Health Technology Assessment 2006; Vol. 10: No. 20

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June 2006

Health Technology Assessment
NHS R&D HTA Programme

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A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1

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Declared competing interests of authors: none

Published June 2006

This report should be referenced as follows:

Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*. A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1. *Health Technol Assess* 2006;**10**(20).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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The research reported in this monograph was commissioned by the HTA Programme as project number 03/64/02. The contractual start date was in June 2004. The draft report began editorial review in July 2005 and was accepted for publication in November 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1

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Objectives: To determine the clinical effectiveness and cost-effectiveness of the administration of intravenous enzyme replacement therapy (ERT) to symptomatic patients for the prevention of long-term damage and symptoms in Fabry's disease and in mucopolysaccharidosis type 1 (MPS1).
Data sources: Electronic databases from inception up to mid-2004. Contact with clinical experts.
Review methods: Relevant studies were identified and assessed using recommended quality criteria.
Results: The results suggested beneficial effects of ERT for Fabry's disease on measures of pain, cardiovascular function and some end-points reflecting neurosensory function. Renal function appeared to be stabilised by ERT. At present there are no utility-related health-related quality of life data on which to assess the relative health gain of ERT in MPS1. In order to be able to demonstrate the full extent of health gain from treatment, it was necessary to review the natural history of untreated patients in each disease in order to try to estimate the health loss prevented. The published information for Fabry's disease tallied with descriptions of a multi-system, life-threatening disorder particularly involving kidney, heart and brain with individual patients exhibiting many manifestations. The fragmentary information reviewed in 16 studies relevant to the natural history of MPS1 did not generate a coherent picture of disease progression and could provide little added value to published narrative reviews. For Fabry's disease, the mean cost per patient (50 kg) treated is around £85,000 per annum in England and Wales. The cost per patient varies considerably by dose. No published evidence reporting an economic evaluation of ERT for Fabry's disease was identified by this review. A dynamic decision model was constructed based on a birth cohort of male patients who are followed up until death. Owing to lack of information reported in the literature, many assumptions had to be applied. The key assumptions were that ERT returns patients to full health and a normal life expectancy. As far as possible, all assumptions favoured rather than detracted from the value of ERT. ERT was assumed to restore patients to full health in the base case. The estimated incremental cost-effectiveness ratio (ICER) in the base case was £252,000 per QALY (agalsidase beta). Univariate sensitivity analysis around the key assumptions produced ICERs ranging from £602,000 to £241,000. The base case unit cost of ERT was taken as £65.1/mg based on the cost of agalsidase beta. The unit cost would have had to be reduced to £9 to obtain an ICER of £30,000 per QALY. For MPS1, the mean cost per child patient (20 kg) treated is approximately £95,000 and an adult (70 kg) around £335,000 per annum in England and Wales. The cost per patient varies considerably by dose. There is no published evidence reporting an economic evaluation of ERT for MPS1 and no study was identified that reported the quality of life of MPS1 patients within a utility format. Furthermore, no or minimal information of the severity and rate of change of clinical manifestations of disease or the impact of ERT on these factors was identified. Information on the effect of ERT on mortality is also lacking owing to the relatively short time that the treatment has been available. Given this lack of data, it was not possible to develop a cost-effectiveness model of ERT treatment for MPS1 as the model would consist almost completely of assumptions based on no published evidence, leading to an incremental cost per QALY result that would be meaningless.

Conclusions: Although ERT for treating the 'average' patient with Fabry's disease exceeds the normal upper threshold for cost-effectiveness seen in NHS policy decisions by over sixfold, and the value for MPS1 is likely to be of a similar order of magnitude, clinicians and the manufacturers argue that, as the disease is classified as an orphan disease under European Union legislation, it has special status, and the NHS has no option but to provide ERT. More information is required before the generalisability of the findings can be determined. Although data from the UK have been used wherever possible, this was very thin indeed. Nonetheless, even large errors in assumptions made will not reduce the ICER to anywhere near the upper level of treatments usually considered cost-effective. In order to overcome limited evidence on the natural history of the disease and the clinical effectiveness of the intervention, the establishment of disease-specific data registries is suggested to facilitate the process of technology assessment and improving patient care. These registries should attempt to include all affected patients in the UK, and collect longitudinal patient level data on clinically relevant problems, interventions received and quality of life in a utility format.

Contents

List of abbreviations

α-gal A	α-galactosidase A
ACE	angiotensin-converting enzyme
AIDS	acquired immunodeficiency syndrome
BMT	bone marrow transplant
BPI	Brief Pain Inventory
CI	confidence interval
CNS	central nervous system
CT	computed tomography
CVA	cerebrovascular accident
DARE	Cochrane Database of Abstracts of Reviews of Effects
ECG	electrocardiogram
EQ5D	EuroQol 5D measure of quality of life
ERT	enzyme replacement therapy
ESRD	end-stage renal disease
EU	European Union
FOS	Fabry Outcome Survey
FVC	forced vital capacity
GAG	glycosaminoglycan
Gb3	globoside
GFR	glomerular filtration rate
GL-3	globotriaosylceramide
HAQ	Health Assessment Questionnaire
HEED	Health Economic Evaluations Database
HRQoL	health-related quality of life
HSCT	haemopoietic stem cell transplant
ICER	incremental cost-effectiveness ratio
IgE	immunoglobulin E
IgG	immunoglobulin G
ITT	intention-to-treat
LSD	lysosomal storage disease
LVH	left ventricular hypertrophy
MI	myocardial infarction
MPS	mucopolysaccharidosis
MPS1	mucopolysaccharidosis type 1
MRI	magnetic resonance imaging
MSSI	Mainz Severity Score Index
MV	mechanical ventilation
NHS CRD	NHS Centre for Reviews and Dissemination
NHS EED	NHS Economic Evaluation Database
NIH	National Institutes of Health
NSAID	non-steroidal anti-inflammatory drug
NSCAG	National Specialist Commissioning Advisory Group

continued

List of abbreviations *continued*

NYHA	New York Heart Association
PPI	present pain intensity
QALY	quality-adjusted life-year
QoL	quality of life
QST	quantitative sensory testing
RCT	randomised controlled trial
RRT	renal replacement therapy
SD	standard deviation
SF-36	Short Form with 36 Items
SF-6D	Short Form with six attributes
TIA	transient ischaemic attack

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Aim and objective

The aim of this review was to determine the clinical effectiveness and cost-effectiveness of the administration of intravenous enzyme replacement therapy (ERT) to symptomatic patients for the prevention of long-term damage and symptoms in Fabry's disease and in mucopolysaccharidosis type 1 (MPS1).

Epidemiology and background

Fabry's disease

Fabry's disease is an inherited X-linked disorder caused by deficient activity of the enzyme α-galactosidase A found in lysosomes. This results in an accumulation of globoside (Gb3) in the lysosomes of many tissues, including kidney, heart and blood vessels.

The classic form of the disease seen in males is characterised by early onset of pain in childhood and gradual progressive organ damage predominantly expressed in kidney, heart and brain, culminating in renal failure by about 40 years of age and increased risk of heart disease and stroke. The same constellation of manifestations is seen in female carriers but incidence is much lower, onset later and severity reduced; many carriers are essentially disease free.

More than 350 Fabry's disease mutations have been identified. At the UK population level, any given mutation is almost completely limited to a single pedigree.

Traditional therapy has comprised palliative care and interventions for specific symptoms.

Agalsidase alpha (Replagal®) and agalsidase beta (Fabrazyme®) are recombinant enzymes, produced in a genetically engineered human cell line and in genetically engineered Chinese hamster ovary cells, respectively. They are given intravenously to replace the defective enzyme and are licensed for use in symptomatic Fabry's disease.

Mucopolysaccharidosis type 1

MPS1 disease is an inherited autosomal recessive disorder caused by deficient activity of the enzyme α-L-iduronidase found in lysosomes. This results in an accumulation of glycosaminoglycans in the lysosomes of cells in many tissues, including connective tissue, brain, heart and liver. Consequences of this abnormal storage include skeletal, respiratory, neurological, cardiac and mobility problems.

MPS1 is heterogeneous and has been classified into three subtypes on clinical features that probably represent a continuum. Hurler syndrome presents in the first years of life and is severe with neurological symptoms and reduced life expectancy of only about one decade. Hurler–Scheie syndrome is an intermediate form with reduced life expectancy of only two to three decades. Scheie syndrome is a milder form with later presentation in which manifestations are greatly attenuated with longer life expectancy than the severer forms. The attenuated forms Scheie and Hurler–Scheie are associated with normal or near normal intellect and greater heterogeneity of manifestations than the Hurler phenotype.

Traditional therapy has comprised palliative care and interventions for specific symptoms.

Laronidase (Aldurazyme®) is a recombinant enzyme produced by genetically engineered Chinese hamster ovary cells. It is licensed to be administered intravenously to treat the non-neurological manifestations of the disease in patients with a confirmed diagnosis of MPS1.

Prevalence

The prevalence of Fabry's disease in the UK is of the order of 0.3 per 100,000, giving estimates of around 150 people affected with the disease in England and Wales, about 70 males and 80 females.

There are currently approximately 53, 33 and 10 live patients with Hurler, Hurler–Scheie and Scheie syndromes in England and Wales and the birth prevalences of these are estimated to be about 0.756, 0.243 and 0.070 per 100,000 live births, respectively.

Difficulties and delays in diagnosis mean that these numbers may be underestimated.

NHS

ERT for Fabry's disease and MPS1 is already used within the NHS. In England, patients with significant clinical symptoms have had access to therapies through six designated treatment centres. Current provision of ERT is said to cost the NHS in England and Wales about £20 million per annum. Although this currently represents a steady state, if ERT reduces disease-specific mortality, the figure will grow as the population being treated ages. Extending use to patients who are mildly symptomatic or asymptomatic individuals as a prophylactic measure would also increase the burden on the NHS.

Evidence about effectiveness

Search strategy

Broad, disease-specific search strategies were employed to capture publications on incidence, prevalence and natural history of the disease and the clinical effectiveness of treatment. These included searches of MEDLINE, EMBASE, CINAHL, Cochrane Library and Science Citation Index from their inception up to mid-2004, scrutiny of bibliographies, contact with clinical experts and identification of ongoing and unpublished studies. Primary studies of any design reporting at least 10 patients were included.

Direction of evidence

All studies are suggestive of benefit with ERT. Infusion-related adverse events, which are in general tolerable, are potentially the biggest disbenefit.

Summary of benefits

Fabry's disease

The effectiveness of ERT for treating patients with Fabry's disease has been studied in three randomised placebo-controlled trials (total $n = 70$ patients; duration: 5–6 months) and 11 uncontrolled before–after studies (total $n = 493$ patients duration up to 24 months). A total of 119 patients were treated with Fabrazyme and the remainder with Replagal or human agalsidase alfa; most patients were male. Further data come from open-label extensions to these studies and other uncontrolled studies.

In general, the studies varied widely in design, quality and end-points measured, making robust conclusions about effectiveness difficult.

The results suggested beneficial effects of ERT on measures of pain, cardiovascular function and some end-points reflecting neurosensory function. Renal function appeared to be stabilised by ERT.

MPS1

Evidence of effectiveness comes solely from two studies, a Phase I/II study enrolling 10 patients and a Phase III/randomised controlled trial (RCT) enrolling 45 patients who were further studied in an open-label extension to the trial. Duration of treatment was up to 98 weeks.

The two studies for the most part enrolled patients with moderate to mild disease (predominantly patients with Hurler–Scheie), and in the RCT the inclusion criteria appear to have selected the more physically able patients.

Outcomes measured in the two studies were a combination of those chosen as likely to reflect readily and rapidly any improvement in patient functional abilities, those related to markers of lysosomal storage, those measuring change in specific disease symptoms and those related to monitoring the safety of the intervention. On the whole, all outcomes demonstrated some degree of improvement on treatment with ERT.

At present there are no utility-related health-related quality of life data on which to assess the relative health gain of ERT in MPS1.

General considerations

Although unlikely to be undertaken, further well-designed comparative trials are required to provide clear evidence of the efficacy and effectiveness of ERT in preventing and treating clinically meaningful manifestations of both Fabry's and MPS1 disease.

How the effects of ERT treatment translate into well-being and survival or the need for services and resources has not been reliably estimated.

Furthermore, in both diseases it is likely that the benefits from treatment might exceed the health gain demonstrated in studies without a control group because such designs are unable to compensate for any deterioration after baseline measurement that would have occurred during the duration of the study in the absence of treatment. Therefore, to be able to demonstrate the full extent of health gain from treatment, it was necessary to review the natural history of untreated patients in each disease in order to try to estimate the health loss prevented.

Natural history

Fabry's disease

Thirty-one studies relevant to the natural history of Fabry's disease were reviewed. A single longitudinal study of a substantial cohort of male patients indicated median survival of approximately 57 years and the development of renal insufficiency at around the third decade, rapidly followed by end-stage renal disease at a median age of about 40 years. The study also provided evidence of a rapid increase in brain lesions after about 40 years consistent with increased risk of transient ischaemic attacks and stroke. Data presented in other studies broadly confirmed these findings. The published information tallied with descriptions of a multi-system, life-threatening disorder particularly involving kidney, heart and brain with individual patients exhibiting many manifestations. No longitudinal analysis of a cohort of female carriers was found. Studies indicated that females are subject to the same constellation of symptoms as males but onset is later, severity reduced and at the individual level the spectrum of manifestations limited. Renal involvement is much less frequent in females. The incidence of disease amongst carriers is uncertain and, although some may be severely affected it is clear many remain essentially disease free.

MPS1

Published information was meagre, especially with regard to Hurler–Scheie and Scheie phenotypes. Analysis of data from the Society for Mucopolysaccharide Diseases (UK) indicated a median survival of 11.5 years for MPS1, but the large proportion of Hurler patients, with an estimated median survival of 8.6 years, drove this estimate. Median survival for the attenuated phenotypes exceeded 30 years. The fragmentary information reviewed in 16 studies relevant to the natural history of MPS1 did not generate a coherent picture of disease progression and could provide little added value to published narrative reviews.

Economic evaluation

Fabry's disease

Costs

The mean cost per patient (50 kg) treated is approximately £85,000 per annum in England and Wales. The cost per patient varies considerably by dose.

Cost per quality-adjusted life-year (QALY)

No published evidence reporting an economic evaluation of ERT for Fabry's disease was identified by this review. A dynamic decision model was constructed based on a birth cohort of male patients who are followed up until death. Owing to lack of information reported in the literature, many assumptions had to be applied. The key assumptions were that ERT returns patients to full health and a normal life expectancy. As far as possible, all assumptions favoured rather than detracted from the value of ERT. ERT was assumed to restore patients to full health in the base case. The estimated incremental cost-effectiveness ratio (ICER) in the base case was £252,000 per QALY (Fabrazyme).

Sensitivity analyses

Univariate sensitivity analysis around the key assumptions produced ICERs ranging from £602,000 to £241,000. The base case unit cost of ERT was taken as £65.1/mg based on the cost of Fabrazyme. The unit cost would have had to be reduced to £9 to obtain an ICER of £30,000 per QALY.

MPS1

Costs

The mean cost per child patient (20 kg) treated is approximately £95,000 and an adult (70 kg) approximately £335,000 per annum in England and Wales. The cost per patient varies considerably by dose.

Cost per QALY

There is no published evidence reporting an economic evaluation of ERT for MPS1 and no study was identified that reported the quality of life of MPS1 patients within a utility format. Furthermore, no or minimal information of the severity and rate of change of clinical manifestations of disease or the impact of ERT on these factors was identified. Information on the effect of ERT on mortality is also lacking owing to the relatively short time that the treatment has been available.

Given this lack of data, it was not possible to develop a cost-effectiveness model of ERT treatment for MPS1 as the model would consist almost completely of assumptions based on no published evidence, leading to an incremental cost per QALY result that would be meaningless.

Other important issues regarding implications

Although ERT for treating the 'average' patient with Fabry's disease exceeds the normal upper threshold for cost-effectiveness seen in NHS policy

decisions by over sixfold, and the value for MPS1 is likely to be of a similar order of magnitude, clinicians and the manufacturers argue that, as the disease is classified as an orphan disease under European Union legislation, it has special status, and the NHS has no option but to provide ERT.

Generalisability of the findings

More information is required before the generalisability of the findings can be determined. Although data from the UK have been used wherever possible, this was very thin indeed. Nonetheless, even large errors in assumptions made will not reduce the ICER to anywhere near the upper level of treatments usually considered cost-effective.

Recommendations and the need for further research

Further research could help clarify the many uncertainties that exist. However, although doing so may be of clinical interest and refine patient care, it is questionable whether, within the current pricing environment, such research would have any substantive impact on policy decisions. It is highly improbable that, whatever the findings of such research, the ICER could be brought down by the orders of magnitude required to make ERT an efficient use of health service resources by current standards. A possible exception to this would be to investigate the most efficient alternative treatment strategies for using ERT in a paediatric population only. Moreover, if under European orphan drug legislation or for equity considerations the NHS feels that it is important to provide these drugs, regardless of its cost-effectiveness, then refining the precision of the ICER estimate becomes superfluous.

At least two ERTs for other lysosomal storage diseases are in Phase III development. It is likely that if these and subsequent ERTs and non-ERT interventions are granted marketing approval, then evaluation of their clinical and cost-effectiveness will also be hampered by limited evidence on the natural history of the disease and the clinical effectiveness of the intervention. To overcome these limitations, the authors of this report recommend the establishment of disease-specific data registries which attempt to include all affected patients in the UK, and collect longitudinal patient level data on clinically relevant problems, interventions received and quality of life in a utility format. Although there are international industry-supported registries for those ERTs already licensed and undoubtedly similar registries will be established for emerging ERTs, these registries are usually only established as a result of gaining regulatory approval for the ERT, and therefore tend to include data only on treated patients. Furthermore, it is the authors' experience that obtaining data from these registries, in a timely manner to undertake a health technology assessment, is not necessarily easy. Disease-specific registries should be established well before marketing approval is granted for an ERT in order to capture sufficient longitudinal evidence on the natural history of the disease in the absence of ERT. The point at which an application is made for orphan drug status might be the latest appropriate time to begin such data collection. Data from registries should be readily accessible (in anonymised form) to facilitate the process of technology assessment and improving patient care. A requirement of such a process should be that the results of any analysis are subject to peer review and placed in the public domain. It is clearly evident to the authors of this report that there is a willingness by clinicians, patients and patient advocacy organisations collectively to support such registries.

Chapter 1

Aim of the review

Gaucher's, Fabry's and mucopolysaccharidosis type 1 (MPS1) diseases are rare inherited conditions, classified as lysosomal storage diseases (LSDs), that in their severest forms may be life-threatening. Each is caused by a particular enzyme deficiency resulting from mutation in the gene coding for a specific lysosomal enzyme. Prior to the development of enzyme replacement therapy (ERT), treatment options were in the main specifically directed at the pathological sequelae individual to the particular LSD. ERT aims to treat patients with these disorders by replacing the mutant or missing enzyme with a functional protein that is infused into the bloodstream and taken up into cellular lysosomes. ERTs therefore represent a generic therapy of potential utility for a wide variety of storage diseases, especially those involving deficient lysosome function. As such, a number of ERTs are in development and are likely to become licensed under orphan drug legislation in the next few years. In the UK, ERT is currently licensed for Gaucher's, Fabry's and MPS1 diseases. The aims of this review were to determine the effectiveness and cost-effectiveness of ERT therapies for Fabry's and MPS1 diseases. The clinical effectiveness and cost-effectiveness of ERT for Gaucher's disease are the subject of a separate HTA report.[1]

Chapter 2
Background

Lysosomes and lysosomal storage diseases

The lysosome is an organelle found in cells and is the principal site of intracellular digestion. It contains a battery of degradative enzymes capable of attacking all the major classes of biological macromolecule. Complex macromolecules such as sphingolipids and mucopolysaccharides are degraded in a series of linked sequential reactions that represent degradative metabolic pathways. Lysosomes are particularly numerous in cells that are especially active in phagocytosis.

LSDs are rare monogenetic autosomal or sex-linked conditions characterised by abnormal accumulation of undegraded or untransported metabolite(s) within the lysosome. As a result, the lysosomes become enlarged and numerous and crowd the cell cytoplasm.[2] A considerable variety of pathologies can develop from this and the clinical manifestations of many LSDs were described long before the discovery of lysosomes. Many LSDs have infantile, juvenile and adult forms; in the adult forms pathology develops more slowly and disability arises mainly from peripheral symptoms. Infantile and juvenile forms more often involve both neurological and peripheral symptoms.

The underlying cause of most LSDs is mutation in a gene coding for a lysosomal enzyme leading to a deficiency in the functional activity of the enzyme.[2,3] The result is gradual accumulation within the lysosome of the particular enzyme's substrate. The tissues and organs that are the site of accumulation, and the pathologies that develop, vary depending on the particular enzyme deficiency. The abnormally high concentration of undegraded metabolite may activate secondary pathways that might lead to potentially toxic products.

Fabry's disease and MPS1 are each members of a different large class of LSDs characterised by the chemical nature of their storage products. Fabry's disease is a sphingolipidosis. In this class of LSD there is a deficiency in the degradation of one of the sphingolipids that are most commonly found in cell membranes. There are more than a dozen sphingolipidoses, amongst which the most common is Gaucher's disease. MPS1 is a mucopolysaccharidosis (MPS); these diseases are characterised by deficient degradation of mucopolysaccharides that are most commonly found as constituents of connective tissue. More than a dozen subtypes of MPS have been described, although there are only seven clearly different diseases in this category.[4]

Treatment for lysosomal storage diseases

Four treatment strategies that directly address the underlying cause of the disease have been suggested for lysosomal storage diseases:[3,5]

- ERT
- enzyme enhancement therapy
- substrate reduction therapy[6]
- gene therapy.

ERT supplies the deficient enzyme and attempts to target this to lysosomes of cells that harbour storage product; it is administered intravenously. Enzyme enhancement therapies aim to increase residual enzyme activity that may be present by providing chaperone-like small molecules that can bind the misfolded or unstable enzyme molecules and increase the probability that they mature to functional lysosomal enzymes. Substrate reduction therapy attempts to reduce the accumulation of storage product by inhibiting an enzyme in its synthetic pathway and reducing its generation. Substrate reduction therapy and enzyme enhancement therapy involve the use of small molecules that can cross the blood-brain barrier and therefore have the potential to benefit patients with neuronopathic manifestations of LSD. They may be administered orally. Gene therapy aims to supply a functional gene copy or copies to substitute the missing function of the gene that has sustained mutation and precipitated the LSD. Delivery systems for effective gene therapy are in development. Engraftment of genetically modified stem cells carrying functional genes represents one approach.

Only ERT has been licensed in Europe for treatment of Fabry's and MPS1 patients. Haematopoietic stem cell transfer to introduce a functional gene is suitable for some conditions, including some MPS1 patients.

Fabry's disease

Clinical, pathological and molecular aspects of Fabry's disease have the been the subject of numerous reviews.[7–13] Fabry's disease is a panethnic LSD transmitted on the X chromosome and caused by deficiency in activity of the lysosomal enzyme α-galactosidase A (α-gal A) that is responsible for the degradation of the globoside sphingolipid globotriaosylceramide, also called ceramide trihexoside or globoside (Gb3). The disease is characterised by progressive multisystem involvement and was first described independently by Fabry and by Anderson in 1898; the storage material was characterised in 1963 and the deficient enzyme identified by Brady and colleagues in 1967.[14]

In early studies, the use of simple synthetic substrates revealed the presence of two lysosomal enzymes with acid α-galactosidase activity; one was termed α-galactosidase A, also called ceramide trihexosidase, and the other α-galactosidase B. Only the former was found to be deficient in Fabry's patients. α-Galactosidase B was subsequently shown to correspond to lysosomal α-*N*-acetylgalactosaminidase and found to be deficient in a rare autosomal neurodegenerative LSD called Schindler's disease.[13]

Nature of the disease

The enzyme deficiency in Fabry's disease results from mutation in the lysosomal α-gal A gene on the Xq22.1 region of the X chromosome, or extremely rarely a Fabry-like condition can result from mutation in the prosaposin gene that codes for protein activators of several lysosomal enzymes. Many mutations in the α-gal A gene have been identified; 356 mutations were listed in the Human Gene Mutation Database when accessed on 8 June 2005.[15] Most mutations are private and are restricted to members of a particular family pedigree.

There are three main phenotypes described in Fabry's disease: the 'classic' phenotype seen in nearly all affected males, the variable and milder form observed in heterozygous females (carriers) and rare atypical male phenotypes (e.g. cardiac variant).

