 2004 34: 236-42

[20] M. Buxton, M. F. Drummond, B. A. van Hout, R. L. Prince, T. A. Sheldon, T. Szucs, and M. Vray. Modelling in economic evaluation: an unavoidable fact of life. *Health Economics* 6:217-227, 1997.

[21] K Kuntz, M Weinstein . Modelling in economic evaluations. In: *Economic evaluation in health care: merging theory with practice*, edited by Drummond M and McGuire A, Oxford:Oxford University Press, 2005, p. 141-171.

[22] Zimran A, Gross E, West C, Sorge J, Kubitz M, Beutler E. Prediction of severity of Gaucher's disease by identification of mutations at DNA level. *The Lancet* 1989; **334** (8659): 349 -352

[23] Zimran A, Kay A, Gelbart T, Garver P, Thurston D, Saven A *et al.* Guacher disease Clinical, laboratory, radiology and genetic features of 53 patients. *Medicine* 1992; **71**(6): 337-353

[24] Whybra C, Kampmann C, Krummenauer F, Ries M, Mengel E, Miebach E *et al.* The Mainz Severity Score Index: a new instrument for quantifying the Anderson Fabry disease phenotype, and the response of new patients to enzyme replacement therapy. *Clinical Genetics* 2004; **65**(4): 299-307

[25] Haley SM, Fragala MA, Aseltine R, Ni P, Skrinar AM. Development of a disease-specific disability instrument for Pompe disease. *Pediatr Rehabil* 2003; 6(2); 77-84

[26] Mehta G, Sims EJ, Culross F, McCormick JD. Potential benefits of the UK cystic fibrosis database 2004. Suppl 44 vol 97 pages 60-71