In many X-linked inherited conditions, female carriers (heterozygotes) are disease free or exhibit only the mildest signs of the disease seen in their affected male relatives. In these cases even after cellular 'random' inactivation of one X chromosome (paternal or maternal) during development[16] the functional gene on the remaining active paternal X chromosomes presumably supplies sufficient normal gene product to obviate disease development. Fabry's disease female carriers appear to represent an exception to this generalisation. Although exhibiting similar multisystem involvement to males, a much wider spectrum of disease severity is seen than in affected males, with later onset of symptoms and relatively reduced severity. These observations are consistent with the proposal that in some female carriers the particular distribution of inactivated paternal X chromosomes results in some organ systems accumulating sufficient storage product to compromise functional integrity. The frequency and severity of disease in female carriers are clearly variable and are a matter of current debate.

The underlying pathology of Fabry's disease is the accumulation of triaosylceramide that occurs in many cell types but especially in vascular endothelial cells, glomerular cells in the kidney, neurones, and cells of heart. Deposition probably starts at birth, or even before birth, and the progressive storage results in gradual evolution of a complex clinical syndrome particularly involving kidney, heart and brain.

The brief description of the major disease manifestations given below applies to the classic phenotype and is based on published reviews.[12,13,17–19]

Skin lesions

Accumulation of Gb3 leads to vascular lesions in the skin that take the form of a characteristic early onset and progressively increasing skin rash made up of angiokeratomas distributed in clusters or singly in the 'bathing trunk' areas of the body, but sometimes in oral mucosa and conjunctiva. The angiokeratomas are typically "red to blue–black punctate"[12] lesions, flat or raised, located in the superficial layers of the skin.

Sweat glands in the skin are affected so that patients have reduced ability to sweat.

Ocular manifestations

Eye involvement encompasses corneal clouding observable by split-lamp microscopy. Other ocular manifestations recorded in hemizygous patients

include lens opacities and retinal and conjunctival vascular lesions; these and corneal clouding are not associated with impaired vision.

Nervous system involvement

Chronic pain is usually described as the most debilitating symptom experienced by Fabry's patients.[12] It is difficult to control with medicines and reportedly may be sufficiently severe for suicide to be contemplated. The majority suffer from a continuous burning pain in the feet and hands accompanied by paresthesias (tingling and feelings of numbness). In addition, episodic severe pain crises affecting the extremities and/or abdomen are experienced. Crises and chronic pain together are attributed major roles in the morbidity of Fabry's disease.

Renal disease

Kidney biopsies bear witness to progressive accumulation of Gb3 in the kidney. Deposits are marked in podocytes and mesangeal cells of the glomeruli, but also occur in cells of collecting tubules and in the walls of larger renal blood vessels. "Renal size increases by about the third decade of life followed by a decrease in the fourth and fifth decades".[12] Shedding of loaded cells allows the detection of characteristic sediments in urine. Eventually proteinuria, renal insufficiency and finally end-stage renal failure are typical developments. Onset of end-stage renal disease (ESRD) reportedly averages around 40 years of age.[19]

Heart disease

Gb3 accumulates in cardiomyocytes and in fibroblasts of heart valves. The heart becomes hypertrophic. Clinical sequelae can include angina pectoris, myocardial ischaemia, arrhythmias, myocardial infarction (MI), congestive heart failure and aortic and mitral valve dysfunction. Heart disease is a common cause of death for Fabry's patients.[12]

Cerebrovascular involvement

'Multifocal small-vessel involvement'[12] in the brain can lead to a variety of consequences that may include nausea/vomiting, head pain, gait ataxia, transient ischaemic attacks (TIAs) and strokes.

Gastrointestinal involvement

Some patients suffer chronic diarrhoea, recurrent abdominal pain, postprandial cramping and sensations of early satiety.

Mainz Severity Score Index

Disease severity scores, such as the Severity Score Index proposed by Zimran and colleagues for Gaucher's disease,[20,21] attempt to gauge quantitatively the severity of the disease in patients with different disease profiles and may aid diagnosis and allow monitoring of disease progression in individual patients or their response to treatment. Whybra and colleagues[22] introduced the Mainz Severity Score Index (MSSI) for Fabry's disease; the MSSI encompasses general, neurological, cardiac and renal manifestations of Fabry's disease[22] and is summarised in *Table 1*. The MSSI classifies signs and symptoms of disease in four categories: general (maximum score = 18), renal (18), cardiovascular (20) and neurological (20). Scores were added up within each category in order to calculate a total overall score (maximum = 76).

Historical therapy

Traditional therapy for Fabry's disease has comprised multiple interventions ranging from palliative care especially for pain [anticonvulsants and non-steroidal anti-inflammatory drugs (NSAIDs)] to surgery and other measures to address life-threatening renal and cardiac involvement. The introductions of dialysis and of renal graft have extended life expectancy.

MPS1

Clinical, pathological and molecular aspects of MPS1 disease have been the subject of a number of reviews.[4,23–25] MPS1 is a panethnic autosomal recessive LSD, caused by a deficiency in the activity of the lysosomal enzyme α-L-iduronidase. Hurler first described the disease in 1919, with a milder form identified by Scheie in 1962. At first these were thought to be separate conditions but were reclassified as MPS1 when the deficient enzyme was shown to be the same in the 1970s.

Nature of the disease

This enzyme has a role in the stepwise degradation of the glycosaminoglycans dermatan sulfate and heparan sulfate and its deficiency leads to the progressive accumulation of dermatan and heparan sulfate throughout the body and their excessive excretion in urine. As accumulation and storage continue there is progressive multisystem involvement, resulting in tissue and organ damage which becomes manifest as loss of function, gradual clinical deterioration and progressive disability.[4] Key areas affected are brain, eyes, ears, nose, throat, heart, lungs, liver, bones and joints.

The gene encoding α-L-iduronidase is located on chromosome 4 at location 4p16.3 and so far there

TABLE 1 *The Mainz Severity Score Index (MSSI)*

General score			Neurological score		
Sign/symptom	**Rating**	**Score**	**Sign/symptom**	**Rating**	**Score**
Characteristic facial appearance	No Yes	0 1	Tinnitus	No Mild Severe	0 1 2
Angiokeratoma	No Some Extensive	0 1 2	Vertigo	No Mild Severe	0 1 2
Oedema	No Yes	0 1	Acroparaesthesia	No Occasional Chronic	0 3 6
Musculoskeletal	No Yes	0 1	Fever pain crisis	No Yes	0 2
Cornea verticillata	No Yes	0 1	Cerebrovascular	No Ischaemic lesions (in MRI/CT) TIA, migraine, stroke	0 1 3 5
Diaphoresis	Normal Hypo/hyper Anhidrosis	0 1 2	Psychiatric/psychosocial		
Abdominal pain	No Yes	0 2	Depression	No Yes	0 1
Diarrhoea/constipation	No Yes	0 1	Fatigue	No Yes	0 1
Haemorrhoids	No Yes	0 1	Reduced activity level	No Yes	0 1
Pulmonary	No Yes	0 2			
NYHA Classification	No Class I Class II Class III Class I	0 1 2 3 4			
	Maximum score	18		Maximum score	20

Cardiovascular score			Renal score		
Sign/symptom	**Rating**	**Score**	**Sign/symptom**	**Rating**	**Score**
Changes in cardiac muscle thickness	No Thickening of wall/ septum LVH seen in ECG Cardiomyopathy (<15 mm) Cardiomyopathy (>15mm)	0 1 6 8 12	Evidence of renal dysfunction	No Proteinuria Tubular dysfunction/ low GFR or creatinine clearance End-stage renal failure (serum creatinine levels >3.5 mg/dl) Dialysis	0 4 8 12 18

continued

TABLE 1 *The Mainz Severity Score Index (MSSI) (cont'd)*

Cardiovascular score			Renal score		
Sign/symptom	**Rating**	**Score**	**Sign/symptom**	**Rating**	**Score**
Valve insufficiency	No	0			
	Yes	1			
ECG abnormalities	No	0			
	Yes	2			
Pacemaker	No	0			
	Yes	4			
Hypertension	No	0			
	Yes	1			
	Maximum score	20		Maximum score	18

CT, computed tomography; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; NYHA, New York Heart Association; TIA, transient ischaemic attack.

have been over 90 different mutations identified.[26] Many mutations are private and are restricted to members of a particular family pedigree, although others are more common, such as W402X and Q70X. Genotype and phenotype correlations are not exact, except that patients with two nonsense alleles which prevent production of any functional enzyme will present with severe disease.[23]

Prevalence is estimated to be of the order of one in 100,000 (see the section 'Prevalence', p. 51 for a review of prevalence studies).

Patients with MPS1 have historically been categorised into one of three clinical syndromes, which from severe through intermediate to milder phenotype are Hurler, Hurler–Scheie and Scheie syndromes. This is somewhat artificial as it is increasingly clear that the disease is a continuum with a broad clinical spectrum of variable presentation and that the categories do not reflect adequately the high degree of heterogeneity of the disease. Assignment to one of these subtypes is made only on the basis of clinical criteria, as they are not distinguishable biochemically. Despite these issues, the utilisation of this classification continues and has been retained in this review to maintain continuity with the published literature.

Patients with Hurler syndrome present early in life with rapidly progressing disease that usually results in death due to neurological/CNS deterioration and/or cardiovascular/respiratory causes prior to the teenage years.

Patients with the intermediate Hurler–Scheie syndrome usually present prior to 10 years of age and often survive into early adulthood with cause of death often related to disease-related cardiac problems or upper airway obstruction.

Patients with Scheie syndrome have slowly progressing disease, which is often not manifest until after 5 years of age. Diagnosis typically may not be made for a number of years. Death typically occurs at middle age or later and a normal lifespan in some patients may be achieved. Complications of the disease and/or surgical procedures for them are often the cause of death. These include heart failure due to cardiomyopathy or disease of the cardiac valves, coronary disease and anaesthetic complications of surgery.

A brief description of the major disease manifestations is given below, with an indication of the extent in each of the three syndromes where possible. This information is taken from a number of published narrative reviews[4,23,24] and reference to information provided by patient advocacy organisations.[27,28] Given the heterogeneity of the disease, patients can experience any of the following problems to any degree of severity.

Growth/height

In children with Hurler syndrome, growth may be above average at first but then slows and can stop completely by the age of 3 years and maximal height is not usually much in excess of 1 m. In contrast, children with attenuated disease grow to a relatively normal height. The height with intermediate disease is variable. Typically short stature is associated with disproportionate appearance, with the trunk being much shorter than normal.

Head and facial features

Coarsening of the facial features is a classic feature of patients with Hurler syndrome. Severe features are enlarged head with prominent forehead, short neck, lips, nostrils and earlobes are thickened and the tongues, gums and palate can be enlarged. The head tends to expand front and backwards in Hurler syndrome owing to the early fusion of cranial sutures, and this also accounts for the prominent forehead. Hair tends to be coarse and straight and there is a tendency to above-average body hair.

In attenuated disease, features are variable and children may not look any different from healthy children, and as adults facial coarsening can be very subtle and/or slowly progressing; others, however, may develop a more classic appearance. Teeth can be poorly formed with weak enamel and widely spaced towards the severe end of the disease spectrum. Ear, nose and throat infections are common.

Respiratory system

The tonsils and adenoids are often enlarged, which can diminish the airway. The trachea can be narrowed by accumulation of glycosaminoglycans (GAGs) and also it can be less rigid. These features, combined with a short neck, all contribute to give rise to breathing problems, including sleep apnoea. Enlarged liver and short trunk can impinge on the diaphragm, also impacting on respiratory function. Patients are vulnerable to pulmonary infections.

These features along with skeletal changes to the vertebrae can make intubation difficult. Respiratory problems associated with surgery are a common cause of death in more severely affected patients.

These features are generally less severe in adults with attenuated disease.

Nervous system

In severe MPS1 there is progressive storage of GAGs in the brain that are responsible for slowing of development by 1–2 years of age. Development may then plateau for a time, followed by progressive deterioration as patients lose their acquired cognitive abilities and patients are usually severely mentally retarded by the time of their death. Even within this severe form there is heterogeneity as some children may only ever say a few words whereas others learn to talk and read prior to deterioration. Other manifestations of the disease may also impact on the development and deterioration of a patient's skills.

Hurler–Scheie patients can have normal intelligence with some having some degree of learning difficulties. In the attenuated form there appears to be no storage of mucopolysaccharides in the brain and patients have normal intelligence and are able to pursue intellectually challenging careers.

The mechanism of pathology of the CNS is thought to be complex and involve not only primary accumulation of GAGs but also secondary accumulation of glycosphingolipids.[4] Other causes of CNS problems include hydrocephalus due to defective reabsorption of spinal fluid and, although commonly seen in the severe phenotype, it is also seen in the attenuated disease. Patients often undergo shunting procedures to treat this problem.

Acute spinal cord compression due to deformation/movement of the vertebrae is a common feature in all severities of MPS1. Compression of the spinal cord due to thickening of the meninges and ligaments is a common feature in the attenuated disease and requires early intervention to decompress the cord to prevent permanent complications.

Cardiovascular system

Cardiovascular problems are a leading cause of death in MPS1.

GAG storage in cardiac tissue and consequential secondary effects of this accumulation lead to progressive cardiac involvement, resulting in a number of conditions involving the heart valves, endocardium, myocardium and coronary arteries. In addition, plaques may restrict the lumen of the aorta and other large vessels.

Common conditions include cardiomyopathy, systemic and pulmonary hypertension, endocardiofibroelastosis, heart murmurs (mitral regurgitation), angina and coronary artery disease.

Heart disease is common in Hurler syndrome. Patients with attenuated disease may have slowly progressing asymptomatic aortic or mitral valve diseases.

Heart valve replacements are an option in those patients able to tolerate the procedure.

Skeletal system

Accumulation of GAGs in bone, cartilage, tendons, ligaments and skin gives rise to significant problems with bone formation and growth and results in a number of musculoskeletal problems throughout the body. Structural remodelling of

bone is common. Progressive skeletal changes are widely seen in all forms of the disease but are most pronounced in the severe phenotype. In Hurler and Hurler–Scheie syndromes vertebrae can be poorly formed, restricting interaction. Some vertebrae may be smaller and misaligned, causing curvature of the spine (gibbus). Neck bones can be unstable and require surgical fusion to aid supporting the head. Spinal nerve entrapment and acute spinal injury may occur.

Spinal problems are common in attenuated disease and may require orthopaedic interventions.

Joint stiffness is a common feature of all phenotypes with progressive reduction in the range of joint motion. This impacts on the ability of the patients to undertake tasks of daily living.

Tendon tightening and skeletal deformities give rise to abnormal gait. As the disease progresses, patients require assistance with mobility. Decreased mobility may further be exacerbated by cardiovascular and respiratory problems.

Hands and feet

Hands can be short, stubby and gradually clawed. Poor hand function resulting from joint contractures is common. Carpal tunnel syndrome is a common feature of the disease due to thickening of ligament in the hand and resulting nerve compression. Originally seen as a problem in Scheie patients, the presence of carpal tunnel syndrome is now assessed more readily in more severe disease.

Ocular and hearing

There are multiple ocular findings, which include reduced visual acuity, corneal clouding, glaucoma, optic nerve compression, photosensitivity and retinal pigment degeneration. Problems are usually bilateral although not necessarily with the same degree of severity. Corneal clouding and elevated intraocular pressure are the most common findings in all MPS1 patients.[4]

Some degree of deafness is common in all types of MPS1 and more so in severe disease, and may be of conductive and/or neurosensory origin owing to a number of factors including the Eustachian tube becoming affected by GAG accumulation, malformation/deterioration of the auditory bones, nerve damage and damage resulting from persistent/recurrent ear infections. Speech development, already possibly affected by neurological and skeletal problems along with tongue and soft tissue enlargement, can also be affected by poor hearing.

Visceral

Hepatomegaly and splenomegaly are common features owing to accumulation of GAGs resulting in abdominal distension. Spleen size may be normal in attenuated disease. Umbilical and inguinal hernias due to weak connective tissue and the result of organomegaly are common in children and are an early sign of the disease. Feeling bloated, pain and gastrointestinal disturbances are commonly reported symptoms.

Historical therapy

There is no curative or single maintenance therapy for MPS1 and the multisystem manifestations of the disease are reflected in its management.

Traditional therapy for MPS1 has comprised multiple interventions ranging from palliative care to surgery and other measures to address specific manifestations of the disease. These include procedures to improve airway function, cardiac disease and orthopaedic problems. Most patients are regularly assessed by a battery of healthcare professionals and individual treatment plans maintained.

Although not curative, bone marrow transplant (BMT) and haemopoietic stem cell transplant (HSCT) procedures for patients with Hurler syndrome have significantly modified the progress of the disease and improved survival in some patients. Advanced skeletal problems and ocular problems, for example, may not respond as well as some other manifestations of the disease. The progress of neurological degeneration may be slowed. However, as the procedure carries a high risk of morbidity and mortality it has not routinely been utilised in Hurler–Scheie and Scheie patients. In Hurler patients the procedure is ideally undertaken prior to 2 years of age and is the predominant treatment in Hurler patients.

Measuring disease severity

Unlike Gaucher's disease and Fabry's disease, no disease-specific severity scoring system for MPS1 has been proposed. There is some indication that one is in development.[29]

Enzyme replacement therapy

ERT for Fabry's disease

α-Galactosidase suitable for intravenous administration has been developed by two

companies for replacement of the missing enzyme in Fabry's patients. Transkaryotic Therapies' product, Replagal® (agalsidase alpha), received licensing approval in Europe in September 2002 for treatment of patients with confirmed diagnosis of Fabry's disease. Genzyme's product, Fabrazyme® (agalsidase beta), was similarly licensed in December 2002. Only Fabrazyme is currently licensed in the USA.

Both agalsidase alpha and beta are produced from cells genetically engineered with the human gene for lysosomal α-gal A. Fabrazyme is produced by Chinese hamster ovary cells and Replagal by a continuous human cell line. Both products are isolated from the cell culture medium and subjected to extensive purification procedures. The surface carbohydrate structure of the two may differ because this part of the enzyme is added by systems that may differ between human and hamster.

A 35-mg vial of Fabrazyme contains lyophilised agalsidase beta together with stabilising mannitol and buffer reagent; when reconstituted with 7 ml of water, the solution contains agalsidase at 5 mg/ml; 7 ml of this (35 mg of agalsidase) is then diluted with isotonic saline. The recommended dose (dispersed in a total volume of 500 ml) is 1 mg/kg body weight, and infusion is repeated every other week. A recommended infusion rate is 15 mg/h but the minimum infusion time should be at least 2 hours. Premedication with antihistamines, analgesics or corticosteroids may be necessary. A 70-kg individual would require two 35-mg vials per infusion and 26 infusions per year, giving an annual cost, at £2269 per 35-mg vial (BNF49), of £118,000.

A 3.5-mg vial of Replagal contains 3.5 mg of agalsidase alpha together with buffer and stabilising agent in a concentrate of 3.5 ml. Vial contents are diluted in 100 ml of isotonic saline to the required dose. The infusion time recommended is 40 minutes. The recommended dose is 0.2 mg/kg body weight repeated every other week. A 70-kg individual would require four vials per infusion and 26 infusions per year giving an annual cost, at £1249 per 3.5-mg vial, of £130,000.

Hence the recommended doses for Replagal and Fabrazyme differ by a factor of five.

ERT for MPS1

α-L-Iduronidase suitable for intravenous administration has been developed for replacement of the missing enzyme in MPS1 patients. This Genzyme/BioMarin product laronidase (Aldurazyme®) received licensing approval in Europe in June 2003 for long-term ERT in patients with a confirmed diagnosis of MPS1 to treat the non-neurological manifestations of the disease.[30] Treatment is utilised mainly in Hurler–Scheie and Scheie patients, as HSCT is usually the treatment of choice in Hurler syndrome.

Laronidase is produced by Chinese hamster ovary cells that harbour the human gene for α-L-iduronidase. The highly purified enzyme is available in vials containing a 5-ml extractable volume delivering 2.9 mg of laronidase at a concentration of 0.58 mg/ml. Vials are for single use only. The recommended dose is 0.58 mg (100 units; 1 ml of vial contents)/kg body weight. The required dose is dispersed in 100 ml (for individuals ≤20 kg) or 250 ml (for individuals >20 kg) of isotonic saline and infused over 2–4 hours. The dose is repeated weekly. Premedication with antihistamines and antipyretics is given if required. A 5-ml vial costs £460.35. The annual cost of treating 5- and 70-kg individuals would be approximately £24,000 and £335,000, respectively.

Current service provision for Fabry's disease and MPS1

The National Specialist Commissioning Advisory Group (NSCAG), which is currently part of the Department of Health, has had responsibility for advising on treatments of a very specialised nature or for very uncommon diseases. Since 1 April 2005 (and currently until 2007), six centres have been nationally designated and funded to provide a service for patients with lysosomal storage disorders. The centres are

- Addenbrooke's Hospital, Cambridge
- Royal Free Hospital, London
- Great Ormond Street Hospital, London
- Central Manchester and Manchester Children's Hospital, Manchester
- Hope Hospital, Salford
- University College Hospital, London.

The service includes diagnostic, assessment and treatment services. This means that the cost of drug treatments, including ERTs, will be funded on a national basis through the designated centres.[31]

Clinicians, patient advocacy groups and NSCAG are currently developing guidelines for the

management of patients with Fabry's disease and MPS1 [Wraith E, Manchester Children's Hospital, personal communication, 2005; Lavery C, Society for Mucopolysaccharide Diseases (UK), personal communication, 2005].

Health Commission Wales, the body responsible for specialist services in Wales, which is part of Welsh Assembly Government, are producing their own policy because of concerns over escalating costs.

Burden on the NHS

The current cost of Fabrazyme is £2269 per 35-mg vial and £325.50 per 5-mg vial; the cost of Replagal is £1249 per 3.5-mg vial.

The annual drug cost of treating a 5-kg infant and a 70-kg adult with Fabrazyme at the recommended dose of 1 mg/kg every 2 weeks is about £8500 (assuming once-only use of vials) and £118,000, respectively. The annual drug cost of treating a 5-kg infant and a 70-kg adult with Replagal at the recommended dose of 0.2 mg/kg every 2 weeks is about £10,000 (assuming separate multiple withdrawals from 3.5-mg vials and the use of eight vials per year) and £130,000, respectively. Once-only use of 3.5-mg Replagal vials for a 5-kg child would greatly inflate the cost since most (>70%) of the vial contents would be wasted. Multi-entry to vials would require special permission from the Medicines Control Agency; in the past this has been granted in similar circumstances for the recombinant protein Enbrel in the treatment of juvenile idiopathic arthritis.

Estimating the financial cost to the NHS is difficult through lack of information regarding numbers treated and doses received. Assuming that about 100 individuals with Fabry's disease with average weight about 50 kg received ERT treatment in England and Wales, then the annual burden to the NHS would be about £8.5 million.

Treatment of MPS1 patients with Aldurazyme costs approximately £4800/kg per annum (52 doses per year at 100 U/kg, at a cost of £92.07 per 100 U). Although Hurler–Scheie and Scheie syndromes are rare, in England and Wales the annual burden to the NHS would be about £5.1 million (see the section 'ERT drug cost', p. 71).

Chapter 3
Methods

Introduction

This review addressed the following questions for each disease:

- What is the prevalence of the disease?
- What is the clinical effectiveness of ERT for the disease?
- What is the natural history of the disease?
- What is the cost-effectiveness of ERT for the disease?

Given the paucity of evidence from randomised controlled trials (RCTs) and controlled studies that compare ERT with alternative treatments, it was decided *a priori* to seek information from all study designs, including uncontrolled or poorly controlled studies, and from patient registries. The aim was to review and synthesise this information in order to estimate best the likely clinical and cost-effectiveness of ERT.

Search strategies

Scoping searches

Scoping searches were performed in order to identify existing systematic reviews and health technology assessments and to inform the development of the review protocol.

Primary studies

Broad search strategies were employed so that publications on effectiveness, natural history of the disease and on prevalence and incidence would be captured. Separate searches for each disease were undertaken using the following bibliographic databases:

- MEDLINE (Ovid) 1966–July week 5 2004
- EMBASE (Ovid) 1980–week 32 2004
- CINAHL (Ovid) 1982–August week 1 2004
- Cochrane Library (CENTRAL) Issue 3 2004
- Science Citation Index (Web of Knowledge) 1981–August 2004.

Search terms included text words and index terms appropriate to each database as follows:

- for Fabry's disease: fabry, fabrys, alpha galactosidase a, ceramide trihexosidase, replagal, agalsidase, fabrazyme
- for MPS1 disease: mps–1, mucopolysaccharidosis type 1, hurler, hurler-scheie, scheie, laronidase, iduronidase, aldurazyme.

Full search strategies are given in Appendix 1.

Ongoing and completed but unpublished studies

The following sources were searched on 17 August 2004:

- National Research Register Issue 3 2004, http://www.update-software.com/National/search.htm. The same strategy for searching CENTRAL as above was used.
- ClinicalTrials.gov, http://www.clinicaltrials.gov/. The register was browsed by alphabetical listing of diseases.
- Current Controlled Trials, http://www.controlled-trials.com/. The register was searched using the same text words as for MEDLINE.

Inclusion and exclusion criteria

References were placed in an electronic bibliographic database and categorised by:

1. whether secondary or primary research and whether purely biological/biochemical in intention
2. presumed study design
3. utility of the research output for the questions addressed in the review (e.g. ERT effectiveness, natural history, prevalence).

Existing systematic reviews were identified to inform all aspects of the report.

Inclusion/exclusion criteria specific to each review question were applied to potentially relevant articles by one reviewer and checked by another. Disagreements were resolved by consensus. The inclusion criteria are outlined in *Table 2*.

TABLE 2 *Inclusion criteria*

Criterion	Incidence/prevalence	Natural history of disease	Effectiveness
Study design	Primary study	Case series, prospective and retrospective cohort studies prior to adoption of ERT[a] with at least 20 patients[b]	Case series, prospective and retrospective cohort studies and RCTs with at least 10 patients
Population	Persons with Fabry's disease or MPS1		
Intervention/ comparator	Not relevant	Not ERT, none or other (e.g. before–after study with non-ERT therapy)	Different ERT or none (i.e. before–after study with ERT) or other (e.g. iminosugar therapy, transplant therapy)
Outcomes	Prevalence or incidence of Fabry's disease or MPS1	Any clinical or patient-relevant outcome (e.g. quality of life, symptoms, clinical signs, organ size, disease markers, frequency of other interventions such as pain relief, dialysis, renal or bone marrow transplantation)	

[a] The adoption of ERT will not necessarily be contemporaneous in all countries.
[b] For MPS1 this was reduced to 10 *post hoc*.

Studies were excluded from the review of effectiveness if they only reported biochemical outcomes.

Data extraction

One reviewer extracted data and a sample were checked by another. Disagreements were resolved by discussion.

Prevalence

Data on type of disease, method and period of ascertainment, population and prevalence rates were extracted from included studies.

Natural history

A data extraction form was developed based on the range of symptoms of each disease described in literature reviews and highlighted in discussions with clinical experts. Information was also extracted regarding the method of patient selection, patient numbers, age, disease status, study duration and design and geographical location.

Clinical effectiveness

Data on study characteristics, quality and results reported were extracted into predefined tables.

Quality assessment

The quality of the studies of ERT effectiveness was assessed according to study design. Disagreements were resolved by consensus. For those studies that were RCTs, cohort or case–control designs, the quality assessment was performed using recommended quality criteria [NHS Centre for Reviews and Dissemination (NHS CRD) Report No. 4, 2nd edition, 2001]. For other studies the following broad criteria based on factors that influence the generalisability of findings reported in case series were used:

- Were eligibility criteria explicit?
- Was the sample source/selection described?
- Were patients assembled at same time?
- Was a method of diagnosis stated?
- Were clinical details described?
- Were individual patient data reported?
- Was outcome assessment blinded?
- Was the blinding method adequately described?
- Was the follow-up time stated?
- Were withdrawals explicitly stated?
- Were reasons for withdrawals stated?

Where the number of patients assigned was the same as the number analysed, but no explicit statements were made on withdrawals, we assigned 'can't tell' to this criterion. Where units were not equal, which can be the result of missing data or withdrawal, and the textual context did not resolve this, it was concluded that withdrawals were unaccounted for.

The relevance of prevalence and natural history studies was assessed for their relevance to the UK context and the review question.

Methods for economic analysis

Existing economic analyses

The following bibliographic databases were searched to identify existing cost studies, economic evaluations and models:

- Cochrane Library (DARE) Issue 3 2004
- Cochrane Library [NHS Economic Evaluation Database (NHS EED)] Issue 3 2004
- HEED July 2003
- MEDLINE (Ovid) 1966–July 2004
- EMBASE (Ovid) 1980–August 2004.

See the section 'Search stategies' (p. 13) and Appendix 1 for search strategies for the Cochrane library, MEDLINE and EMBASE. The Health Economic Evaluations Database (HEED) was searched using a combination terms for the drugs as in MEDLINE and filtered by disease.

To be included in the review, studies had to analyse the treatment of Fabry's or MPS1 disease in terms of both the costs and effectiveness. There were no language exclusions.

Methods for undertaking an economic evaluation are described for Fabry's disease in the section 'Modelling the cost-effectiveness of ERT for Fabry's disease' (p. 45) and for MPS1 in the section 'Modelling the cost-effectiveness of ERT for MPS1 disease' (p. 71).

Chapter 4

Results: Fabry's disease

Search results

Existing systematic reviews

No systematic reviews of Fabry's disease were identified.

Primary studies – number and types of studies identified

After removal of duplicate references, the literature search yielded 2309 references; of these, 185 were judged to be potentially relevant for the prevalence, natural history or effectiveness reviews (*Figure 1*).

Prevalence

Fabry's disease is rare and its exact prevalence is unknown. Eight out of 22 potentially useful studies satisfied the inclusion criteria for the review on prevalence. Six studies described prevalence or birth prevalence in national populations;[32–38] two other studies provided total numbers detected.[38,39]

These studies are summarised in *Table 3*. Studies reporting prevalence in entire countries were done in the UK,[32,33] Australia,[39,39,40] The Netherlands,[35] Spain[38] and Turkey.[36] In three studies only one case was reported,[36–38] which is likely to make calculation of the prevalence subject to error. Apart from these studies, the estimates of prevalence were of a similar order of magnitude ranging from 0.21 to 0.85 cases per 100,000.

Two studies describing the clinical manifestations of the disease in males and females in the UK, using a register of all cases found between 1980 and 1995, reported prevalences of 0.27 cases per 100,000 population for males and 0.29 for females.[32,33] In the study of males, patients were ascertained on the basis of low α-galactosidase levels; in the study of females, carriers were identified by genetic assessment following diagnosis of Fabry's disease in their family or incidental findings of clinical symptoms. These registers in the UK are no longer being maintained.

Using these prevalence rates and the 2001 census data for the number of males and females,[41] one would expect about 77 male cases and 88 female carriers of Fabry's disease in the UK, and 68 male and 77 female cases in England and Wales. What proportion of these female carriers would be symptomatic is unclear.

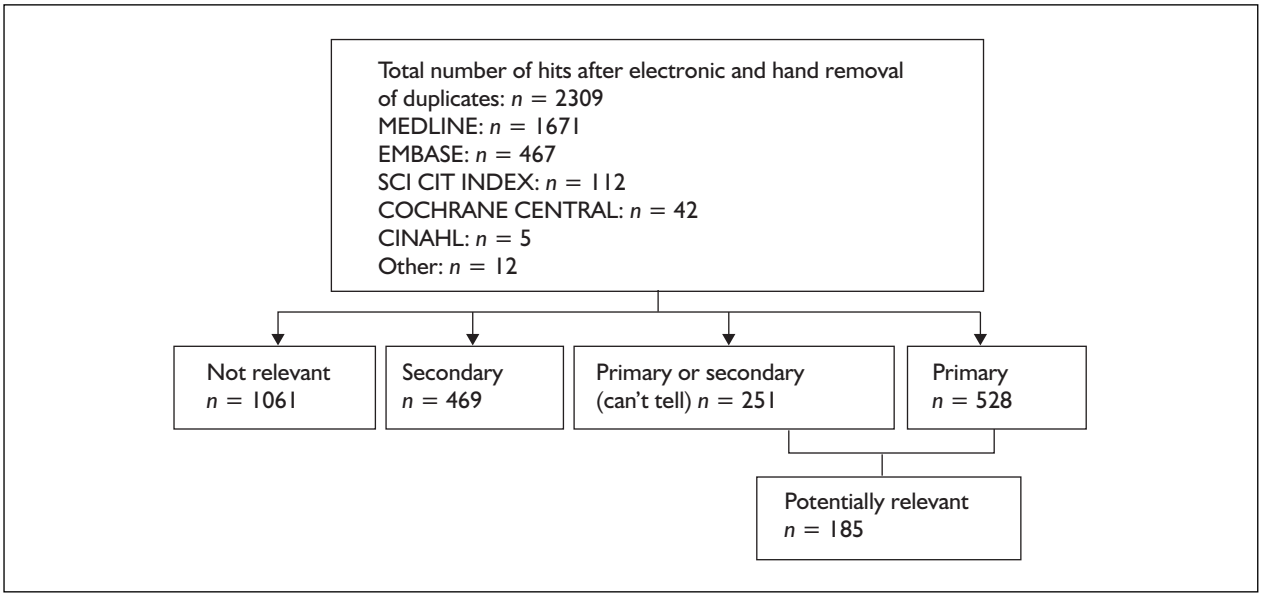

FIGURE 1 *Results of the literature search*

TABLE 3 *Studies of prevalence of Fabry's disease*

Study	Output and method	Source	Ascertainment period	Total no. of cases	No. per 100000
MacDermot, (2001)[32] UK (males only)	Prevalence	Records from Regional Genetic Units and Enzyme Reference Laboratories; records from individual doctor	1980–95	98	0.27
MacDermot, (2001)[33] UK (females only)	Prevalence of obligate carriers	By family history, from the UK AFD register	1980–95	60	0.29
Meikle (1999)[40] Australia	Birth prevalence (number of postnatal plus prenatal enzymatic diagnoses divided by number of births)	Two centres holding all enzymatic analyses in Australia	1980–96	36	0.85
Poorthuis, (1999)[35] The Netherlands	Birth prevalence (number of cases born within a certain period divided by total number of live births in the same period)	All the laboratories making pre- and postnatal diagnoses of LSDs in The Netherlands	1970–96	27	0.21
Ozkara (2004)[36] Turkey	Birth prevalence (number of cases born within a certain time period divided by total number of live births in the same period)	Two main reference centres for diagnosis of sphingolipidoses by enzyme analysis of patients under 5 years suspected of LSD	1997–2002	1	0.015
Pinto (2004)[37] North Portugal	Birth prevalence (number of postnatal plus prenatal enzymatic diagnoses divided by number of live births[a]) in north Portugal	One centre providing all pre- and postnatal diagnoses of LSDs in Portugal	1982–2001	1	0.12
Pollard (1980)[39] Australia and New Zealand	Number detected	Referrals to Adelaide Children's Hospital of patients suspected of LSD	1974–9	18	Not reported
Chabas (1988)[38] Spain	Number detected	Single centre making diagnoses by enzymatic analysis	1976–1987	1	Not reported

[a] During birth period (between birth years of youngest and oldest patients).
AFD, Anderson Fabry's disease.

Estimates of prevalence are likely to under-represent females and 'cardiac variants'. Females are heterozygous carriers of the disease and clinical manifestations are variable. Enzyme levels in females are a poor indicator of carrier status and they may only be diagnosed when Fabry's disease is found in their families. The 'cardiac variant' of Fabry's disease has been reported in a few cases, in which globotriaosylceramide (GL-3) was deposited only in cardiac tissues and the patients presented (or died) after age 50 years with cardiomyopathy.[32]

Two other studies based on entire countries reported birth prevalences of 0.85 (Australia)[40] and 0.21 (The Netherlands)[35] per 100,000 population. In both of these studies, patients were identified from centres that made pre- and postnatal diagnoses of lysosomal storage diseases using enzymatic analysis.

Clinical effectiveness of ERT for Fabry's disease

Quantity and quality of research available

Of 99 potentially useful papers, 27 fulfilled the criteria for effectiveness and 72 were excluded. Three included papers were abstracts, of which

TABLE 4 *Main characteristics of publications derived from the RCT by Eng and colleagues*[45]

Study	Study design	Population: *n* Male: female Age range	Intervention		Duration of study	Outcomes assessed and times
			Intervention (*n*) [duration of infusion]	Comparator (*n*)		
Eng (2001), EU, UK, USA[45]	Placebo-controlled RCT and open-label continuation	*n* = 58 56:2 17–61 years	Fabrazyme 1 mg/kg i.v. every 2 weeks (27) (*n* = 58 in extension) [0.25 mg/minute]	Placebo (29) (*n* = 0 in extension)	Controlled phase, 20 weeks; open-label extension, 6 months	Primary: GL-3 clearance from renal capillary endothelial cells Assessed at week 20 and end of extension Secondary: GL-3 in plasma, endomyocardium and skin, pain (McGill Pain Questionnaire), QoL (SF-36) Assessed at week 20
Thurberg (2002), USA[47]	Same trial as RCT and extension by Eng *et al.*;[45] different outcome reported	*n* = 58 56:2 17–61 years	Fabrazyme 1 mg/kg i.v. every 2 weeks (29) (*n* = 58 in extension) [0.25 mg/minute]	None	Controlled phase: 20 weeks; open-label extension to 6 months	GL-3 clearance from different renal cell types
Thurberg (2004), USA[48]	Same trial as by Eng *et al.*; [45] further extension of non-comparative before–after phase; different outcomes reported	*n* = 58 56:2 17–61 years	Fabrazyme 1 mg/kg i.v. every 2 weeks (*n* = 58) [0.25 mg/minute]	None	Open-label extension to 36 months	GL-3 clearance from different dermal cell types
Wilcox (2004), USA[49]	Same trial as by Eng *et al.*[45] and Thurberg *et al.*;[48] different outcomes reported	*n* = 58 56:2 17–61 years	Fabrazyme 1 mg/kg i.v. every 2 weeks (*n* = 58) [0.25 mg/minute]	None	Open-label extension to 36 months	Renal function (S Cr, GFR), QoL (SF-36), pain (McGill Pain Questionnaire), use of pain medication, adverse events, development of antibodies Assessed every 6 months

QoL, quality of life; SCr, serum creatinine; SF-36, Short Form with 36 Items.

two were preliminary reports of subsequently published and included studies.[42,43] For the third abstract,[44] no fully published study was found and it contained limited information. For these reasons, the abstracts are not considered further in this report. The 24 remaining included papers are listed in *Tables 4*, *5*, *6* and *8* and are described in the following sections.

No randomised or non-randomised studies that compared effectiveness of Fabrazyme with Replagal were identified.

TABLE 5 *Main characteristics of publications derived from the RCT by Schiffmann and colleagues*[42]

Study	Study design	Population: *n* Male: female Age range	Intervention			Outcomes assessed and times
			Intervention (*n*) [duration of infusion]	Comparator (*n*)	Duration of study	
Schiffmann (2001), USA[42]	Placebo-controlled RCT	*n* = 26 26:0 19–47 years	Replagal 0.2 mg/kg i.v. every 2 weeks (14) [20 or 40 minutes]	Placebo (12)	24 weeks	Neuropathic pain (BPI), pain-related QoL, renal parameters, cardiac conduction, plasma GL-3 levels, body weight, safety Assessed at week 24
Moore (2001), USA[50]	Same trial as by Schiffmann *et al.*[42]	*n* = 26 26:0	Replagal 0.2 mg/kg i.v. every 2 weeks (14) [20 or 40 minutes]	Placebo (12)	24 weeks	Cerebral blood flow
Moore (2002), USA[51]	Same trial as by Schiffmann *et al.*[42]	*n* = 26 26:0	Replagal 0.2 mg/kg i.v. every 2 weeks (14) [20 or 40 minutes]	Placebo (12)	24 weeks	Cerebral blood flow response to visual stimulation and acetazolamide
Moore (2002), USA[52]	Same trial as by Schiffmann *et al.*[42] with open-label continuation (all patients)	*n* = 26 26:0	Replagal 0.2 mg/kg i.v. every 2 weeks (14) [20 or 40 minutes]	Placebo (12)	24 weeks and 18-month extension	Cerebral blood flow
Schiffmann (2003), USA[53]	Non-comparative before–after extension of RCT by Schiffmann *et al.*[42]	*n* = 26 26:0 19–47 years	Replagal 0.2 mg/kg i.v. every 2 weeks (26) [40 minutes]	None	3 years	Neuropathic pain (BPI, assessed at months 18, 24), QST assessed 6-monthly, nerve conduction studies assessed at baseline and after 2.5 years on ERT, sweat function (QSART) assessed at 3 years

BPI, Brief Pain Inventory; QST quantitative sensory testing.

Studies can be broadly classified into two types: RCTs with open-label extensions [see the section 'RCTs and their extensions' (below), and *Tables 4*, *5* and *6*] and non-randomised studies [see the section 'Non-randomised studies' (p. 24) and *Table 8*].

The characteristics and quality of studies in each of these groups are described below.

RCTs and their extensions

Three placebo-controlled RCTs were identified, by Eng and colleagues,[45] Schiffmann and colleagues[42] and Hajioff and colleagues.[46] The main characteristics of these studies are summarised in *Tables 4–6*.

The RCT report of Eng and colleagues[45] included results of an open-label continuation phase. A

TABLE 6 *Main characteristics of publications derived from the RCT by Hajioff and colleagues*[46]

Study	Study design	Population: *n* Male: female Age range	Intervention		Duration of study	Outcomes assessed and times
			Intervention (*n*) [duration of infusion]	Comparator (*n*)		
Hajioff (2003), UK[46]	Placebo-controlled RCT and open-label continuation (all patients)	*n* = 15 15:0 25–49 years	Replagal 0.2 mg/kg i.v. every 2 weeks (7) (*n* = 15 in extension) [40 minutes]	Placebo (8) (*n* = 0 in extension)	Controlled phase: 6 months; open-label extension: 24 months	Hearing loss Assessed at baseline, months 6, 18, 30
Hajioff (2003), UK[54]	Same trial as RCT and extension by Hajioff *et al.*;[46] further extension with addition of 8 men and 2 women	*n* = 25 23:2	Replagal 0.2 mg/kg i.v. every 2 weeks (25) [40 minutes]	None	Extension to 42 months (new patients had ERT for 6–30 months)	Hearing loss Assessed at months 18, 30

TABLE 7 *Summary of quality of the RCTs*

Quality criterion	Eng (2001)[45]	Schiffmann (2001)[42]	Hajioff (2003)[46]
Was assignment described as random?	Yes	Yes	Yes
Was method of randomisation described?	No	No	No
Was the method really random?	Can't tell	Can't tell	Can't tell
Was allocation of treatment concealed?	Can't tell	Yes	No
Who was blinded to treatment?	Assessor of kidney samples	All	Can't tell
Was the method of blinding adequately described?	Yes	Yes	No
Were eligibility criteria described?	Yes	No	No
Were groups comparable at study entry?	Yes	Yes, except pain scores	Yes
Were groups treated identically apart from intervention?	Yes	Can't tell	Can't tell
Was ITT used?	Can't tell	Yes	Can't tell
Were all patients accounted for?	Yes	Yes	Yes[a]
Were reasons for withdrawals stated?	Yes	Yes	NA
Was a power calculation done?	No	No	No

[a] The number of patients analysed was the same as the number stated to be in the study; there was no report of withdrawals.

later publication, by Thurberg and colleagues,[47] described different outcomes from both the randomised and this extension phase. Two more recent publications, by Thurberg and colleagues[48] and Wilcox and colleagues,[49] described further extensions and additional outcomes from both the randomised and extension phases.

Results from the RCT by Schiffmann and colleagues, were first described in 2001.[42] Different outcomes from this RCT were subsequently reported by Moore and colleagues.[50,51] Results from non-comparative extensions to 18 months and to 3 years were described by Moore and colleagues[52] and Schiffmann and colleagues,[53] respectively.

The RCT report by Hajioff and colleagues[46] included results from a non-comparative extension. A further report described a longer extension and enrolled additional patients.[54]

TABLE 8 *Non-randomised studies: major characteristics*

Study	Study design	Population: *n* Male:female Age range	Intervention Active treatment [duration of infusion]	Comparator (*n*)	Duration of study	Outcomes assessed and times
Schiffmann (2000), USA[63]	Non-comparative before–after (single infusion only)	*n* = 10 10:0 21–46 years	α-Gal A (human) (different doses) (20 minutes, 14 minutes in one patient)	None	Single infusion given	GL-3 concentrations (hepatic, urine sediment, plasma), safety, α-gal A pharmacokinetics
Dehout (2003), EU[65]	Preliminary report of non-comparative before–after study by Beck *et al.*[43,62]	*n* = 234 Age and gender not stated	Replagal (no details given) [not reported]	None	12 months	GFR estimated by serum creatinine levels
Beck (2004), EU (FOS)[43]	Non-comparative before–after	*n* = 314 treated patients 203:111 20–57 years	Replagal (0.2 mg/kg i.v. every 2 weeks [40 minutes]	None	≥12 months (*n* = 188) ≥24 months (*n* = 92)	Pain (BPI), renal function, heart size, QoL (EQ5D)
Hoffmann (2005), EU (FOS)[62]	Non-comparative before–after (same study as by Beck *et al.*[43])	*n* = 314 treated patients 203:111	Replagal (0.2 mg/kg i.v. every 2 weeks [40 minutes]	None	≥12 months (*n* = 188) ≥24 months (*n* = 92)	Pain (BPI), QoL (EQ5D)
Baehner (2003), Germany[55]	Non-comparative before–after	*n* = 15 0:15 20–66 years	Replagal 0.2 mg/kg every other week [40 minutes]	None (baseline QoL scores were compared with those in two other non-Fabry's populations)	17–41 weeks	Left ventricular mass, QRS duration, safety, pharmacokinetic profile, GL-3 levels, QoL (SF-36). Assessed at baseline, 13, 27, 41 weeks
Conti (2003), Italy[57]	Non-comparative before–after	*n* = 14 10:4 14–57 years	Replagal 0.2 mg/kg every other week (*n* = 12) [not reported]	None	6 months (*n* = 8) 12 months (*n* = 4)	Otological symptoms, audiological and vestibular tests. Assessed at baseline, 6 months, 12 months
Dehout (2004), EU[58]	Non-comparative before–after	*n* = 11 9:2 17–46 years	Replagal 0.2 mg/kg every other week [40 minutes]	None	6 months (all patients), 12 months (6 patients)	Gastrointestinal symptoms (abdominal pain and diarrhoea). Assessed at baseline, 6 months, 12 months
Whybra (2004), Germany[22]	Non-comparative before–after	*n* = 39 24:15 19–67 years	Replagal (0.2 mg/kg i.v. every 2 weeks [40 minutes]	None (baseline score compared with that in 23 non-Fabry's patients)	12 months	Score on MSSI (includes general, neurological, cardiovascular, renal outcomes). Assessed at baseline, 12 months

continued

TABLE 8 *Non-randomised studies: major characteristics (cont'd)*

Study	Study design	Population: *n* Male:female Age range	Intervention Active treatment [duration of infusion]	Comparator (*n*)	Duration of study	Outcomes assessed and times
Hilz (2004), Germany[61]	Before–after case series	*n* = 22:0	Fabrazyme (0.9–1.1 mg/kg every 2 weeks) [not reported]	None (compared with values in untreated healthy controls, *n* = 25)	23 months (*n* = 11), 18 months after 5 months placebo (*n* = 11)	Neuropathic pain (Total Symptom Score, TSS), nerve fibre dysfunction (vibratory, cold and heat–pain detection threshold testing). Pain assessed at baseline and end of treatment period. Nerve fibre dysfunction measured at baseline, at 5 or 6 months, week after last infusion
Guffon (2004), France[60]	Retrospective non-comparative	*n* = 17 15:2 16–55 years	Fabrazyme (1 mg/kg every 2 weeks) [not reported]	None	Mean: 18.7 months (range: 6–29)	Pain severity, heat tolerance, gastrointestinal symptoms, physical activity, fatigue, and psychological status at baseline (retrospective) and after treatment
Weidemann (2003), Germany[64]	Non-comparative before–after	*n* = 16 14:2	Fabrazyme (1 mg/kg every 2 weeks) [not reported]	None	12 months	Myocardial function (e.g. left ventricular wall thickness, myocardial mass, systolic strain). Assessed at baseline, 12 months
Eng (2001), USA[59]	Non-comparative dose escalation study (Phase 1/2)	*n* = 15 15:0 18–45 years	Fabrazyme (5 different dosing regimens) [2 hours]	None	10 weeks maximum (5 infusions, different periods)	Reduction in plasma and tissue GL-3, pain (Short Form McGill Pain Questionnaire), QoL (SF-36), adverse events. Assessed at baseline and after 5th infusion
Cianciaruso (2003), Italy (Italian)[56]	Non-comparative before–after Preliminary report	*n* = 20 18:2 (only 4 patients treated at time of report)	Fabrazyme 1 mg/kg biweekly [2 hours]	None	"initial results of the trial" reported	Side-effects, pain, use of analgesia, well-being, proteinuria (preliminary results, long-term results to be reported after 1 year of treatment)

EQ5D, EuroQoL 5D measure of quality of life; FOS, Fabry Outcome Survey.

Quality of RCTs and their extensions

The quality of the three RCTs is summarised in *Table* 7. None described the method of randomisation or a power calculation. Only Schiffmann and colleagues[42] reported intention-to-treat (ITT) analysis. Two trials[42,45] were reasonably well reported, although patient selection, randomisation, and concealment of allocation were unclear or incompletely described. In that by Eng and colleagues,[45] only outcome assessors were reported to be blinded, and it was not clear whether ITT analysis was used. The baseline characteristics for the compared groups were clearly comparable in the Eng trial[45] only. In the Schiffmann trial,[42] the groups differed at baseline in the primary outcome, pain, which was more severe in the placebo group.

The RCT report of Hajioff and colleagues[46] lacked sufficient detail to be able to judge trial quality reliably. It was not possible to tell whether groups were comparable at study entry or if they were treated identically (other than for intervention and comparator).

Three further publications[50–52] reported results from the randomised phase of the Schiffmann RCT.[42] The study design in these publications was difficult to categorise and lack of detail precluded quality assessment. Data from these were not extracted because of the irrelevance of the outcome measure (regional cerebral blood flow).

Open-label extensions[47-49,53,54] were described for each of the three RCTs. In general, details were less complete in these publications than in the descriptions of the original RCTs. In most the likelihood of missing data was indicated because different participant numbers were reported for different study outcomes. The follow-up time was stated in all reports and appeared sufficiently long for detection of changes in outcome measures. For at least some outcomes, each report was explicit in distinguishing between patients from original intervention and placebo groups.

Non-randomised studies

Thirteen publications reporting 11 studies were identified as observational, non-comparative, before–after trials;[55] their major characteristics are summarised in *Table 8*.[22,43,56–65] One early study assessed the effects of only a single infusion of enzyme.[63] One was a preliminary report[65] of a study subsequently described in full in two papers.[43,62] One study was a dose-ranging Phase I/II trial[59] and another was a retrospective questionnaire-based study.[60]

In these studies, 90 patients were treated with Fabrazyme and 393 with Replagal and the study duration varied from 17 weeks to about 24 months. The Fabry Outcome Survey (FOS) study[43] included the largest number of patients. No study was designed with a control group that was assessed along with the treated group at baseline and during or after the treatment period; however, several made comparisons with values reported for healthy controls[61] or patients with other chronic conditions.[22,55]

Quality of non-randomised studies

The quality of the non-randomised studies is summarised in *Table 9*. Patient inclusion criteria were provided in six studies,[55,58–61,64] but in three of these[58,61,64] diagnosis of Fabry's disease was the only criterion reported. The remaining studies provided little information about patients' enrolment. Exclusion criteria were reported in only four studies.[59,61,63,64] The sample source was stated in only one study,[60] but consecutive enrolment was stated or implied in all studies except the retrospective trial.[60] There were no explicit reports of withdrawals in any of the studies; however, *n* varied for different outcomes in several studies,[43,55,59,60] with few reasons given for the missing data. Of the 11 studies, one only[55] used blinding of an outcome assessment. Follow-up times were stated in all studies and in most appeared to be long enough to assess changes in the measured outcomes.

In the FOS study,[43,62] the time point of the baseline was not clear: outcome values accepted as baseline values were those reported up to 6 months preceding the start of ERT or 3 months after starting ERT (changes in the variables measured were thought to be unlikely within this period).

Results of efficacy studies

Quality of life (QoL) was measured in four studies: one RCT[45,49] and three uncontrolled studies.[43,55,56,59,62] Studies reporting QoL measures are reviewed in the section 'Health-related quality of life in the published literature' (p. 41). No studies measured other primary clinical outcomes relevant for the review question, such as mortality, ESRD, stroke, heart failure or MI. Most studies measured symptom-related surrogate markers that might reasonably be expected to reflect patient well-being; these included pain, diarrhoea, hearing loss and fatigue. Additional surrogate outcomes related to the morbidity of Fabry's disease were measures of renal and cardiac function.

TABLE 9 *Summary of quality of 11 non-randomised studies*

Quality criterion	Categorisation according to quality criteria			
	Yes	No	Can't tell	Not determined or not applicable
Were eligibility criteria explicit?	6	4	1	
Was sample source/selection described?	1	10		
Were patients assembled at same time?	1	4	6	
Was a method of diagnosis stated?	10	1		
Were clinical details described?	7	4		
Were individual patient data reported?	6	5		
Was outcome assessment blinded?	1	10		
Was blinding method adequately described?	1			10
Was follow-up time stated?	10		1	
Were withdrawals explicitly stated or excluded?			11	
Was follow-up long enough for outcomes to occur?	8	1	2	
Were there any missing data?	4	2	5	

The studies identified showed extreme heterogeneity in the outcomes measured and also the format of reporting the results (e.g. expressing the results descriptively without reporting numbers,[49,55,57,59] reporting the number of patients with particular outcomes rather than the outcome values,[58] using scoring methods not used in other studies,[60] and not reporting *n* for individual outcomes[42,53]), which precludes any meaningful combination of values to generate overall effect sizes. The results are summarised below by outcome under the general categories of pain-related outcomes, renal manifestations, cardiovascular manifestations, neurological manifestations, disease severity score, adverse events and other outcomes. Within each of these sections results are reported for the RCTs (and extension phases) separate from the findings of the non-randomised studies in order to facilitate assessing the results in a hierarchy of evidence. Results are not described for some outcomes considered to be not directly related to disease severity or progression.[51,52]

Pain-related outcomes

RCTs and extensions

Pain was measured in the RCTs by Eng and colleagues[45] and Schiffmann and colleagues[42,] and their open-label extensions[45,49,53] (see Appendix 2, *Table 37*).

In the RCT by Eng and colleagues,[45] pain was measured as a secondary outcome using the Short Form McGill Pain Questionnaire. This questionnaire is administered by a clinician and measures a patient's subjective pain experience. The main component consists of 15 descriptors (11 sensory, four affective), which are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate and 3 = severe. Five scores are completed. Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective and total descriptors. The questionnaire also includes a single measure of present pain intensity (PPI) and a visual analogue scale.[66] Total scores can range from 0 to 45, with higher scores indicating more severe pain.[45]

The scores for all five sections of the questionnaire were low in all patients throughout the study.[45] Although scores decreased significantly within each group in the 5-month controlled phase, there were no significant differences between the two groups.[45]

In the open-label extension to the RCT,[45,49] scores remained low to 36 months.[49] Five of 34 patients (15%) were able to stop the use of pain medications during the extension phase.[49]

In the Schiffmann RCT,[42] pain was assessed by the BPI tool. The BPI contains nine pain-related questions, each answered by circling a number on a 0–10 scale.[67] It is used to measure both pain intensity (sensory dimension) and pain interference (reactive dimension) in the patient's life. Patients rate their pain severity at its worst and least in the last week, on average and 'right now'. The level of pain interference is rated in seven contexts: work, activity, mood, enjoyment, sleep, walking and relationships. The BPI also assesses the patient's pain intervention, pain quality and perception of the cause of pain. The BPI has been shown to be responsive to interventions to treat pain.[62]

In the trial,[42] the primary outcome was the 'pain at its worst' item from the BPI. Other pain outcomes reported were the mean score of all the severity items and the mean score of the pain-related QoL items. Baseline scores were lower in the ERT-treated group than in the placebo group; however, significantly greater decreases from baseline to 6 months were seen in all three measures in the ERT group compared with the placebo group.[42] Four of 11 patients in the ERT group taking pain medications were able to discontinue by week eight of the RCT, compared with none of 12 patients in the placebo group.[42]

In the extension phase at 24 months, pain scores were significantly reduced in the patients who were switched to ERT; no further significant changes occurred. Two additional patients stopped medications during the extension.[53]

Non-randomised studies

A variety of pain outcome measures were reported in six of the non-randomised before-after studies[56,58–62] (see Appendix 2, *Table 38*).

The BPI score was used in one study which is described in two publications, by Beck and colleagues[43] and Hoffmann and colleagues.[62] Although the cohort of patients studied appears to be the same in the two studies (same number in database, same number of treated patients, males and females, same graph for the QoL results), the results for most of the BPI scores and for the numbers of patients for these scores are different. In *Table 38* (Appendix 2), the values from the article with the most detailed information are given[62] (one of the authors, A Mehta, has stated by personal communication that these results are the correct ones). Items from the BPI reported in this study are the worst pain, least pain, average pain and pain now.[62] Significant decreases were found after 2 years of treatment, but not after 1 year of treatment, for worst pain, average pain and pain now.

Different outcome measures were used in the other four studies. Treatment with ERT for 6 months was associated with a significant reduction in abdominal pain severity and frequency.[58] In a retrospective questionnaire, patients reported significant reductions in the severity of pain in extremities and number of pain crises, but not duration of pain crises, after a mean of 18 months of ERT.[60] The Total Symptom Score (which assesses the pain character, frequency and severity at the time of examination of neuropathic pain) was significantly reduced after 18–23 months of treatment with ERT.[61] In a short dose-finding study (48 hours to 2 weeks; five infusions of ERT only), overall pain and present pain intensity scores on the Short-Form McGill Pain Questionnaire were reported to be significantly reduced with all doses used (no further details were given).[59]

The data available suggest a beneficial effect of ERT on pain experienced by Fabry's disease patients, although the evidence is weakened by the generally low scores, lack of difference between groups in the RCT by Eng and colleagues,[45] the heterogeneity of measures used and the poor quality of reporting.

Renal manifestations

Outcomes relating to renal function are shown in Appendix 2, *Table 39*. The glomerular filtration rate (GFR) was estimated from the creatinine clearance in the Schiffmann RCT,[42] which also reported inulin clearance. Creatinine clearance remained stable over the 6-month study period in the ERT-treated group, whereas it decreased in the placebo-treated group, with a significant difference between the groups. Inulin clearance was likewise stable in the ERT-treated group and decreased in the placebo-treated group.[42] Glomerular histology was assessed in biopsies by two blinded assessors.[42] The proportion of normal glomeruli was reported to be increased in the ERT-treated group and decreased in the placebo-treated group, with a significant difference between the two groups.[42]

Creatinine clearance was measured in three uncontrolled before–after studies,[43,49,55] in which patients were treated with ERT for periods ranging from 6 to 56 months. Reported baseline values were lower than normal in some patients in two of these studies.[43,49] None of the uncontrolled studies found an effect of ERT on the estimated GFR.

In the short dose-finding study,[59] no ERT-related change was observed in renal structure determined by MRI scans.

Overall, ERT appeared to have a stabilising effect on creatinine clearance, based on the small number of patients in the RCT and the lack of deterioration in the uncontrolled studies.

Cardiovascular manifestations

Heart function was assessed by measurements of myocardial and left ventricular mass, left ventricular wall thickness, ECG (QRS complex duration) and echocardiogram (see Appendix 2, *Table 40*).

In the only RCT in which it was measured, QRS complex duration was decreased after 6 months of treatment with ERT, but increased in the placebo group.[42] The difference between the groups was significant.

QRS duration was also measured in one uncontrolled study, and found to be significantly decreased relative to baseline at 27 weeks of ERT, but not at 13 or 41 weeks, compared with baseline.[55]

Uncontrolled studies reported significantly decreased myocardial mass, left ventricular mass or ventricular wall thickness after about 6 months[55] up to 12 months[64] or 24 months[43] of ERT. Longitudinal and radial function of the left ventricle were measured using colour Doppler myocardial imaging.[64] Both measures were significantly increased after 12 months of ERT.

The results, although limited, suggest a beneficial effect of ERT on QRS complex duration and hypertrophy.

Neurological manifestations

The effect of ERT on neurological manifestations is tabulated in Appendix 2, *Table 41*. Hearing loss was assessed in one RCT and an open-label extension.[46,54] No effect of ERT was seen in the controlled phase, but at 18, 30 and 42 months of the uncontrolled extension, improvements were reported. However, these findings must be interpreted with caution because of very poor reporting of the study.

In a small uncontrolled study, no definitive changes in hearing loss and audiological evaluation results were found after 6 or 12 months of treatment with ERT.[57]

Measures of peripheral sensory abnormalities were outcomes in three non-comparative studies.[53,60,61] Schiffmann and colleagues[53] measured cold and warm sensation thresholds in the foot. Statistically significant improvements after 3 years' treatment were reported; however, the threshold changes observed were extremely modest. Heat tolerance (measured on a scale of 1–10) was significantly increased after a mean of 18.7 months of treatment in a study of 17 patients.[60] In another small study, vibratory detection and heat–pain perception thresholds were increased after 18–24 months of ERT, although vibratory detection thresholds were in the normal range throughout the study.[61]

In a retrospective uncontrolled study, a mean of 18 months of treatment with ERT was associated with significant improvements (patient-rated on scales of 1–10) in fatigue, 'psychological status' and frequency of physical exercise.[60]

No firm general conclusions can be drawn about neurological function from these results.

Other outcomes

Data on other key outcomes are tabulated in Appendix 2, *Table 42*.

Weight loss

In the Schiffmann RCT,[42] body weight (of adult male patients) was slightly but significantly increased (1.5 kg) in patients after being treated with ERT for 6 months, compared with a slight decrease (–1.4 kg) in placebo-treated patients.

Plasma globotriaosylceramide

In the Eng RCT,[45] plasma GL-3 concentrations fell to undetectable levels in the ERT group (after 5 months of treatment), with a small reduction seen in the placebo-treated patients. The difference between groups was statistically significant. In the 6-month open-label continuation of this trial, plasma GL-3 fell to undetectable levels in those patients given ERT who had previously been in the placebo group. In the Schiffmann RCT,[42] plasma GL-3 concentrations showed a significantly greater decrease (of about 50%) in ERT-treated patients than in placebo-treated patients (about 8%) after 6 months. In a non-comparative before–after study, a decrease was reported after 13 weeks of treatment but not after 27 weeks.[55]

GL-3 in renal, heart and skin endothelial cells was also measured in the Eng RCT.[45] In 69% of patients on ERT, renal cells became cleared of GL-3, compared with no patients on placebo. Heart and skin GL-3 scores showed statistically significant greater decrease in the ERT group compared with the placebo group. After 6 or 11 months of ERT in the open-label phase, clearance was high (78–100%) in vascular endothelial, mesangial and interstitial cells and moderate in other kidney cell types.[47] Glomerular podocytes seemed to be particularly resistant to GL-3 clearance. Complete clearance of GL-3 was maintained in skin endothelial cells in most patients, with less effect seen in smooth muscle and perineurium cells, after 30 months of treatment.[48]

Diarrhoea
Two non-comparative before–after studies assessed diarrhoea frequency or frequency of bowel movements after 6 or 18 months of treatment with ERT.[58,60] The number of patients with higher frequencies of diarrhoea was lower after ERT[58] and the number of bowel movements per day was significantly decreased.[60]

Diaphoresis
In the dose-escalation study by Eng and colleagues involving only five doses of ERT, patients anecdotally reported an increased ability to sweat.[59] An infusion of ERT was reported to increase the acute sweat response to iontophoresed acetylcholine, measured once at the end of a 3-year study.[53] This sweat response returned to the pre-infusion level after 7 days.

Effects of ERT on disease severity (Mainz Severity Score Index)
Data on the effect of ERT on disease severity can be found in Appendix 2, *Table 43*. The before–after study by Whybra and colleagues[22] that introduced the MSSI classified signs and symptoms in four categories: general (maximum score = 18), renal (18), cardiovascular (20) and neurological (20). Scores were added up within each category and to calculate a total overall score (maximum = 76).

In the general category, which included abdominal pain, diarrhoea and diaphoresis, but no other measures of pain, a two-point improvement was seen after 1 year of ERT. The renal score encompassed GFR or creatinine clearance and various measures of renal dysfunction to assess the effect of ERT on kidney disease. No statistically significant improvement was found (zero score change) after 1 year of ERT. A significant improvement by two points in the MSSI composite score for cardiovascular manifestations (including thickening of wall/septum of the left ventricle) was found after 1 year of ERT. There was a three-point significant improvement in the composite MSSI score for neurological manifestations (including tinnitus, vertigo, acroparaesthesia, fatigue and physical activity level) after 1 year of ERT.

The overall MSSI score (including the scores for the general, renal, cardiovascular and neurological categories) was improved by nine points (an absolute increase of 12% in the score) after 1 year of ERT.[22]

Adverse events
Data on adverse events are tabulated in Appendix 2, *Table 44*.

Infusion-related reactions occurred in 59% of patients treated with Fabrazyme in the 6-month RCT of Eng and colleagues,[45] but the incidence decreased in the extension phase to 15% at 36 months.[49] A similar proportion of patients (57%) had infusion reactions in the RCT of Schiffmann and colleagues, in which patients were treated with Replagal.[42] In the third RCT (Replagal), the incidence was one of seven patients.[46] In the larger non-randomised study based on the FOS population, 12% of patients (treated with Replagal) reported infusion reactions.[43] Reactions listed in the studies were rigors, fever, headache, chills, pain related to Fabry's disease, hypertension, malaise and skin rash. All studies that mentioned reactions stated that premedication with antihistamines, low-dose corticosteroids, 'preventative medications', or reducing the infusion rate, controlled these reactions and that subsequent reactions tended to be milder.[42,43,45,46] One patient in the study by Eng and colleagues[45] had a positive skin test to recombinant α-gal A after his eighth infusion, and discontinued treatment. In the study by Beck and colleagues,[43] one patient withdrew because of infusion reactions. In the other two studies,[42,46] all patients continued with treatment.

Few studies reported specific adverse event rates. Several stated that most events observed were symptoms that typically occur in patients with Fabry's disease, such as abdominal and skeletal pain, hearing loss and constipation, and therefore were unlikely to be attributable specifically to an effect of treatment.[42,45,55] The FOS study reported serious adverse events in 38 of 314 (12%) patients, including stroke, TIA, arrhythmias, renal disorder, vertigo and sudden deafness; again, none of these were considered to be related to treatment with ERT.[43]

Development of immunoglobulin G (IgG) antibodies to ERT was reported in three studies: in 88%[45] and 53%[59] of patients treated with Fabrazyme and in 21% with Replagal.[42] High titres of IgG antibodies against infused enzyme coupled with repeated infusions may increase the likelihood of immediate hypersensitivity reactions.

Clinical trials in children
Two trials of ERT in children aged 18 years or younger have recently been completed although the results have not yet been published (Wraith E, Manchester Children's Hospital, personal communication, 2005). In one trial, Replagal was given to 13 patients for 6 months. Pain scores improved or were unchanged from baseline in 12

of 13 patients. The treatment was reported to be well tolerated and all patients continued for 6 months. In the other trial, Fabrazyme 1 mg/kg was given biweekly to 16 children for 48 weeks; treatment was withdrawn from one patient because of a serious adverse event. Pain was the primary end-point, but the results are not yet available. GL-3 concentrations in plasma and skin were normalised after 24 weeks.

On-going studies

A Phase 4 post-licensing randomised study of Fabrazyme, required by the US Food and Drug Administration, has been completed. This trial enrolled 82 Fabry's patients and monitored renal, cardiac and cerebrovascular events and death. Currently, the results of this study do not appear to have been published in a peer-reviewed journal.

Summary of effectiveness

Since ERT for Fabry's patients has only been licensed since 2002, it is not surprising that no evidence is available on its effectiveness for important patient-related outcomes such as mortality, long-term QoL and avoidance or delay of ESRD, heart failure or stroke.

The small patient numbers in the controlled trials, the marked heterogeneity of the end-points measured throughout the entire body of evidence and problems with poor study design, quality and reporting mean that it is difficult to draw firm conclusions about the effect of ERT on meaningful clinical outcomes in patients with Fabry's disease.

Most of the evidence of the effectiveness of ERT comes from 11 before–after studies (with no appropriate comparator groups), in which a total of 90 patients were treated with Fabrazyme and 403 with Replagal or human agalsidase alfa. Three randomised placebo-controlled trials have been published, by Eng and colleagues,[45] Schiffmann and colleagues,[42] and Hajioff and colleagues.[46] In these studies, 29 patients receiving Fabrazyme and 21 patients receiving Replagal were studied for 5–6 months in the placebo-controlled phase, with open-label extensions in two of the trials to 12 months. Most patients in the studies were male.

As expected from the diverse clinical manifestations of Fabry's disease, end-points measured varied widely across studies. The most relevant end-points fell into the categories of pain and renal, cardiac and neurological manifestations. QoL was measured in five studies. In one uncontrolled study, an overall disease severity score was calculated based on assigning scores to individual multi-organ symptoms, the MSSI. The overall score was significantly improved by 12% after 1 year of ERT in this study.

Pain was measured (by multicomponent indices) in the controlled trials by Eng and colleagues,[45] and Schiffmann and colleagues,[42] and scores were decreased from baseline after 5 months of treatment in one study (although there were no differences between the ERT and placebo-treated groups). In the other controlled trial, the decreases over 6 months seen with ERT were greater than with placebo, but the baseline scores were significantly lower in the ERT group. In the five uncontrolled studies that measured pain-related end-points before and after treatment with ERT, the results generally indicated improvement in some measures (but not in others). Overall, the evidence suggested a beneficial effect of ERT on pain experienced by Fabry's disease patients.

Renal function was assessed (primarily by estimation of the GFR or creatinine clearance) in the controlled trial by Schiffmann and colleagues[42] and in several uncontrolled studies. ERT was associated with stable values of creatinine clearance during the 6-month treatment period (compared with a decrease in the placebo group) in the controlled study. No effect of ERT was seen in the uncontrolled studies.

Measures of cardiac function included the QRS complex duration and various measures of hypertrophy. The controlled trial by Schiffmann and colleagues,[42] found a significant difference in the change in QRS duration in the ERT group compared with the placebo-treated group. Several uncontrolled studies reported decreases in ventricular mass, wall thickness and myocardial mass after ERT. The studies generally suggested improvements in these measures of heart function.

A variety of end-points were included in the neurological category. Hearing loss was assessed in one of the controlled trials (by Hajioff and colleagues[46]), which found no effect of ERT during the controlled phase, but an improvement during uncontrolled extension of the trial to 42 months.[54] No effect of ERT on hearing was seen in one of the uncontrolled studies. Some measures of peripheral sensory abnormalities showed improvements after ERT in uncontrolled studies. One retrospective before–after study reported significant improvements in patient-rated fatigue, 'psychological status' and frequency of physical exercise.[60]

Concentrations of GL-3 in plasma and other tissues were measured in several studies because its accumulation was thought to cause the clinical symptoms of Fabry's disease. Reduction in GL-3 concentrations was reported after ERT, but no study has shown an association between these changes and clinical outcomes.

Improvements in QoL with ERT have been reported [see the section 'Health-related quality of life in the published literature' (p. 41)].

Infusion-related reactions were the most common reported adverse event in the studies, occurring in 12–59% of patients. These were stated to be prevented by pre-infusion medication and milder with subsequent infusions. Two patients were reported to have withdrawn because of infusion reactions. Few studies reported other specific adverse events and, when mentioned, these were stated to be symptoms expected in patients with Fabry's disease.

Unfortunately, although two ERTs are available for Fabry's patients, there has been no head-to-head comparison of their relative effectiveness in either randomised or non-randomised studies. Heterogeneity between studies precluded meaningful indirect comparisons in this report. Furthermore, the striking fivefold difference in recommended dose for the two Fabry's disease ERT interventions warrants further comment.

If we assume that functionally significant structural differences exist between the proteins (because an identical gene has been processed by different cells) and further assume: (1) that dose-ranging studies were well conducted and resulted in 'correct' dose recommendations; and (2) that recommended doses are about equally effective; then we would conclude that agalsidase alpha is about five times more efficient (per milligram of protein) than the beta form, but since the former is also about five times more expensive (per milligram of protein), the cost-effectiveness of the two would be about the same.

On the other hand, if we alter our assumption regarding functionally important structural differences, that is, assume that the proteins are functionally indistinguishable, but retain our other two assumptions, then we would conclude that the recommended dose for either or both is not well founded. If the agalsidase alpha recommended dose was 'correct' then the agalsidase beta would be used at a redundantly fivefold too high dose that could be reduced to a lower level with an attendant cost saving approaching 80%. On the other hand, if the recommended dose for Fabrazyme was correct, then, given functional identity of the proteins, we would not expect the assumption regarding equal effectiveness to hold; in other words, the therapeutic response from the recommended alpha dose would be substantially sub-optimum. Increasing the alpha dose fivefold would result in annual cost of £650,000 for a 70-kg adult.

Given these considerations, it is clear that evidence regarding the correctness of the recommended dose levels and evidence regarding their relative effectiveness (e.g. from head-to-head randomised comparison) would have considerable importance for determining the cost-effectiveness of ERT for Fabry's disease.

Lee and colleagues[68] undertook an extensive biochemical and pharmacological comparison of the two proteins and concluded, "the two protein preparations appear to be functionally indistinguishable … these studies provide no rationale for the use of these proteins at different therapeutic doses."

The cost of treatment is approximately the same for both drugs despite the large discrepancy in dose regimes; there are attendant implications regarding the production cost of these very expensive interventions.

Natural history of Fabry's disease

In order to assess the health benefits of ERT, it is necessary to understand the course of disease in the absence of ERT treatment. Therefore, this section addresses the evidence bearing on the expected progression of Fabry's disease.

Quantity and type of research available

Of 61 potentially useful publications, 31 fulfilled the inclusion criteria. Ideally studies would be of large cohorts that represent patients who would be candidates for ERT, in which the severity of all manifestations of the disease was quantified repeatedly from inception of disease to death. Because of the rarity of Fabry's disease, the comparative lack of awareness amongst physicians, the gradual and varied evolution of the multi-organ disease manifestations and the multiple subdivisions of medical specialties, such studies do not exist.

Most relevant to the review question are those aspects of Fabry's disease that impact on patient

health-related quality of life (HRQoL), survival and the deployment of expensive interventions. We therefore sought information regarding the prevalence, age of onset, severity and progression of pain, pain crises and acroparasthesia, of insufficiency and failure of renal function, of cardiovascular and cerebrovascular involvement and the frequency of use and types of intervention available for treatment of Fabry's disease patients. QoL studies are reviewed in the section 'Review of quality of life data in Fabry's disease' (p. 41).

Because studies were predominantly single time-point surveys of groups of patients, an approximate indication of disease progression was mostly obtainable only from studies that presented age-dependent profiles of well-defined disease manifestations. Because of delayed diagnosis for many patients (i.e. separation of disease onset from time of correct diagnosis), those studies that retrospectively attempted to determine age of onset were considered useful; age at diagnosis was considered an indication of operational characteristics of healthcare systems rather than a meaningful disease parameter.

Studies of multiple manifestations of Fabry's disease

Seven studies[32,33,69–73] reported on reasonably large cohorts (≥20 male hemizygotes or ≥20 female heterozygotes) in which the source of patients and the frequency of multiple manifestations were described. A brief description of these seven studies is given below.

MacDermot and colleagues (2001) (hemizygous cohort)[32]

This study examined a cohort of 98 UK hemizygous Fabry's disease patients. Age at onset of disease manifestations and proportions of patients exhibiting manifestation were reported. Some information regarding disease progression, the results from a psychosocial questionnaire administered to a subset (n = 46) and age-at-death data were also presented. According to the authors, the cohort of 98 probably encompassed nearly all diagnosed UK patients with confirmed diagnosis to 2000 and at the time of publication was the largest group yet examined regarding the natural history of Fabry's disease; as such, it probably represents the most relevant published study for the review question addressed in this report. Individual patient data were not provided.

The genotype of all kindreds except one were documented[74] and found to be different. This means that an attempt to model natural history on genotype for UK patients would be equivalent to modelling by family. Within families (and therefore within genotype), considerable differences in disease manifestation and progression were observed that extended even to identical twins.

Cases were ascertained by contact with all regional genetic units in the UK and with the help of the national patient support group that had maintained a genetic register for 15 years. Clinical details were diligently sought and obtained from hospital and GP patient records and other sources including patient questionnaires.

Mehta and colleagues (2004)[69]

This paper reported baseline (pre-ERT) and demographic information about 366 Fabry's disease patients entered into the European Fabry Outcome Survey (FOS) database. This is the largest cohort for which data have been published. Data were obtained via physician or nurse specialist clinical assessments. The database is for all patients who are receiving or are candidates for agalsidase alpha (Replagal). Individuals in receipt of agalsidase beta (Fabrazyme) are excluded from the registry.

At the time of this analysis 241, (65.8%) of the 366 registrants were in receipt of Replagal, of whom 201 (55%) were male hemizygotes and 165 (45%) female heterozygotes. About 12% (n = 44) were stated to be UK patients. In earlier publications, MacDermot and colleagues[32,33] reported on 98 male and 60 female UK patients; it is likely that less than 50% of UK patients were represented in the FOS database at this time. Entry into the database clearly depends on action by physicians in participating states; it is likely that this may vary.

Data were presented on the prevalence of disease manifestations by age band. Information on mortality, delay in diagnosis and use of medications was also provided.

MacDermot and colleagues (2001) (heterozygote cohort)[33]

This paper examined a cohort of 60 UK heterozygous female carriers representing 75% of those known to the UK Anderson Fabry's Disease register who were over 18 years of age. Information was mainly obtained by patient questionnaire. Data on age of onset, proportions experiencing manifestations, mortality and patient responses about reproductive decisions and emotional health were presented.

Galanos and colleagues (2002)[71]
Twenty-nine hemizygotes and 38 heterozygotes were examined in this Australian study. Patients were ascertained with the help of a patient support group and from medical records of a nephrology unit. Data on prevalence of disease manifestations were obtained partly by patient questionnaire and partly from medical records. Applying gene incidence estimates for Fabry's disease, the authors concluded that their sample represented a modest proportion of all likely cases in Australia.

Whybra and colleagues (2001)[72]
This was a German study of 20 heterozygous female carriers. Details of patient selection were meagre. Data concerning age of onset and proportions exhibiting disease manifestations were reported; information was gained from 'comprehensive clinical examination'.

Germain and colleagues (2002)[73]
This was a French study of 22 consecutive hemizygous male patients followed at a clinical genetics unit of a hospital in Paris. Individual patient data were provided. Prevalence of disease manifestations by age group was reported.

Ries and colleagues (2003)[70]
This paper was termed a study of adolescent and child Fabry's patients. The authors reported on 20 heterozygotes and 15 hemizygotes with ages ranging from 1 to 21 years. Patients were selected from several European countries and were identified following systematic pedigree analysis of 25 families. The MSSI was used and prevalence of the major disease manifestations was reported.

Studies focusing on a single or few manifestations of Fabry's disease
A further 24 studies have been included that provide information focused on one or only a few particular disease manifestations such as kidney disease,[75–78] cardiovascular/cardiac involvement,[79–87] cerebrovascular manifestations,[88–91] ocular,[92,93] vascular,[50] pulmonary,[94] psychiatric,[95] gastrointestinal[96] and auditory complications.[73]

The results presented in the natural history studies are summarised by disease manifestation.

Double counting and atypical phenotypes
Studies generally failed to make clear whether any of the patients entered into a study were the same individuals who had previously been described in an earlier publication. In these circumstances, it is possible that the same data were used in more than one study. This particularly applied where several reports had been published in close succession from a single centre (e.g. by Kampmann and colleagues;[80,81] Mehta and colleagues[86] and Bass and colleagues;[87] Linhart and colleagues[84] Senechal and Gemain[97] and Germain and colleagues[73]) and where patients from several countries have been entered into a broader database such as the FOS database, even though they may have already featured in national publications (e.g. by Barba Romero and De Lorenzo[98]). In order to minimise double counting of patients where overlap of data appeared probable, the larger or more comprehensive of the studies was selected. The FOS study of Mehta and colleagues[69] has been considered in addition to several national studies[32,33] for purposes of comparison and consistency.

Atypical cardiac and renal variants of Fabry's disease have been reported and discussed in the literature.[99–105] They have been ascertained upon re-examination of the origin of disease in patients undergoing renal dialysis or treatment for LVH. These patients are reported to lack classical phenotypic manifestations of Fabry's disease such as neuropathic pain, rash and ocular changes but carry α-gal A mutations and exhibit either isolated late onset cardiac[100,102,103,105] or renal[101,104] manifestations. These phenotypes are probably rare,[69,106] but their existence implies that previous estimates of Fabry's prevalence may be too low. The natural history of these specific phenotypes is not considered here.

Mortality

An early estimate of mean age at death of male patients stood at 41 years,[107] but this preceded the development of renal replacement therapies (RRTs). Four publications report more recent mortality data.[32,33,69,82]

Results from Branton and colleagues[82] were used by the same group[108] in a Kaplan–Meier analysis to estimate the median survival to be approximately 57 years for a cohort of 105 hemizygous National Institutes of Health (NIH) patients. The mean age at death of the 18 patients who had died was 50 years with very varied causes of death identified.

MacDermot and colleagues[32] estimated the mean and median age at death of 50 hemizygotes to be 48.5 years [95% confidence interval (CI) 46 to 51.1 years] and 50 years (25th and 75th centiles 40 and 56 years), respectively, with causes of death most commonly attributed to renal failure and cerebrovascular accidents (CVAs). This appears to

TABLE 10 *Manifestation of pain in male hemizygote patients*

Study	Sample age (years)	Age at onset (years)	Currently with pain (%)	Duration	Severity (McGill scale 0–10)	Medication
MacDermot (2001)[32] (n = 98) UK	Mean 35 (95% CI 32 to 38)	Mean 10.1	83	29% constant; 54% constant and recurrently excruciating	Mean 5.0	60% anticonvulsants (phenytoin, carbamazepine, etc.) 40% NSAIDs
Germain (2002)[73] (n = 22) France	Mean 39 (95% CI 33 to 45)	Not reported	77	Not reported	Not reported	Not reported
Mehta (2004)[69] (n = 201) Europe (11 countries)	Mean 35.5 (95% CI 33.7 to 37.3)	Mean 9.4	84	Not reported	Not reported	75% analgesics
Galanos (2002)[71] (n = 29) Australia	Not reported	Early or middle childhood	100	Not reported	Not reported	62% anticonvulsants or NSAID

be an underestimate of life expectancy since possibly surviving members of such a cohort were not included. Mean age at death of diseased relatives of persons in the FOS registry was reported by Mehta and colleagues[69] to be 45.5 years [standard deviation (SD) 12.6; n = 42] and 55.4 years SD 14.9; n = 24) for males and females; 55% of males died from renal failure, and cardiac disease was the most common cause (26%) for females. MacDermot and colleagues[33] reported a median age at death of 70 years for females (n = 32). These values are again unlikely to be meaningful estimates of the life expectancy of hemizygotes and heterozygotes because the possibility of live patients in the cohort was ignored.

From these estimates, it appears reasonable to assume that median survival in the absence of ERT approaches about 60 years for hemizygous males and substantially longer for carrier heterozygous females.

Pain in Fabry's disease

In several studies, the majority of both hemizygotes (77–100%) and heterozygotes (53–90%) have been reported to experience pain (*Tables 10* and *11*).[32,33,69,71–73] Mean age of onset is during the first two decades but appears to be lower for males.

Severity of pain, when determined, was reportedly considerable and sufficient to impact on HRQoL.[32,33] Galanos and colleagues[71] reported a tendency for severity and frequency to decrease in males with increasing age and MacDermot and colleagues[32] recorded that in a few patients pain had disappeared, but it is evident that for the majority pain was a life-long experience.

More than half of the male patients and fewer than half of the female patients took medication for pain; NSAIDs and anticonvulsants such as phenytoin and carbamazepine were the most likely drugs to be used.

Renal involvement in Fabry's disease

Kidney disease involvement reported in Fabry's patients ranges from preclinical observation of various aspects of renal pathology using ultrasound and/or MRI imaging methods,[75] through renal insufficiency to ESRD requiring dialysis or graft. Renal manifestations observed in male and female patient populations are summarised in *Tables 12* and *13*.

The NIH prospective cohort study of 105 hemizygotes found that 78% of patients had clinically significant renal disease (proteinuria and/or chronic functional insufficiency).[82] Mean age at onset of proteinuria was 34 years and of functional insufficiency was 42 years. ESRD had developed in 23% of patients and according to Kaplan–Meier analysis ESRD occurred at a median age 47 years. All patients who survived to 55 years of age developed ESRD. All ESRD patients received dialysis and about half received a renal graft.

TABLE 11 *Manifestation of pain/acroparaesthesia in heterozygous female patients*

Study	Sample age (years)	Age at onset (years)	Experienced pain (%)	Duration	Severity (McGill scale 0–10)	Medication
MacDermot (2001)[33] (*n* = 60) UK	Mean 45 (95% CI 41 to 49)	Mean 15	70	56% constant. 14% had stopped	Mean 6.8	17 anticonvulsants (phenytoin, carbamazepine, etc.) >42% NSAIDs
Whybra (2001)[72] (*n* = 20) Germany	Mean 38 (range 12 to 65)	Mean 10	90	Not reported	Not reported	Not reported
Mehta (2004)[69] (*n* = 155) Europe (11 countries)	Mean 41.4 (95% CI 38.7 to 44.1)	Mean 16.9	Mean 16.9	Not reported	Not reported	Not reported
Galanos (2002)[71] (*n* = 38) Australia	Not reported	Early or middle childhood	53	Not reported	Not reported	25% anticonvulsant (phenytoin, carbamazepine, etc.) or NSAIDs
Ries (2003)[70] (paediatric population; *n* = 20) Europe	Mean 12.72 (95% CI 10.3 to 15.1) (range 1.5–20)	Not reported	65	Not reported	Not reported	Not reported

TABLE 12 *Renal manifestations in hemizygous patients*

Study	Sample age (years)	Proteinuria (%)	Functional insufficiency (%)	EDS (%)	Renal replacement therapy dialysis/graft	Medication
MacDermot (2001)[32] (*n* = 98) UK	Mean 35 (95% CI 32 to 38)	84 (*n* = 44)	47 (based on GFR or serum creatinine)	31 (*n* = 84)	31 (assumed) (mean age of onset: dialysis 37 years, graft 40 years)	Not reported
Galanos (2002)[71] (*n* = 29) Australia	Not reported	69	Not reported	38	17 graft	Not reported
Germain (2002)[73] (*n* = 22) France	Mean 39 (95% CI 33–45)	Not reported	27	40	27 graft 13 dialysis	Not reported
Mehta (2004)[69] (*n* = 201) Europe	Mean 35.5 (95% CI 33.7 to 37.3)	44	Not reported	17	10 graft 7 dialysis	Not reported
Branton (2002)[82] (*n* = 105) USA	Not reported	63 (mean age at onset 34 years)	37 (median age at onset 42 years)	23 (median age at onset 47 years)	23 dialysis and/or graft 13 graft, most preceded by dialysis	19% angiotensin antagonists (30% developed hypertension)
Glass (2004)[75] (*n* = 76)	Range 7–53	Not reported	43	Not reported	Not reported	Not reported

TABLE 13 *Renal manifestations in heterozygous patients*

Study	Age of whole cohort (years)	Mean age at onset (years)	Proteinuria (%)	Functional insufficiency (%)	ESRD (%)	Renal replacement therapy graft/dialysis (%)
MacDermot (2001)[33] (n = 60) UK	Mean 44.9 (95% CI 14 to 49)	Dialysis 36 (n = 2)	Not reported	35 (self-reported result of urine/blood test; n = 20)	3.3	3.3 (dialysis)
Whybra (2001)[72] (n = 20) Germany	Mean 38 (range 12–65)	Not reported	Not reported	55 (reduced GFR)	Not reported	Not reported
Galanos (2002)[71] (n = 38) Australia	Not reported	Not reported	21	Not reported	Not reported	Not reported
Mehta (2004)[69] (n = 155) Europe (11 countries)	Mean 41.4 (95% CI 38.7 to 44.1)	Not reported	33	Not reported	1	1 (dialysis then graft)
Ries (2003)[70] (paediatric population; n = 20) Europe	Mean 12.72 (95% CI 10.3 to 15.1) (range 1.5–20)	Not reported	15	Not reported	Not reported	Not reported

The prospective study of Branton and colleagues[82] supports the proposition that most hemizygous Fabry's patients eventually progress to ESRD that will require renal replacement therapy and the few who escape this prospect die prematurely of other causes or belong to the rare subgroup of patients classified as 'cardiac variants'. Progression from renal insufficiency to ESRD was rapid, averaging about 4–5 years. It cannot be discounted that this inference is not over-pessimistic because the NIH cohort might preferentially reflect more severely affected hemizygotes. Looking at the cross-sectional studies is required to see if the prevalence of kidney manifestations by age lends support to this hypothesis.

The largest available cross-sectional study (n = 201), based on the FOS database,[69] reported that 17% of those over 18 years of age had ESRD and 80% of those in their fifth decade had renal involvement; unfortunately, the number of patients analysed was not reported and 'renal involvement' was not defined. The UK study[32] reported that 31% of 84 hemizygotes reached ESRD (children were excluded from the analysis); if this figure is translated to the whole cohort (n = 98), then 26% developed ESRD in a population with a mean age of approximately 37–40 years. This is a comparable, if slightly worse, scenario to 23% of the NIH patients reaching ESRD at a median age of 47 years. In the UK study,[32] 84% had proteinuria but unfortunately only 44 of 98 patients were studied and their data may have been available because of clinical suspicion of renal involvement. ESRD was reported for 38% of hemizygotes in the Australian study[71] but age of patients was not provided; in the French study[73] (mean age 39 years, n = 22), 40% had reached ESRD. Hence the limited cross-sectional data available, other than for the FOS study, indicate that the NIH sample of patients was not unduly unrepresentative of hemizygous Fabry's patients.

No prospective study of renal involvement in heterozygous patients was identified. Cross-sectional surveys were fewer and smaller than for male hemizygotes. It appears that renal involvement is rarer and on average less serious than for hemizygotes. Nevertheless, some female patients develop kidney involvement, 15–33% reportedly developing proteinuria and 35–55% renal insufficiency amongst samples with mean age ranging from 13 to 45 years, but only a small proportion progressing to ESRD (1 and 3% in two small studies).[33,69–71] The male-to-female ratio of Fabry's patients who had received RRT and registered in the large US and European databases for renal disease was reported to be 7.3:1

(88%:12%), in contrast to other disease categories in the databases where the gender ratio was ~1:1.[77,78] This could indicate that the low rate of ESRD reported for female patients in the studies reported in *Table 13* may reflect a lack of older heterozygotes in the populations studied.

Thadhani and colleagues[77]analysed the US Renal Disease System database, identified Fabry's patients (n = 95) whose dialysis was initiated in 1985 to 1993 and reported a 4-year median patient survival post dialysis; 63% survival (95% CI 50–75%) was observed at 3-year post dialysis; mean age at start of dialysis was 41 years (SD 9) and 42% proceeded to a renal graft within 3 years. For a similar European series[78] (ERA–EDTA database; n = 83, 12% female, 87% male), the mean age at start of dialysis was 42.3 years and patient survival at 1, 3 and 5 years after start of dialysis was 86, 60 and 41%, respectively.[78] Of the 83 European patients, 33 (40%) received a renal graft; graft survival and patient survival at 1 and 3 years were 78 and 72% and 91 and 84%, respectively. Fabry's patients exhibited poorer survival post-dialysis than other RRT patients in both US and European registries. Analysis of the US database of Fabry's patients who received renal grafts between 1988 and 1998 indicated 5 and 10-year graft survival of 75 and 56%, respectively, and a 5-year patient survival of 83%.[109] These rates were similar to those for matched controls who were grafted because of other pathology; the increased risk of cardiovascular complications seen in ESRD patients does not appear greater in Fabry's patients relative to others with ESRD. Poorer outcomes for Fabry's patients reported in earlier small studies have been attributed to the use of different immunosuppressive regimes to prevent graft rejection.[110]

The information in these studies indicates that male patients develop functional renal insufficiency that rapidly progresses to ESRD that sets in on average at about 40 years of age.

Cardiovascular/cardiac involvement in Fabry's disease

Reported cardiac involvement in Fabry's disease ranges from preclinical changes detectable by ultrasound[79] to various symptomatic manifestations including angina, intermittent claudication, dyspnoea, arrhythmia, congestive heart failure, ischaemic heart disease and thromboembolic events; these manifestations are attributed to pathology in the myocardium, cardiac valves and cardiac conduction system. Studies have used various criteria to define cardiovascular manifestations. Prevalence data of cardiac involvement reported in natural history studies are summarised in *Tables 14* and *15*.

Cardiac involvement in hemizygotes is common, with 69% of patients in the FOS database exhibiting symptoms. Studies (n = 5) of populations with mean age in the range 32–39 years reported LVH in 46–88% of patients with mean age of onset about 40 years.[32,72,97] The studies of Galanos and colleagues[71] and Kampmann and colleagues[80] reported similarly high rates of LVH (71 and 77%, respectively). Evidence indicative of conduction and valve abnormalities was more variable with less than half of patients in these populations being affected or detected. Unfortunately, use of interventions was not reported.

The study of Kampmann and colleagues (n = 55) was a wide-ranging evaluation of possible cardiac involvement undertaken in a population of heterozygotes ascertained through extensive pedigree analysis.[81] The results imply a high prevalence of cardiac manifestations in female carriers with 65% exhibiting LVH and all patients older than 45 years having LVH. These values are much higher than those observed by MacDermot and colleagues,[33] but in this study results were obtained from patient response to a questionnaire asking about test results obtained in the previous year. A relatively high LVH prevalence (40%) was also reported by Galanos and colleagues,[71] but it is not entirely clear how much information resulted from clinical investigation and how much from patient response to questionnaires. Evidence of valve abnormality was reported for between 23 and 48% of heterozygotes.

Unfortunately, the use of interventions for cardiovascular manifestations was unreported except for the mention of three mitral valve replacements amongst the 60 patients reviewed by MacDermot and colleagues.[33] A recent review described interventions for cardiac and cerebrovascular involvement in Fabry's disease as non-specific and symptomatic, which presumably might encompass beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, anticoagulants and advice regarding lifestyle changes. Intravenous galactose infusion has recently been found useful for a cardiac variant who had residual α-galactosidase activity.[111]

Cerebrovascular manifestations in Fabry's disease

Cerebrovascular involvement in Fabry's disease manifests mainly as stroke and TIAs. Increased risk

TABLE 14 *Cardiac manifestations in hemizygous patients*

Study[a]	Sample age (years)	Chest pains; palpitations (%)	LVH (%)	Valve abnormalities (%)	ECG abnormality/ arrhythmia (%)
MacDermot (2001)[32] (n = 98) UK	Mean 35 (95% CI 32 to 38)	56 (n = 61)	88 (n = 34) Mean age at onset 42 years	29 (n = 34) (mitral valve regurgitation and/ or aortic valve thickening)	PR interval within normal range (n = 34)
Galanos (2002)[71] (n = 29) Australia	Not reported	62	77	37 (mitral valve abnormality)	23 abnormal (shortened PR interval)
Senechal (2003)[97] (n = 20) France	Mean 37 (95% CI 30.4 to 43.6)	20 (angina)	60	25 (mitral valve abnormality) 45 (mitral valve regurgitation) 10 (aortic valve abnormality)	40 abnormal (shortened PR interval) 35 conduction abnormalities
Mehta (2004)[69] (n = 201) Europe	Mean 35.5 (95% CI 33.7 to 37.3)	Not reported	46 Mean age at onset 38 years	69 showed cardiac involvement including LVH, arrhythmias and dyspnoea	
Kampmann (2002)[80] (n = 41) Germany	Not reported	Not reported	71 (51 severe)	Not reported	Not reported
Goldman (1986)[85] (n = 23) USA	Mean 28.6 (95% CI 22.5 to 34.6)	Not reported		54 (mitral valve prolapse)	Not reported
Bass (1980)[87] (n = 25) USA	Mean 31.7 (CI 27.1 to 36.2)	Not reported	48 (n = 21)	5 (mitral valve prolapse) 14 (aortic valve abnormality)	Not reported

[a] For the study of Linhart and colleagues[83] (n = 21) (Czech Republic), it was not possible to disaggregate hemizygote from heterozygote data. The study of Germain and colleagues[73] (n = 22) (France) is assumed to have patients represented in Senechal and colleagues.[97]

of these manifestations is thought to depend on structural changes in small arteries in the brain due to accumulation of storage material, possibly exacerbated in some cases by renal and/or cardiovascular disease predisposing to embolism and hypertension. A wide variety of symptoms observable in Fabry's disease patients may be attributable to cerebrovascular involvement including paresis, vertigo, diplopia, speech defect, nystagmus, nausea/vomiting, headache, ataxia and memory loss.[112] Other symptoms such as seizures and personality changes have been reported.[95] Altered cerebral metabolism and/or blood flow have been implicated in CNS manifestations.[52,113,114]

Evidence reported in natural history studies of cerebrovascular involvement amongst hemizygotes is summarised in *Table 16*.

Cruchfield and colleagues[89] conducted a prospective study of cerebrovascular disease in an NIH series of hemizygotes with classic Fabry's disease, described by Schiffmann and colleagues[88] as consecutive patients. MRI-detectable cerebral lesions were found in 68% of patients (age range 6–63 years) with mean age of onset at 43 years. Lesion load increased rapidly after the age of 45 years so that no patient over the age of 54 years was free of lesions. Only 37.5% of patients with detectable lesions were symptomatic. With age-related rapid increase in cerebral lesions, the proportions of patients with involvement found in cross-sectional studies will largely reflect the age spectrum of patients. Such studies indicate that between one-quarter[32] and nearly half[73] of hemizygotes in populations of mean age between about 30 and 40 years probably experience

TABLE 15 *Cardiac manifestations in heterozygous populations*

Study[a]	Sample age (years)	Chest pains; palpitations (%)	LVH (%)	Valve abnormalities (%)	ECG abnormality/ arrhythmia (%)
MacDermot (2001)[33] (*n* = 60) UK	Mean 44.9 (95% CI 14 to 49)	52 (*n* = 60)	19 (*n* = 21)	48 (*n* = 21) [3/60 mitral vs replacements]	33% Arrhythmia (*n* = 21)
Galanos (2002)[71] (*n* = 38) Australia	Not reported	29 palpitations (20 intermittent claudication)	40 (*n* = 20)	23 (mitral valve prolapse or incompetence)	25 (shortened PR interval; *n* = 20) 8 (documented atrial fibrillation)
Mehta (2004)[69] (*n* = 155) Europe	Mean 41.4 (95% CI 38.7 to 44.1)	Not reported	28; mean age at onset 55 years	Not reported	Not reported
Kampmann 2002[b81] (*n* = 55) Germany	Mean 39.6 (95% CI 34.9 to 44.3) (range 6.1 to 70.8)	Not reported	64 (all aged >45 years had LVH)	25.5 (aortic valve thickening) 25.5 (mitral valve thickening and very mild insufficiency) 11 (mitral valve prolapse)	Not reported
Whybra (2001)[72] (*n* = 20) Germany	Mean 38 (range 12–65)	Not reported	50 (mitral valve abnormality, septum thickening, cardiomyopathy)		'ECG often normal'
Ries (2003)[70] (*n* = 20; paediatric population) Europe	Mean 12.7 (95% CI 10.3 to 15.1)	Not reported	20 cardiac abnormalities (ECG, mitral valve regurgitation, septum enlargement)		

[a] For the study of Linhart and colleagues[83] (*n* = 21) (Czech Republic), it was not possible to disaggregate hemizygote from heterozygote data.
[b] It is possible some patients were also represented in the study of Whybra 2001.[72]

cerebrovascular involvement. The FOS database study[69] indicates a lower proportion of only 12%.

Table 17 summarises evidence reported in natural history papers regarding cerebrovascular manifestations in heterozygotes.

It is clear that cerebrovascular involvement occurs in heterozygotes but its extent is difficult to gauge from the meagre evidence available. Remarkably, the FOS study[69] indicated a greater prevalence amongst females (27%) than males (12%) although the mean age of onset was greater. Other studies (e.g. Mitsias and Levine in a review of 52 case reports[112]) indicate a high rate of recurrence of cerebrovascular events in both hemi- and heterozygotes.

Other manifestations in Fabry's disease

In addition to pain, renal, cardiac and cerebrovascular manifestations of Fabry's disease, studies have highlighted the presence of several other signs and debilitating symptoms. Evidence from natural history publications describing the prevalence of these is summarised in *Table 18*.

Summary of natural history studies of Fabry's disease

The evidence reviewed above is consistent with the widely stated description of Fabry's disease as a multi-system disorder characterised by pain, progressive renal insufficiency with added morbidity from cardio- and cerebrovascular involvement and associated with significant impact on QoL and diminished lifespan.[115] The particular constellation of manifestations experienced varies between individual patients, as do their time of onset and rate of progression, so that the disease is characterised by a broad clinical spectrum.

Whereas an authoritative review published in 2001[12] stated that heterozygous females were

TABLE 16 *Cerebrovascular manifestations in hemizygous patients*

Study	Sample age (years)	TIA and/or CVA (%)	TIA (%)	CVA / stroke (%)	MRI-detected lesions (%)
MacDermot (2001)[32] (*n* = 98) UK	Mean 35 (95% CI 32 to 38)	24 (18 dementia, associated with CVA/TIA) (*n* = 70; <18 years old excluded)	Mean age at onset: 39 years	Mean age at onset 40 years	Not reported
Galanos (2002)[71] (*n* = 29) Australia	Not reported	31	Not reported	Not reported	Not reported
Mehta (2004)[69] (*n* = 201) Europe	Mean 35.5 (95% CI 33.7 to 37.3)	12 (mean age at onset 28.8 years)	Not reported	Not reported	Not reported
Grewal[a] (1994)[91] [*n* = 34] USA	Range 6 to 64	Not reported	Not reported	24 (mean age at onset 29 years)	Not reported
Germain (2002)[73] (*n* = 22) France	Mean 39 (95% CI 33.1 to 44.8)	50% (TIA or MRI-detected lesions) (*n* = 20)	Not reported	Not reported	Not reported
Utsumi[b] (1997)[90] (*n* = 45) Japan	Not reported	Not reported	Not reported	9	Not reported
Crutchfield[a] (1998)[89] (*n* = 50) USA	Range 6–63	Not reported	17	25.5 (symptomatic stroke)	68 (37.5 symptomatic) (mean age of onset 43 years)

[a] Possible overlap of patients.
[b] Includes 10 patients with cardiac variant Fabry's disease.

TABLE 17 *Cerebrovascular manifestations in heterozygotes*

Study	Sample age (years)	TIA and/or CVA (%)	TIA (%)	CVA/stroke (%)	Vertigo, tinnitus, headache (%)
MacDermot (2001)[33] (*n* = 60) UK	Mean 44.9 (95% CI 14 to 49)	21.5	Mean age at onset 52 years	Mean age at onset 42 years	Not reported
Galanos (2002)[71] (*n* = 38) Australia	Not reported	5	Not reported	Not reported	Not reported
Whybra (2001)[72] (*n* = 20) Germany	Mean 38 (range 12–65)	Not reported	Not reported	Not reported	85
Mehta (2004)[69] (*n* = 155) Europe	Mean 41.4 (95% CI 38.7 to 44.1)	27 (mean age at onset 43 years)	Not reported	Not reported	Not reported
Ries 2003[70] (*n* = 20; paediatric population) Europe	Mean 12.7 (95% CI 10.3 to 15.1)	Not reported	Not reported	Not reported	25 (includes other neurological manifestations, e.g. reduced activity, fatigue, depression)

TABLE 18 *Other manifestations in Fabry's disease*

Study	Sample age (years)	Gastrointestinal involvement (%)	Rash/ angiokeratoma (%)	Hypohydrosis/ anhydrosis (%)	Hearing loss (%)	Pulmonary involvement *%)
Hemizygous patients						
MacDermot (2001)[32] (*n* = 98) UK	Mean 35 (95% CI 32 to 38)	6 (vomiting, nausea, chronic diarrhoea, abdominal pain)	73	56	41 (self-reported)	Not reported
Germain (2002)[73] (*n* = 22) France	Mean 39 (95% CI 33.1 to 44.8)	Not reported	Not reported	Not reported	50 (clinically established)	Not reported
Mehta (2004)[69] (*n* = 201) Europe, (11 countries)	Mean 35.5 (95% CI 33.7 to 37.3)	55 (abdominal pain, diarrhoea)	78	Not reported	57 (clinically established)	Not reported
Galanos (2002)[71] (*n* = 29) Australia	Not reported	90 (chronic diarrhoea)	93	93	14 (self-reported)	Not reported
Brown (1997)[94] (*n* = 25)	Mean 33.3 (95% CI 28.9 to 37.7)	Not reported	Not reported	Not reported	Not reported	36% airway obstruction (spirometry)
Heterozygous patients						
MacDermot (2001)[33] (*n* = 60) UK	Mean 44.9 (95% CI 14 to 49)	58.3 (self-reported)	35	33	23 (self-reported)	Not reported
Whybra (2001)[72] (*n* = 20) Germany	Mean 38 (range 12–65)	50 (vomiting, nausea)	55	Not reported	Not reported	Not reported
Mehta (2004)[69] (*n* = 155) Europe, (11 countries)	Mean 41.4 (95% CI 38.7 to 44.1)	50 (diarrhoea, abdominal pain)	50	Not reported	47	Not reported
Galanos (2002)[71] (*n* = 38) Australia	Not reported	11 (chronic diarrhoea)	13	11	Not reported	Not reported
Ries (2003)[70] (*n* = 20; paediatric population) Europe	Mean 12.7 (95% CI 10.3 to 15.1)	20 (diarrhoea, vomiting, nausea)	30	25	Not reported	Not reported

usually asymptomatic, the more recent surveys reviewed above indicate that most carrier females identified experience at least one of the manifestations seen in hemizygous males. The prevalence of most manifestations is, however, lower in females and mean age at onset greater. In the FOS study,[69] the average delay between onset of symptoms and diagnosis was 13.7 and 16.3 years for males and females, respectively.

In the absence of an effective intervention, the progression of organ damage in males appears to be inexorable with the earliest life-threatening manifestation likely to be kidney disease

culminating in ESRD that requires RRT, usually initiated as haemodialysis or peritoneal dialysis and often followed subsequently by renal graft. Male patients who do not reach ESRD by their fifth decade will be those who have died prematurely from other causes or who have the cardiac variant of Fabry's disease. The prevalence of the cardiac variant is uncertain. The FOS database study[69] found 'no evidence' of a milder late-onset variant with pathology limited to the heart; however, analysis of 154 consecutive patients at a UK referral centre for hypertrophic cardiomyopathy revealed six patients with previously undiagnosed Fabry's disease, of whom five showed none of the other symptoms of the classic form of the disease. Based on the large US and European renal disease databases, the mean age for commencement of dialysis appears to be between 38 and 41 years.[77,78]

Economic analysis: Fabry's disease

Review of quality of life data in Fabry's disease

QoL information is critical for the construction of a model of cost-effectiveness and therefore this section reviews any published study of QoL in Fabry's disease irrespective of whether ERT was a consideration in the study. The methods used to identify the literature reviewed are described in the section 'Search stategies' (p. 13). In addition to the published literature, the review team were given some access to a dataset containing HRQoL information on patients with Fabry's disease from a paper by Miners and colleagues.[116] Results of further analysis of this data are presented in the section 'HRQoL for the data set of Miners and colleagues' (p. 44) and Appendix 3. All identified studies on the QoL of Fabry's patients are outlined below.

Health-related quality of life in the published literature

Eng and colleagues (2001)[45]

This multi-centre, double-blind, placebo-controlled trial and subsequent open-label study has already been described in the section 'Clinical effectiveness of ERT for Fabry's disease' (p. 18).

QoL was measured in both ERT (Fabrazyme) and placebo groups using the SF-36. This tool evaluates QoL on eight health-related aspects: physical function, social function, physical role, emotional role, mental health, energy, pain and general health perception. It is not clear exactly when this instrument was administered to both groups. The baseline results were compared with the mean change in scores, so it can be assumed that the instrument was administered at baseline and then at some point into the trial (possibly after the 20 weeks had expired; however, this is not clear).

The only results provided were qualitative results reporting that the patients in the treatment group had significant improvements in two components of the SF-36 instrument (physical and emotional), whereas patients in the placebo group had significant improvements in the physical and body-pain components. Since the QoL was significantly improved in both groups, this makes it impossible to differentiate treatment-related effects from placebo effects.

Wilcox and colleagues (2004)[49]

This was an open-label extension study to the trial by Eng and colleagues[45] and has been described in the section 'Clinical effectiveness of ERT for Fabry's disease' (p. 18). Patients who had previously received Fabrazyme in the trial received a total of 36 months of treatment and patients who received placebo in the trial received 30 months of treatment. Along with a number of other assessments, the SF-36 instrument was administered every 6 months during the extension study. Eight of 58 patients enrolled in the open-label extension had withdrawn by the end of the study.

The paper reported qualitatively that a slight improvement was observed during the study in both treatment groups for most of the SF-36 dimensions but that these changes were not statistically significant.

Baehner and colleagues (2003)[55]

This paper reported a single-centre, open-label study to evaluate the safety, clinical efficacy and pharmacokinetic profile of agalsidase alfa (Replagal) in heterozygous female patients. The SF-36 instrument was applied to measure QoL.

Patient age ranged from 20 to 66 years (mean 45.3 years). Mean age at diagnosis was 40 years. In the majority of patients (10/15, 67%), the disease had affected more than six organ systems. The SF-36 instrument was administered at baseline (n =15), at week 13 (n = 14) and at week 27 (n = 10). Comparative baseline SF-36 results were also presented for female rheumatoid arthritis patients and for the female German general population. Aggregate mean values were presented for each SF-36 domain score. At baseline, the SF-36 mean scores were lower than those for the

female German general population and for females with rheumatoid arthritis (in general health, vitality, social function, role emotional and mental health domains). By week 27, improvements in QoL (compared with baseline in the female Fabry's sample) were statistically significant for the mean summary score of physical functioning and the individual mean scores for physical functioning, role-physical and general health.

To convert the SF-36 results into utility values, the patient-specific SF-36 scores are required. Since this paper only reported the aggregate mean domain scores, utility values cannot be derived.

Gold and colleagues (2002)[117]
This study was designed to:

- better understand patients' perception of HRQoL in the absence of specific therapy
- compare these observations with those for the general US population and other chronic disease state
- determine potential predictors of HRQoL for Fabry's patients.

The study focused on male Fabry's patients in the absence of ERT. The HRQoL of these patients was compared with that of untreated patients with Gaucher's disease and patients with AIDS, ESRD and strokes.

Two hundred patients/caregivers were approached to participate and 43% completed the SF-36 instrument (12 patients by telephone and 73 by mail). A total of 53 male patients responded with 39 self-completion and 14 proxy-completion (mostly parents/guardians of children).

Some 17% of the sample were <20 years old, 26.4% were 20–40 years old and 56.6% were >40 years old (n = 53 male patients). SF-36 scores were much lower in the Fabry's patients compared with scores from the general US population and this finding extended across all eight domains of the instrument.

Comparison of the aggregate SF-36 scores for each domain with those of other patient groups revealed that Fabry's patients were almost identical in physical function, role-physical, bodily pain, vitality and role-emotional with the AIDS patients (only slightly better in the social function domain and mental health scores). In general, the dialysis patients had a more favourable profile (although lower on physical function). The physical and emotional role domain scores were comparable between the Fabry's and haemodialysis patients. Stroke patients and Gaucher's disease patients had a higher HRQoL across all domains of the SF-36 than the Fabry's patients.

For each of the eight domains of the SF-36, simple linear regression analysis was undertaken to try to estimate and understand the impact of age, co-morbidities and symptom levels on HRQoL.

Within the Fabry's patients, using the 20–40-year age group as the reference group, the >40-year age group had significantly lower physical function ("likely due to the progression of renal disease as well as cumulative increase in patients suffering from stroke and heart problems"). All the other domains in this age group showed a decrease in HRQoL but this effect was not significant. There were no significant differences between the <20-year age group and the 20–40-year age group (across any domain).

Heart conditions or having pain appear to have substantial associations with all eight domains of the SF-36 tool. The presence of a heart condition had most impact on physical and emotional domains. Being bothered by anhidrosis (absence of sweating) was the next biggest symptom predictor of HRQoL (causing a reduction). The results presented in the paper represent simple associations between each of the SF-36 domains and each of the co-morbidities and symptom scales. Hence it was not possible to determine the interaction between the clinical manifestations of the disease and HRQoL. As only the aggregate mean SF-36 domain scores are presented, utility values cannot be derived from this paper.

Beck and colleagues (2004)[43]
This paper reports the QoL of patients registered with the FOS. The QoL results are superseded by the results presented by Hoffmann and colleagues[62] discussed below.

Hoffmann and colleagues (2005)[62]
This paper presented a detailed analysis of the QoL of the same patients discussed by Beck and colleagues.[43] It describes the QoL in patients who were enrolled in the FOS. A total of 545 patients were registered in the database and 58% of patients in the FOS were receiving intravenous ERT with Replagal every 2 weeks at a dose of 0.2 mg/kg. QoL was measured using the EQ5D instrument at baseline (6 months before to 3 months after the commencement of treatment) and after 12 and 24 months of treatment.

TABLE 19 *EQ5D utility baseline scores for patients in the FOS database*

	EQ5D utility score	
Patients	**Median (10th–90th percentile)**	**Mean (SD)**
All patients (n = 120)	0.76 (0.13–1.00)	0.66 (0.32)
Women (n = 47)	0.80 (0.12–1.00)	0.67 (0.34)
Men (n = 73)	0.76 (0.14–1.00)	0.66 (0.31)

Baseline EQ5D values are presented for 120 patients in *Table 19*. No difference was observed in the utility score between the sexes.

The paper gives the utility scores for 59 patients (20 female, 39 male) for baseline and 1 year after treatment. The mean (SD) EQ5D score was 0.64 (0.32) at baseline and significantly improved to 0.74 (0.26) after 12 months of treatment with Replagal ($p < 0.05$). Again, no differences were found between men and women.

Utility scores were presented for 28 patients (four female, 24 male) for baseline and 2 years after treatment. The mean (SD) EQ5D score was 0.50 (0.32) at baseline and reading from a graph in the paper approximately 0.70 after 1 year and 0.65 after 2 years of treatment.

The authors concluded that ERT with Replagal significantly improved QoL in patients after 1 year of treatment and that this effect was sustained in the second year of treatment.

It is interesting to note the difference in baseline utility values between the groups analysed in the paper. The baseline utility score for both the full sample (n = 120) and for patients who received 1 year of treatment (n = 59) were similar (0.66 and 0.64). However, the baseline utility for patients who received 2 years of treatment was much lower (0.50). One possible explanation could be that this group had more severe disease and therefore were selected to be treated with ERT first. This could be why the QoL score after 2 years of treatment (approximately 0.65) is actually only the same as the baseline score (0.66) for the full sample.

Eng and colleagues (2001)[59]
This paper reported on a multi-dose, open-label, single-centre, dose escalation study of Fabrazyme. Fifteen male Fabry's patients aged 16 years and over were enrolled to receive five identical doses from one of five Fabrazyme dosing regimes (three patients per group): 0.3, 1.0 mg/kg or 3.0 mg/kg every 14 days, or 1.0 or 3.0 mg/kg every 48 hours. Patients completed the SF-36 questionnaire at baseline and after infusion five. The results were reported qualitatively as "Improvements in several quality-of-life measures also were noted. However, assessments of pain and quality of life require more rigorous evaluation in a larger, double-blind study, to minimise possible placebo effects".

Miners and colleagues (2002)[116]
This paper reported on the HRQoL of untreated male patients and drew comparison with patient reference groups. The patients were targeted through the Anderson Fabry's Disease UK register, a register that appears no longer to exist. Fifty-nine patients agreed to fill out three HRQoL questionnaires, the SF-36, EQ5D and a specially devised Fabry's disease-specific questionnaire. Thirty-eight patients completed all three questionnaires. The mean age was 37.2 years and 73% reported a history of heart-related problems. *Table 20* presents the results extracted from this paper:

Univariate analysis reported in the paper showed that the EQ5D and SF-36 scores were significantly associated with age. Individuals who had experienced at least one stroke scored a significantly lower EQ5D score. No other significant associations were found between HRQoL scores and the other independent variables such as general health and heart-related problems.

The HRQoL scores of the Fabry's patients were compared with those of the UK general population and those of individuals with severe haemophilia. Fabry's patients scored significantly lower EQ5D and SF-36 mental component and physical component summary scores compared with the general male population after adjustments had been made for the effects of age ($p < 0.05$). When compared with male patients with severe haemophilia, Fabry's patients scored significantly lower on the mental component summary score but the EQ5D and the physical component summary scores were equivalent.

TABLE 20 *SF-36 and EQ5D scores for patients in the Anderson Fabry's Disease UK register*

	SF36 scores (*n* = 38): mean (SD)	EQ5D utility scores (*n* = 38): mean (SD)
Physical functioning	65.6 (31.3)	0.56 (0.35)
Physical limitations	53.9 (45.9)	
Pain	55.8 (31.1)	
General health	37.6 (24.0)	
Energy	41.3 (24.4)	
Social functioning	57.0 (31.1)	
Mental limitations	56.1 (47.8)	
Mental health	60.7 (21.5)	
Physical component summary	35.5 (14.7)	
Mental component summary	41.5 (13.8)	

HRQoL for the data set of Miners and colleagues

Dr A Miners provided access to the dataset used within Miners and colleagues' paper[116] and a full summary of analyses undertaken for this report can be found in Appendix 3. Briefly, the short-form SF-36 recorded for the Fabry's patients was converted into short-form SF-6D information to calculate utility values.[118] The mean utility score for the male untreated Fabry's patients was 0.63 (SD 0.16). Regression analysis was undertaken to describe the relationship between the SF-6D and EQ5D score and each of the patient clinical characteristics. When univariate analysis of each of the clinical variables against SF-6D and EQ5D was performed, only age and problems with swollen ankles emerged as having a significant negative relationship with QoL.

Health-related quality of life: conclusions

Understanding how the various symptoms of Fabry's disease impact upon the QoL of patients is a challenge given the complexity and the nature of the disease. Of the eight papers reviewed, two report QoL in response to treatment with Fabrazyme, three in response to treatment with Replagal and two were on patients who were untreated.

Five papers applied the SF-36 instrument to measure QoL; two used the EQ5D instrument and one the SF-36 and the EQ5D instrument. None of the papers that report SF-36 scores converted the values into utility scores; all report aggregate average domain scores. Average utility scores are provided in the papers that applied the EQ5D instrument.

Beck and colleagues[43] and Hoffmann and colleagues[62] report QoL of Fabry's patients from the same cohort. Since the latter is the more recent and detailed paper, it is assumed to supersede the results reported by Beck and colleagues.[43] Hoffmann and colleagues report the baseline QoL utility score of all Fabry's patients within the Fabry Outcome Study as 0.66.[62] The baseline utility scores are also provided for two sub-samples within this cohort: patients who had received 1 year of treatment (0.64) and patients who had received 2 years of treatment (0.50). Miners and colleagues report the utility score of untreated Fabry's male patients to be 0.56 when the EQ5D instrument is applied and 0.63 when the SF-36 instrument is applied.[116] Therefore, the evidence suggests that the utility values associated with the QoL of untreated Fabry's patients falls somewhere within the region of 0.50–0.66.

With respect to the impact of ERT treatment on the QoL of Fabry's patients, the only paper that reported this in the form of utility scores was that by Hoffmann and colleagues.[62] This paper reported that for one group of patients for which there were data after 1 year of treatment, the utility score rose from 0.64 to 0.74. For patients for whom there were data after 2 years of treatment, the QoL rose from 0.50 to approximately 0.65. This suggests that over the course of 1–2 years, ERT increases the QoL of a Fabry's patient by between 0.10 and 0.15.

Three papers compared the QoL of Fabry's patients with that of either the general population or patients within chronic disease health states. Patients who had Fabry's disease were found to have a lower QoL than average scores from the general population and patients with rheumatoid arthritis, Gaucher's disease and stroke. The QoL of Fabry's disease patients was equivalent to that of haemophilia patients and patients with AIDS. These results suggest that the clinical manifestations associated with Fabry's disease can have a large impact on the QoL of patients.

Existing economic analyses of ERT

No published evidence reporting an economic evaluation of ERT for Fabry's disease was identified in the review.

Modelling the cost-effectiveness of ERT for Fabry's disease

The objective of an economic analysis is to estimate the cost-effectiveness of ERT in the management of Fabry's disease compared with standard supportive care. The relative lack of information and constraints of time precluded a comprehensive modelling analysis. Outlined in the section below is the analysis that was undertaken exclusively on the basis of currently published data and it is therefore limited by the relative paucity of evidence. Although alternative data sources do exist, it was not possible to access relevant information from these sources to inform a cost-effectiveness model within the time frame for this report. The difficulties are discussed in the section 'Feasibility and future research' (p. 73). If full access to alternative data sources could have been achieved, then it would undoubtedly have been feasible to construct a more detailed model, an example of which is presented in Appendix 4.

Structure of the decision model

In the absence of access to unpublished registry data to inform an understanding of the contribution of the various clinical manifestations to QoL, several assumptions have been made to simplify the decision model. Given these data restrictions, the main objective of the analyses was to provide a clearer understanding of the likely costs associated with treating Fabry's disease over a patient's lifetime. To do this, the model explicitly considered the resource impact from all major cost-incurring events associated with Fabry's disease. The lifetime risk of developing and costs associated with renal insufficiency, cardiac events and cerebrovascular symptoms were explicitly modelled. All other Fabry's disease symptoms were modelled implicitly. Several assumptions were made in constructing the decision model and these are outlined in detail below.

The model considered a birth cohort of male patients that were followed up until death. The primary outcome generated by the model was cost-effectiveness measured in terms of cost per quality-adjusted life-year (QALY) compared with symptomatic treatment (i.e. no ERT being available). Costs were expressed in 2003–4 prices. Discount rates of 3.5% were applied to costs and QALYs. Unfortunately, owing to data limitations and the lack of understanding concerning the correlation between the clinical symptoms of the disease, a probabilistic sensitivity analysis was not deemed sensible in the model.

Untreated cohort

In the model, patients were assigned an independent lifetime risk of developing each of the following clinical symptoms: renal insufficiency, cardiac symptoms, cerebrovascular symptoms, neuropathic pain, angiokeratoma, hypertension and hyperlipidaemia. The risks were assumed to be independent as there were no data to inform on the correlation between the clinical symptoms. The risks associated with each of the clinical events are presented in *Table 21*.

Branton and colleagues[108] presented a Kaplan–Meier analysis of the probability of developing renal syndromes, providing data on the proportion of patients surviving without chronic renal insufficiency over time. This Kaplan–Meier analysis was used to estimate a survival Weibull model for estimating yearly transition probabilities of developing ESRD. Patients who develop ESRD go on to receive either dialysis or a graft transplant with an associated acceptance or rejection rate.

Crutchfield and colleagues[89] conducted a prospective study of cerebrovascular disease in an NIH series of male patients with Fabry's disease (n = 50). The study found that 25% developed a stroke with a mean age of onset of 43 years. Mehta and colleagues reported the incidence of cerebrovascular symptoms according to age of entry into the FOS database and from this it was assumed that no patient was likely to develop stroke before 20 years of age.[69] From this information, it was assumed that 12.5% of patients would develop a stroke over a period of 23 years and, by assuming a constant risk, the risk is then estimated to be 0.009 (accounting for death as a competing state). By using the definition of a disabling stroke as a patient who is "defined as functionally dependant after 1 year", the risk of developing a disabling and a mild stroke was obtained from the Oxford Community Stroke Project study.[119]

To calculate the annual risk of developing cardiac symptoms, a regression model was estimated using data reported by Mehta and colleagues on the signs of cardiac symptoms by age group.[69]

As there were no data to inform on the associated mortality risk from developing each of the clinical

TABLE 21 *Model parameters – probabilities, utilities and costs*

Parameter	Value
Risks and probabilities	
Annual risk of ESRD	Weibull function
Probability of dialysis	0.57
Probability of graft transplant	0.43
Annual probability of graft failure	0.0517
Annual risk of stroke	0.006
Probability of disabling stroke	0.35
Probability of minor stroke	0.65
Risk of cardiac symptoms	Time dependent
Probability of LVH (after 35 years)	0.88
Probability of MV (after 35 years)	0.03
Utilities	
Untreated	0.6
Treated	0.94, age dependent
Annual costs	
Renal dialysis	23,504
Graft transplant	10,249
Graft rejection	23,681
Functioning graft	886
LVH	20
MV	1,928
Disabling stroke	14,150
Mild stroke	1,364
Other	
Neuropathic pain	78
Hypertension	40
Hyperlipidaemia	235

MV, mechanical ventilation.

symptoms, a single overall mortality rate for the untreated cohort was assumed. Using a Kaplan–Meier analysis of probability of death in Fabry's patients,[108] a Weibull model was chosen as the most appropriate form for the survival analysis. Death from other causes was taken from the UK Government Actuary's Department (2001–3) and from these combined sources the life expectancy of the untreated cohort was estimated to be 54.8 years.[120]

Treated cohort

To assess the cost-effectiveness of ERT, it was assumed that patients regain full health immediately upon treatment and become ill immediately were it to be stopped. Patients treated with ERT were assumed to have no Fabry's disease-specific mortality. Therefore, the probability of death was thus equivalent to that of the general population.[120] All these assumptions mean that in essence the model assumed a 'perfect drug scenario', favouring ERT treatment and leading to a lower ICER.

Quality of life

The treated cohort were assumed to have a QoL equivalent to the normal population and therefore were assigned utilities corresponding to the mean, age-adjusted, own health weights derived from the Measurement and Valuation of Health study.[121]

Based on the outcome from the review of the QoL literature, the utility value used to weight the life-years of the untreated cohort in the model was 0.6 (a mid-point value between 0.50 and 0.66).[62,116]

Costs

Monitoring costs were assumed to be the same for the treated and untreated cohorts and therefore the model excludes these costs.

The treatment costs associated with each of the clinical events are presented in *Table 21*. Renal insufficiency patients were assumed to receive either dialysis or a graft transplant. The costs and likely proportion of patients receiving dialysis or a graft transplant along with the associated

TABLE 22 *Base case analysis – cost-effectiveness of ERT: cost per QALY*

Mean cost untreated (£)	Mean cost treated (£)	Mean QALY untreated	Mean QALY treated	Incremental cost (£)	Incremental QALY	ICER (£/QALY)	*N*
34,329.88	2,572,122	14.69	24.76	2,537,792	10.07	252,112	100

TABLE 23 *Cost-effectiveness of ERT: sensitivity analysis 1: cost per QALY*

Mean cost untreated (£)	Mean cost treated (£)	Mean QALY untreated	Mean QALY treated	Incremental cost (£)	Incremental QALY	ICER (£/QALY)	*N*
34,329.88	2,572,122	14.69	18.90	2,537,792	4.21	602,831	100

success/rejection rate were derived from a recent systematic review of immunosuppressive regimens in renal transplantation.[122]

For patients who develop cardiac symptoms, it was assumed that after 35 years of age, 88% were expected to develop left ventricular hypertrophy and 3% to require mitral valve replacement based on data reported by MacDermot and colleagues.[32] Treatment costs associated with these conditions were estimated using standard sources.[123,124]

All patients who develop a stroke were assumed to be treated. The estimated cost of a mild stroke event, taking into account outpatient and primary care, was obtained from a previous UK modelling study[125] that utilised published data from Scotland.[126,127] The estimated mean cost of a disabling stroke taking into account hospital and rehabilitation care and long-term costs associated with such an event were obtained from estimates from a published stroke care model.[128]

Using draft treatment guidelines (Wraith E, Manchester Children's Hospital, personal communication, 2005), all other costs associated with Fabry's disease, such as the treatment of neuropathic pain, hypertension and hyperlipidaemia, were included in the model as an additional cost. This cost was estimated using an average weight that considers the expected annual probability of the patient developing each clinical symptom in turn.

Fabrazyme is sold in a 5-mg vial and each 5-mg vial costs £325.50; the recommended dose is 1 mg/kg biweekly.[124] Replagal is sold in a 3.5-mg vial and each 3.5-mg vial costs £1249;[129] the recommended dose is 0.2 mg/kg biweekly.[130] Therefore, for a 50-kg patient (assumed average weight across adults and children), the annual cost of Fabrazyme is £84,630 and that of Replagal is £92,782. Drug costs were estimated on the basis of multiple uses of one vial. The model considered the cost associated with Fabrazyme, which being cheaper relative to the cost of Replagal, provided a cost per QALY estimate that favoured ERT treatment for Fabry's disease. The model considered average costs by age using population average weights taken from the Health Survey Report.[131]

Results

Base case analysis

The base case results present the incremental cost per QALY (*Table 22*). For the full cohort of patients, the incremental cost per QALY is £252,000.

Sensitivity analysis

Analysis 1 – ERT does not restore full health

In the base case analysis, all treated patients are assumed to experience normal health. However, it is likely that ERT does not prevent or overcome all disease symptoms and that patients remain in a 'mild' disease state. On the basis of the utility information reported by Hoffmann and colleagues,[62] ERT increases the QoL of a Fabry's patient by anything between 0.10 and 0.15 over the course of 2 years. Sensitivity analysis 1 therefore relaxed this assumption by allowing treated patients to gain a utility increment of 0.10 from treatment (rather than experience normal health). The additional costs of a 'mild' Fabry's disease state are not factored in. The results are shown in *Table 23*.

In this scenario, the cost-effectiveness of ERT worsened. For the overall patient cohort, the ICER was in excess of £600,000/QALY.

Analysis 2 – life expectancy of untreated cohort set to 50 years

The base case model assumed that ERT is a lifelong treatment and estimated that the life expectancy of the untreated cohort is 54.8 years.

TABLE 24 *Cost-effectiveness of ERT: sensitivity analysis 2: cost per QALY*

Mean cost untreated (£)	Mean cost treated (£)	Mean QALY untreated	Mean QALY treated	Incremental cost (£)	Incremental QALY	ICER (£)	*N*
27,690.32	2,572,122	14.21	24.76	2,544,432	10.56	241,063	100

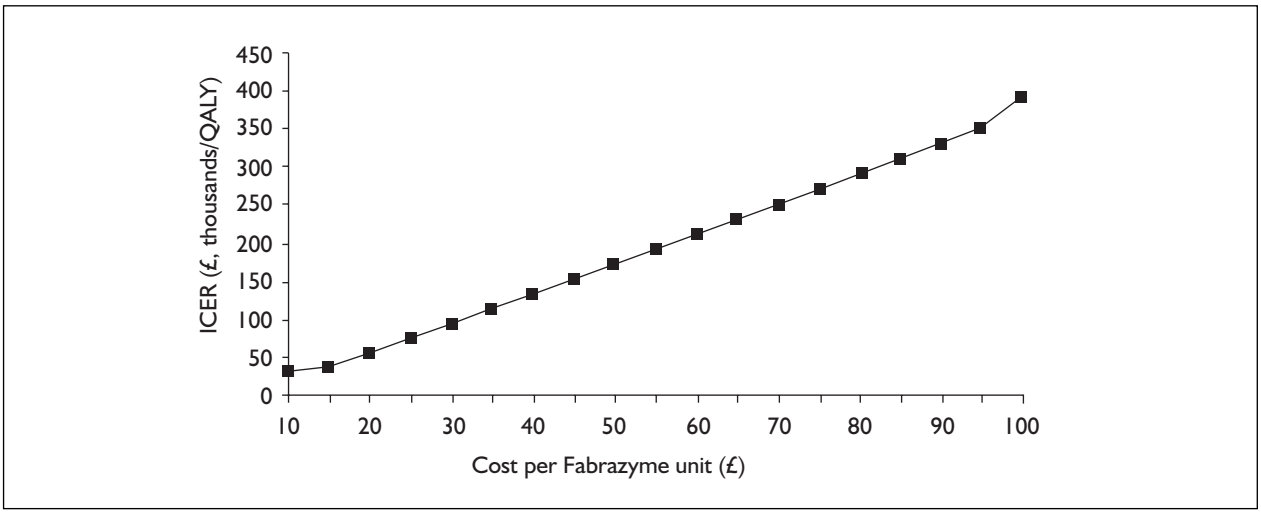

FIGURE 2 *Sensitivity analysis – effect of drug cost on the ICER of ERT for Fabry's disease (1 unit = 1 mg of Fabrazyme)*

To test the sensitivity of the ICER to this estimation, the life expectancy of the untreated cohort was reduced to 50 years. The ICER was only marginally improved to £241,000/QALY (*Table 24*).

Analysis 3 – changes in drug cost

ERT is a relatively costly treatment. In sensitivity analysis 3, the extent to which the unit cost of ERT drives the cost-effectiveness model was identified. The cost per milligram was varied between £10 and £100 (base case £65.1) and the resulting ICERs are plotted in *Figure 2*.

An ICER of £30,000/QALY was generated where the price per milligram of Fabrazyme was £9. Where the price per milligram of ERT was £50, the ICER rose to £192,000/QALY.

Main results

The estimated cost per QALY gained from ERT treatment was £252,000. However, this figure must be considered in the light of the many assumptions that have been described within the modelling section. Alternative scenarios were considered in one-way sensitivity analyses. Cost-effectiveness ratios were substantially increased if ERT did not return patients to an asymptomatic state. The cost-effectiveness was improved if the life expectancy of the untreated cohort was reduced to 50 years. Under the assumptions inherent within the model, for the ICER to reach a value of £30,000/QALY the unit cost of ERT must be set at £9/mg.

Discussion

The economic model has been designed to provide a clearer understanding of the likely costs associated with treating Fabry's disease over a patient's lifetime. It is recognised that a major assumption within the model is the assignment of independent risks of developing each of the clinical symptoms. A more realistic assumption would have been to assign correlated risks; however, no access to data was available to inform on what these correlations were likely to be. The model did, however, take into account all major lifetime cost-incurring events (alongside the minor costs) and thus provides an indication of the cost-effectiveness of ERT for Fabry's disease.

It was disappointing that access to the FOS database was not possible within the time frame allocated to the review. The FOS database represents a rich source of observational data and would have proved invaluable to the modelling exercise.

A number of substantial assumptions were required to produce an estimate of the

cost-effectiveness of ERT in Fabry's disease; most notably, that ERT puts patients in an asymptomatic state with a normal life expectancy. However, this assumption, like most of the others utilised in the model, favours rather than detracts from the value of ERT. A single composite overall mortality rate for the untreated cohort was also assumed as no data were available to inform on the associated mortality risk from developing each of the clinical symptoms associated with Fabry's disease. It is normal when evaluating a disease to assume an additional mortality risk as a direct result of developing each clinical symptom; however, an all-encompassing mortality risk was derived from a Kaplan–Meier analysis of probability of death in Fabry's patients[82] and these were the best data available.

Chapter 5
Results: MPS1 disease

Search results

Existing systematic reviews
No existing systematic reviews were identified on the clinical or cost-effectiveness of ERT for MPS1.

Primary studies – number and types of studies identified
After removal of duplicate references, the literature search yielded 1853 references. Of these, 15 articles were initially deemed potentially relevant to determining the prevalence of MPS1, 144 articles potentially relevant to a review of natural history and 16 articles potentially relevant to assessing the clinical effectiveness of ERT.

Many of the relevant articles identified, in particular for the clinical effectiveness review, were conference abstracts. Given that conference abstracts are difficult to identify, we cannot be sure that we have identified all those relevant to each section of this report.

Prevalence

MPS1 is a rare disease and the exact prevalence of the condition is unknown. Findings of the ten studies that satisfied the inclusion criteria are outlined in *Table 25*.

Several studies report the number of cases but are unclear about the denominator (e.g. total number of births).[132–134]

The most reliable and most relevant studies to the UK population and to this review are the studies from British Columbia,[135,136] Northern Ireland[137] Western Australia,[40,138] The Netherlands[35] and the UK West Midlands.[139]

The estimates of disease frequency are fairly consistent across the studies, which is unsurprising in view of the common ancestry of the populations. Three of the studies (The Netherlands,[35] West Midlands,[139] Australia[40]) report disease frequency for all MPS1 not distinguishing between subgroups, giving a frequency of 0.99–1.19 per 100,000 live births.

Four studies give some indication of the frequency of Hurler, Hurler–Scheie and/or Scheie subtypes.[135–138] Hurler varies from 0.69 to 1.3 cases per 100,000 births (n = 4; British Columbia × 2, Northern Ireland, Western Australia) and Scheie from 0.08 to 0.16 per 100,000 (n = 2; British Columbia × 2). Variation in rates from the vertical reports from British Columbia appeared to be due to no additional cases of Hurler and Scheie disease being reported from 1972 to 1986, giving a lower frequency in the report covering these years of the order of 50% for Hurler syndrome compared with the earlier report from British Columbia and the studies from Northern Ireland and The Netherlands.

UK prevalence
The two studies conducted in the UK (West Midlands, Northern Ireland) give estimates comparable to those in other countries.[137,139]

The Society for Mucopolysaccharide Diseases (UK) attempts to maintain a register of all patients with any of the MPS diseases. The Society believes that it has compiled a register of all UK patients diagnosed with MPS1 since 1981. For this report, the MPS Society kindly made available anonymised data including date of birth information for all 196 MPS1 patients held in the register up to 31 May 2005. Of the 196 births, 171 occurred within England and Wales (the remaining 25 births were in Scotland and Northern Ireland). The 3-year running average by year for MPS1 births is shown in *Figure 3*, where it is compared with the 3-year running average for all births in England and Wales.[140] Three-year running averages are utilised in order to smooth chance year-on-year fluctuations.

The total number of births and the total number of MPS1 births in England and Wales in the period 1981–2003 were 15,611,220[140] and 167, respectively giving a calculated birth prevalence of 1.07 per 100,000 births (*Table 26*).

Of the 167 MPS1 births 118, 38 and 11 were diagnosed as Hurler, Hurler–Scheie and Scheie, respectively, which calculates to a birth prevalence of 0.756, 0.243 and 0.070, respectively (*Table 26*).

TABLE 25 *Prevalence studies on MPS1*

Study	Output and method	Ascertainment period	Subtype	No. per 100,000
Lowry (1971)[135] British Columbia	Disease 'frequency', birth prevalence (no. of cases in period/no. of live births during period)	1952–68	Hurler Scheie	0.99 0.16
Lowry (1990)[136a] British Columbia	Disease 'frequency', birth prevalence (no. of cases in period/no. of live births during period)	1952–86	Hurler Scheie	0.69 0.08
Nelson[137] (1997) Northern Ireland	Disease 'incidence', birth prevalence (medical records, laboratory records, register of disease) (no. of enzymatically confirmed diagnosis during period/no. of live births during period)	1958–85	Hurler Hurler–Scheie Scheie	1.3 0.36 No cases
Nelson (2003)[138] Western Australia	Birth prevalence (medical records, laboratory records, Society for MPS, Western Australia, records of birth defects) (no. of cases diagnosed pre- and post-natally/total no. number of births in same period)	1969–96	Hurler Hurler–Scheie Scheie	0.93 ± 0.72 No cases No cases
Poorthuis (1999)[35] The Netherlands	Birth prevalence (records from clinical genetics centres) (no. of enzymatically confirmed diagnoses in period/no. of live births in period)	1970–96	All	1.19
Meikle (1999)[40] Australia	Birth prevalence (patient referral records, national referral laboratory) (no. of enzymatically confirmed diagnoses during period/no. of live births during period)	1980–96	Hurler–Scheie[c]	1.14
Hutchesson (1998)[139] West Midlands, UK	Disease frequency[b] (no. of cases born in period/no. of neonates tested for PKU in period)[b]	1981–91	All	0.99
Schaap (1980)[132] Israel	No detected (national survey of patients)	1970–9	NA	
Coelho (1997)[133] Brazil	No. detected (referrals to specialist diagnostic centre)	1982–95	NA	
Menedendez-Sainz (2003)[134] Cuba	No. detected (national clinic for referral)	1986–2000	NA	

NA, not applicable.
[a] Update of Lowry and Renwick[135] with overlapping data.
[b] Calculated from data given in paper.
[c] Unclear whether referring to Hurler–Scheie subtype or all Hurler, Hurler–Scheie and Scheie.

All these values are comparable to those in the published studies in *Table 25*.

Clinical effectiveness

Of 16 potentially useful articles, 11 met the inclusion criteria.[141–151] The reasons for exclusion were the study containing less than 10 patients ($n = 3$ all case reports on single patients),[152–154] article not being a primary study[155] and study only presenting pharmacokinetic data on laronidase with no clinically relevant outcomes.[143] The three excluded case reports were all on the utilisation of laronidase as a pretreatment to BMT in order to facilitate the surgical procedure and recovery.

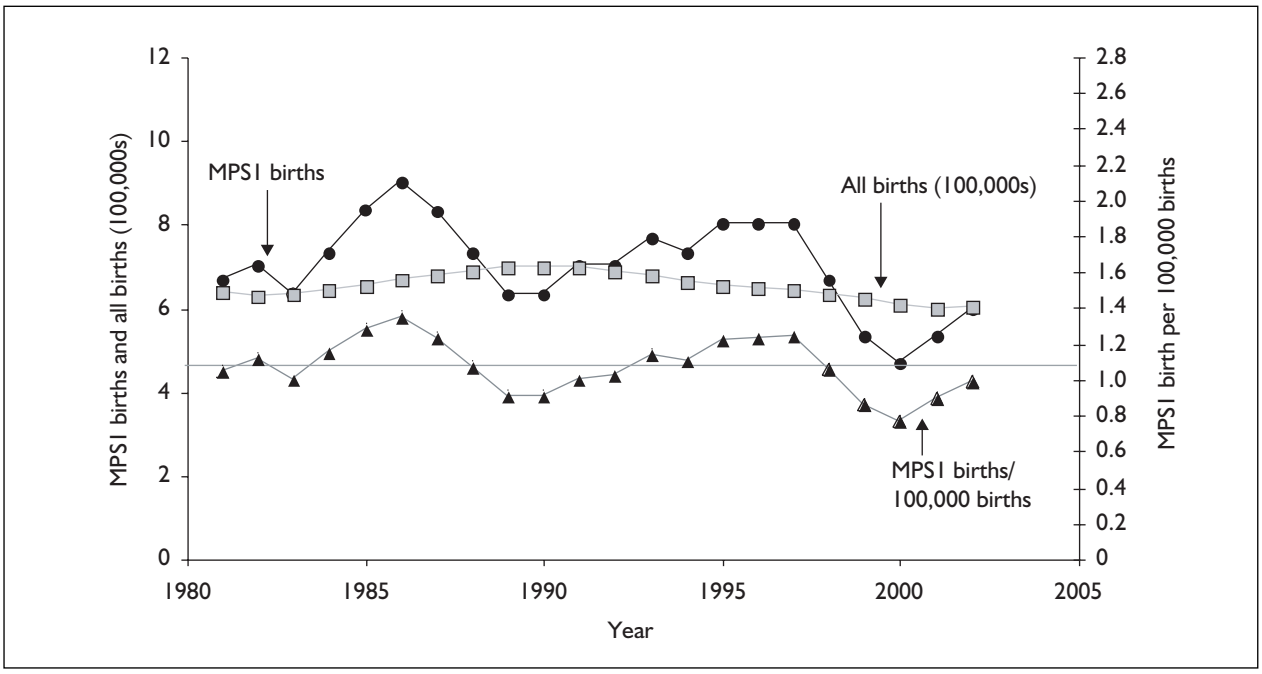

FIGURE 3 *Three-year running averages for MPS1 and all live births in England and Wales. The horizontal line represents the overall birth prevalence (1.07 per 100,000 live births) for MPS1 in England and Wales.*

TABLE 26 *Birth prevalence of MPS1 in England and Wales*

Phenotype[a]	No. of births 1981–2003	Birth prevalence/100,000 births
England and Wales general population	15,611,220	
MPS1 all	167	1.07
MPS1 H	118	0.756
MPS1 HS	38	0.243
MPS1 S	11	0.070

[a] H, Hurler; HS, Hurler–Scheie; S, Scheie.
Data from Society for Mucopolysaccharide Diseases (UK).

Of the 11 included articles, only three[141–143] were full papers, the other eight being abstracts.[144–151] These articles constitute reports of only three separate studies. Details of these studies/articles are given in *Table 27*.

One study was a Phase I/II uncontrolled trial,[142,143,151] one a Phase III placebo-controlled RCT with open label extension[144,146,147,149,150] and one an ongoing Phase II open-label study in MPS1 patients less than 5 years of age.[145,148] As the last is an ongoing study with the only publications being abstracts describing the study design and limited early safety and efficacy data, it is not dealt with in detail in this report.

A narrative review by Wraith,[4] published as this report was being compiled, draws together some of the data on the effectiveness of ERT only published so far in abstract form.

General considerations

The overriding feature is the very small number of studies on the effectiveness of ERT for MPS1, and that these enrol a small number of patients. These are due in part to the relative newness of the intervention and the rarity of the disease.

There is only one study containing a controlled phase, and this is of 6 months' duration. Maximum follow-up of open-label studies is 5 years.

None of the included studies measured what would be considered as the primary outcomes for this review, such as utility-related HRQoL or

TABLE 27 *Characteristics of included effectiveness studies*

Study/design	Publication	Population	Follow-up	Outcomes	Comments
Phase I/II	Kakkis (1999),[151] Kakkis (2001),[143] Kakavanos (2003)[142]	$N = 10$ (1 × H, 8 × HS, 1 × S)	52 weeks	α-L-Iduronidase activity in leucocytes, liver and spleen volume, urinary GAG excretion, height, weight, NYHA classification, range of joint motion, sleep apnoea, ophthalmic assessment, adverse events	One full paper and two abstracts identified. Specific patients' inclusion criteria not stated
Phase III RCT	Wraith (2004)[141]	$N = 45$ (22 in ERT arm) (1 × H, 37 × HS, 7 × S) At least 5 years old with measurable disease, fibroblast/leucocyte α-L-iduronidase <10% of normal, able to reproduce a forced vital capacity manoeuvre that was ≤80% of predicted normal, stand independently and walk a minimum of 5 m in 6 minutes	26 weeks	Forced vital capacity, 6-minute walking distance, liver volume, urinary GAG excretion, sleep studies/apnoea, shoulder flexion, disability score index of health assessment questionnaire, adverse events	One full paper identified
With extension	Clarke (2002),[150] Clarke (2003),[147] Bajbouj (2003),[146] Pastores (2003),[149] Clarke (2004)[144]	As above	Up to 98 weeks on ERT for those initially on ERT in the RCT phase ($n = 22$) Up to 72 weeks on ERT for those initially in the placebo arm ($n = 23$)	Forced vital capacity, 6-minute walking distance, shoulder flexion, disability score index Other outcomes not segregated by initial allocation: liver volume, urinary GAG excretion	No full paper is available for the extension phase of this RCT. Data come from multiple abstracts. Not all outcomes have been reported for the full length of follow-up
Phase II open-label, <5 years old study	Guffon (2003),[148] Cox (2004)[145]	$N = 20$ Under 5 years of age without haematopoietic stem cell transplant	Ongoing. 26-week data presented on 12 patients	Adverse events, urinary GAG excretion	Two abstracts identified. Ongoing study. Data only available on 12 patients at 26 weeks follow-up

H, Hurler; HS, Hurler–Scheie; S, Scheie.

mortality. Studies for the most part measured symptom-related surrogate markers or clinical indicators that might reasonably be expected to reflect patient well-being; these outcomes included organ volume, urinary GAG excretion, joint flexion, sleep-related problems (apnoea), disability score index of health assessment questionnaire, 6-minute walking distance and forced vital capacity. Adverse events were also reported.

The limited number of studies, their differing design and limited overlap in the outcomes measured preclude any meaningful combination of measures to generate overall effect sizes.

Phase I/II open-label study

The open-label uncontrolled before–after study by Kakkis and colleagues[143] was a safety and efficacy study, which enrolled 10 patients. Ranging from 5 to 22 years old (mean 12.4 ± 4.86), eight patients had Hurler–Scheie and one each Hurler and Scheie subtypes. The duration of the study was initially 26 weeks but it was subsequently extended to 52 weeks and beyond. Patients received 125,000 U/kg of rh α-L-iduronidase (equivalent to 100 SI U/kg of laronidase) weekly by intravenous infusion. Outcomes were measured periodically. After safety, primary efficacy outcomes were liver and spleen volumes and urinary GAG levels. Secondary outcomes were height, weight, eye abnormalities, sleep studies, airway and cardiac function and joint motion.

Quality assessment reveals that it is unclear whether explicit eligibility criteria were applied for patient entry into the study or how the sample and source of the sample were chosen. On the other hand, clinical details of the patients and related previous surgical interventions are described. It is unclear whether any of the outcomes were assessed blindly and it is unclear if there were withdrawals from the study. Individual patient data are given for some outcomes and aggregate data for others.

Phase III study and open-label extension

The RCT by Wraith and colleagues[141] was an international study that randomised 45 patients to either laronidase (100 U/kg by single weekly intravenous infusion) or to placebo for 26 weeks. Outcomes were measured periodically during this period. After this time, all patients received laronidase in an open-label extension to the trial for an additional 72 weeks. The primary outcomes measured were 6-minute walking distance and the percentage of predicted normal respiratory forced vital capacity (FVC). These outcomes were selected "driven by the need to demonstrate treatment effect in the short term although the disease involves many organs and tissues and is slowly progressive,"[4] and in consultation with EU and US regulatory authorities. Secondary outcomes included urinary GAG excretion, liver volume, sleep studies, shoulder mobility (flexion), the disability score component of the adult and child versions of the Health Assessment Questionnaire (HAQ) and safety assessments.

Quality assessment reveals that although the trial was described as randomised, the method of randomisation and how allocation of treatment was concealed are not mentioned. Patients' eligibility criteria for enrolment in the study were clearly described. Patients had to be at least 5 years old with measurable disease (fibroblast/leucocyte α-L-iduronidase <10% of normal), able to reproduce a forced vital capacity manoeuvre that was <80% of predicted normal, stand independently and walk a minimum of 5 m in 6 minutes. Patients were excluded if they had had prior tracheostomy or bone marrow transplant, were pregnant or lactating, had recently been administered an investigational drug, possessed a known sensitivity to laronidase or other components of the infusion or had a condition or circumstance that could affect compliance. Patients ranged in age from 6 to 43 years (mean 15.5 ± 8.0) and were predominantly of the Hurler–Scheie phenotype (n = 37; Hurler = 1, Scheie = 7). Given all these characteristics, patients could potentially have had relatively mild disease.

Based on baseline characteristics, after randomisation both treatment and placebo groups appeared to be similar. The trial was also described as double blind but limited information on who was actually blinded and how blinding was achieved was given other than that outcomes assessors for MRIs and sleep studies were blinded. There appear to be no withdrawals from the study and for the randomised phase at least data on the primary outcomes appear to be reported for all patients and for secondary outcomes are almost comprehensive. Mostly aggregate data were reported and individual patient data were not given.

Assessment of the quality of the open-label extension phase of this trial is not possible as all the reports in the public domain are conference abstracts. Although the data from the extension phase of the trial are presented below, caution should be applied as using data presented only in abstracts is fraught with potential biases due to the limitations of the format.

Given that neither study measured the primary outcome for the review of mortality and utility-related QoL and that there is no severity score framework on which to base reporting of outcomes, as there is with Fabry's [see the section 'Mainz Severity Score Index' (p. 5)] and Gaucher's diseases,[1] outcomes are reported below in an order primarily dictated by the priority order outlined in the Phase III trial.

TABLE 28 *Effect of laronidase of forced vital respiratory capacity*[a]

Phase	Week	Forced vital capacity			
		Placebo/ERT: % of predicted normal ± SD	Change from baseline	ERT/ERT: % of predicted normal ± SD	Change from baseline
Randomised	0	54.2 ± 16.0		48.4 ± 14.5	
	4		–1.5		2.0
	8		–1.2		3.0
	12		–0.6		1.4
	16		–1.5		1.25
	20		–1.5		0.8
	26	53.5 ± 14.2	–0.7 ± 5.9	53.3 ± 18.5	4.9 ± 8.7
Open-label	50		–0.6		5.9
	72		3.0		6.6
	98		4.9 (–0.7[a])		10.2 (–0.2[b])

[a] Data and SD for baseline and 26 weeks of the randomised phase taken from data presented in the trial report by Wraith and colleagues[141] and data for 4, 8, 16 and 20 weeks read from *Figure 1* in the same paper. Data for open-label phase were obtained from the abstracts by Clarke and colleagues,[144,147,150] SDs were only available at baseline and at the end of the randomised phase. ERT/ERT = group treated with laronidase in both randomised and open-label phase. Placebo/ERT = group treated with placebo in randomised phase and laronidase in open-label phase.
[b] Predicted normal FVC determined by using current instead of baseline height.

Six-minute walking distance

Data on the 6-minute walking distance for the randomised and the open-label phase are presented in *Figure 4*.

It is evident there was considerable variation in ambulatory ability between patients at baseline as denoted by the large SD about the mean. This is perhaps not surprising given the age range of the patients and the likely spectrum of disease-related effects within the study population. One-third of the patients were able to walk at least the lower limit of normal community ambulation at baseline.[4] Patients allocated to receive placebo had a higher mean ambulatory ability at baseline than those allocated to receive ERT, although this appears to be not statistically significant. Both groups experienced an initial decrease in mean walking distance, which has been attributed to a training/eagerness effect at the baseline assessment.[4] After 26 weeks, patients receiving laronidase demonstrated a mean increase in distance of 20 m, whereas the placebo group decreased by a mean of 18 m. These differences are marginally statistically significant (Wilcoxon rank sum $p = 0.066$; analysis of covariance $p = 0.039$).[141]

In the open-label phase the improvement in the laronidase treatment groups was maintained although it ceased to increase further after the first year of treatment and remained constant for the remaining year of the observation. The change from baseline levels was statistically significant. On commencing laronidase treatment the group initially treated with placebo showed an increase in mean walking distance over the first 26 weeks, of treatment of the same order of magnitude as that seen in the laronidase-treated group over the same period in the randomised phase. This increase in mean walking distance appeared to be maintained over the duration of the study and reached statistical significance compared with levels at the end of the randomised phase at 72 weeks but not 98 weeks. The decrease in mean change in this group seen at 98 weeks the authors of the study attributed to just two patients.[4]

Forced vital capacity

Data on the FVC as an indicator of respiratory function for the randomised and the open-label phase are presented in *Table 28*.

At baseline the mean FVC was around 50% of predicted normal values, which is classed by the American Thoracic Society as a severe restrictive abnormality.[141] However, the range of FVC values was fairly large and would encompass a range of severity of respiratory function abnormalities.

A modest 10% improvement in FVC from baseline was measured in the laronidase-treated group during the randomised phase of the study. In contrast, that for the placebo group decreased slightly. The difference between placebo and

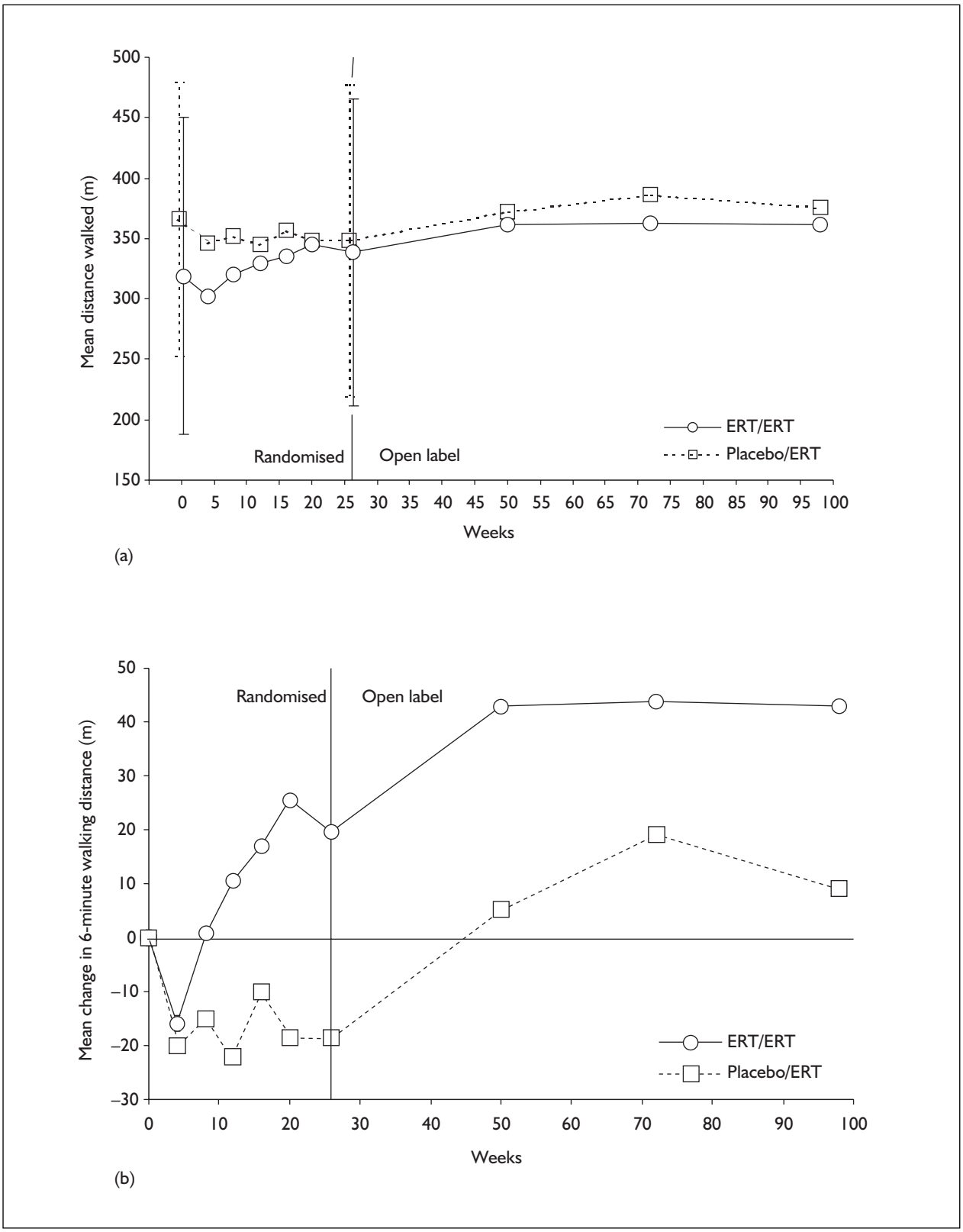

FIGURE 4. *Effect of laronidase on 6-minute walking distance. (a) Effect on total mean walking distance; (b) mean change from baseline. Data and SD for baseline and 26 weeks of the randomised phase taken from data presented in the trial report by Wraith and colleagues*[141] *and data for 4, 8, 16 and 20 weeks read from Figure 2 in the same paper. Data for open-label phase were obtained from the abstracts by Clarke and colleagues.*[144,147,150] *As mean change from baseline data was presented in these abstracts it was added to mean baseline values to create the total mean walking distances in (a). SDs were only available at baseline and at the end of the randomised phase and are represented by the error bars. ERT/ERT = group treated with laronidase in both randomised and open-label phase. Placebo/ERT = group treated with placebo in randomised phase and laronidase in open-label phase.*

treatment groups was 5.6% and statistically significant. The latter difference is equivalent to an 11.5% improvement. The American Thoracic Society judges an improvement of over 11% over a few weeks/months as being clinically significant.[141]

Improvements appear to continue into the open-label phase in those initially treated with laronidase. The placebo group gained improvement on switching to laronidase in the open-label phase; the improvement over baseline was statistically significant.

The RCT and for the most part the open-label extension study utilised baseline height to determine predicted FVC, rather than current height at time of FVC measurement. The authors' rationale was to control for any height changes related to the laronidase treatment releasing joint contractures in addition to growth. Hence using baseline height may overestimate the treatment effect, as the predicted normal FVC may be an underestimation compared with if based on final height.[156] The authors of the trial recalculated results based on final height and still noted a statistically significant result between treatment and placebo groups, albeit with a smaller mean difference between groups (4.3% as opposed to 5.6%).[141]

Urinary GAG excretion

Urinary GAG excretion along with organ volume are utilised as markers for reduction in lysosomal storage.

Urinary GAG excretion was measured in both the Phase I/II and Phase III studies.

In the Phase III study, there was a mean decrease in urinary GAGs of 54.1% in the laronidase-treated patients and a mean increase in the placebo patients of 47.3% at the end of the 26-week study period. The difference between groups was statistically significant. The decrease in the treatment group was dramatic and occurred during the first 4 weeks after treatment began and then remained low for the duration. This low mean level approached the upper limit for normal GAG urinary levels. It should be noted that data from one patient in each group were missing from the analysis at the end of the randomised phase. No explanation is given for these missing data, but it is unlikely that they would significantly alter the findings.

For the most part, no data are presented in the identified abstracts for the open-label phase of this study. The only data suggest that there was a mean reduction of 68.9% in the group initially given placebo after transferring to laronidase treatment for 24 weeks.[150]

In the Phase I/II study, there was a statistically significant mean decrease from baseline level after 52 weeks of treatment of 63% (53–74%). The major decline occurred within the first few weeks of treatment. Hence the findings are similar to those in the Phase III study.

Missed infusions can result in elevation of urinary GAGs.[4]

Organ volume

In the Phase III study, during the randomised phase the mean liver volume decreased by 18.9% in the laronidase-treated patients but increased by 1.3% in the placebo group (difference 20%, $p = 0.001$). Four patients in the treatment group had normal liver volumes at baseline, as did eight of the placebo group. At the end of the randomised phase, of those with abnormal baseline liver volumes 72% had normalised in the laronidase group and only 21% in the placebo group. Data appear to be missing from one patient in the placebo group. Rates of change in liver volume are not given. The methods of determining liver volume were not given.

In the extension phase to this study, liver volume continued to be measured but was not adequately reported in the abstracts to allow mention here.

In the Phase I/II study, liver volume as a percentage of body weight was measured as a volume from abdominal MRI scan and converted to weight assuming 1 g/ml of tissue. Liver volume decreased by an average of 25% (range 5–37%; $p < 0.0001$) after 52 weeks of treatment, and after 26 weeks was already within the normal range in eight patients. The degree of decline in volume was of a similar order of magnitude to that seen in the Phase III study. The decrease in liver volume appeared most rapid in the first 12 weeks of treatment before the rate of improvement slowed to a steadier decline, which appears to have been maintained to at least the last measurement in the study at 52 weeks.

Spleen volume appears to have been measured only in the Phase I/II study and decreased by a mean of 20% (range 13–42%; $p < 0.001$). No further information is given.

Weight and height

Weight and height were only reported for the Phase I/II study. There was a significant increase in the mean rate of growth in the six prepubescent patients in the study from 2.80 to 5.17 cm/year ($p < 0.001$).

Body weight increased in all patients by a mean of 3.2 kg (9%). The increase was greater in the prepubescent patients at 17% (mean gain 4.2 kg). The rate of weight gain increased in these patients from 1.66 to 3.83 kg/year ($p < 0.04$).

Motion

Range of joint motion studies were conducted in both the Phase I/II and Phase III studies and extension thereof.

In the randomised phase of the Phase III study, a wide range of shoulder flexion functions were evident at baseline. There was no significant difference in mean change in shoulder flexion (mean of both shoulders) after 26 weeks between those treated with laronidase or placebo. A *post hoc* subgroup analysis in those patients most severely affected suggests that laronidase improves mean range of movement whereas those on placebo experience a mean decline in range of motion.

Shoulder and knee flexion and extension are reported for those patients with the most severe restriction of motion (below baseline median value) in the open-label extension, and indicate a mean improvement at 48 and 72 weeks of treatment compared with baseline.[146]

In the Phase I/II study, there were statistically significant improvements in mean extension of both elbows and non-significant improvements in both knees. There was also a mean improvement in range of motion of shoulder flexion, although this was only measured on eight of the 10 patients.

Across the two studies it appears that joints with the greatest degree of restriction have the greatest improvement. Anecdotal information in the Phase I/II study suggests that patients reported an increase in physical activity such as ability to wash hair and play sports better.

Airway function

Airway function was measured in both studies as the number of occurrences of apnoea during sleep studies.

In the Phase III study, nearly 50% of patients had normal baseline levels of apnoea. The number of events in the laronidase treated group during the randomised phase decreased by a mean of 3.6 events per hour compared with the placebo group. This finding was not statistically significant. Subgroup analysis of those patients who had baseline levels suggestive of apnoea indicated a statistically significant 11.4 events per hour treatment benefit over placebo. Given that this subgroup analysis was undertaken *post hoc*, it should be treated with caution.

No report of any sleep studies in the open-label extension phase of the Phase III study were identified.

In the Phase I/II study, seven out of 10 patients had apnoea at baseline. The mean number of episodes decreased from 2.1 to 1 event per hour, with a decrease from 155 to 60 total events per night.

Cardiac function

Cardiac function was measured in the Phase I/II study as a change in NYHA class. At baseline no patient had a score (class I) indicative of normal functionality (no symptoms and no limitations in ordinary physical activity). Three patients had a class II score (symptoms on ordinary activity and slight limitation of activity), six a class III score (symptoms with less than ordinary activity and marked limitation of activity) and one a class IV score (symptoms with any type of activity or rest). After 1 year of treatment, all patients had improved by one or two classes and five patients gained a class I score. A further patient is reported to have achieved this score after a further year of treatment.[4]

In interpreting these findings, several factors need to be considered. The NYHA classification is subjective with a score elicited as a result of serial interviews with patients and/or carers. In the above study there were no objective data from echocardiographic studies to verify any direct cardiac benefit and that improvement in the functional scores might be a reflection of benefit of treatment on other aspects of the disease other than cardiac function.

The Phase III trial did not measure cardiac function.

Ophthalmic problems

There was some attempt to assess the effect of laronidase on eye disease in the phase I/II study. Limited analysis seems to indicate that there was no change in the degree of corneal clouding in the eight patients with this problem.

Subjective assessment suggests that some patients experienced a decrease in photophobia or conjunctival irritation and an increase in visual acuity. These ocular findings should be treated with caution owing to the subjective nature of their assessment.

Ocular outcomes were not reported/measured in the Phase III study or the open-label extension.

Disability index score

The disability index scores of the adult and child versions of the HAQ were utilised to measure patient-reported changes in disability in the Phase III study and open-label extension. The HAQ is a generic instrument designed to evaluate the long-term influence of multiple chronic illnesses. The disability score index is one of a number of domains of the questionnaire (others include pain) and it attempts to ascertain patient abilities in a number of areas (dressing, rising, eating, walking, hygiene, reach, grip and usual activities). It is scored from 0 to 3 with scores of 0 to 1 generally considered to represent mild to moderate difficulty, 1 to 2 moderate to severe disability and 2 to 3 severe to very severe disability. Average scores that have been reported in a population-based study are 0.49 and in osteoarthritis and rheumatoid arthritis patients are 0.8 and 1.2, respectively.[157]

Baseline mean disability scores were 1.9 for the placebo group and 2 for the laronidase group, indicating moderate to severe disability. Changes after 26 weeks were reported as small and similar for both groups, and no further information is given in the paper by Wraith and colleagues.[141] Further information in the abstract by Pastores and colleagues suggests that the change in the score in the treatment group was a mean improvement of 0.3.[149] A change of 0.22 has been suggested to represent the minimum clinically important difference.[157] The abstract reports a similar improvement (mean improvement of 0.2) in patients initially treated with placebo after receiving laronidase for 24 weeks of the open-label phase of the study. Further information around the patient data is required for this outcome to permit a full assessment of effect of laronidase.

Adverse events

Other than the included studies outlined in *Table 27*, further information to address this section was taken from the recent narrative review by Wraith[4] as it contained supporting detail and in particular information on a severe adverse event.

In the RCT, infusion-related reactions occurred in both groups, 32% of patients receiving laronidase and 48% of patients receiving placebo.[141] These events included flushing, fever, headache and rash. The occurrence of these and other adverse events were similar between the two groups. In the open-label phase 50% of patients experienced a mild to moderate infusion reaction that was managed by adjusting the rate of infusion and/or antihistamine/antipyretic medication.

IgG antibodies to laronidase were present in 91% (20/22 patients) of treated patients in the randomised phase with seroconversion occurring after a mean of 52.6 ± 24.1 days. Immunogenicity testing of patients receiving laronidase in the randomised phase or open-label extension revealed seroconversion in 89% of patients with a mean time to convert of 51 ± 41 days (range 20–259 days). It is reported that no effect of antibody formation on safety or efficacy has been seen.[4]

One patient who crossed from placebo to laronidase in the open-label phase experienced two severe laronidase-related adverse events resulting in a severe hypersensitivity and dyspnoea requiring an emergency tracheostomy. The patient's restrictive lung function and pre-existing compromised airway has been indicated as an exacerbatory factor.[4] The patient tested positive for immunoglobulin E (IgE) antibodies.

Adverse events are also reported in the Phase I/II study. As the laronidase formulation was changed to one with fewer Chinese hamster ovary cell impurities 2 years into the study, the infusion-related and immune reactions reported by Kakkis and colleagues for the first 52 weeks of the study are potentially meaningless, as all patients developed IgG antibodies to Chinese hamster ovary cell proteins.[143] A study by Kakavanos and colleagues on the same population, assessing antibodies to rh α-L-iduronidase, noted that five out of 10 patients developed titres which were above normal at some point during 104 weeks of study but titres fell to normal levels in three of the five before the end of the assessment period.[142] Three patients died in the extension to the Phase I/II study, of disease and/or surgery-related problems. None were ascribed to be treatment related.

Compliance

Compliance with treatment was only reported for the Phase III study and was good in that each group received more than 97% of planned interventions.

Intervention type and dose
The preparations utilised in the early part of the Phase I/II and the Phase III/open-label extension are not necessarily identical owing to the change to reduce contamination in Chinese hamster ovary cell proteins outlined above. The active units of rh α-L-iduronidase appear to be identical at 100 SI U/kg.

Subgroups of patients
Analysis of data by patient subgroups of patients based on genotype, phenotype and/or clinical parameters and interventions received were not undertaken in the above studies. This is understandable given the very small populations enrolled.

Ongoing studies
Ongoing studies on the effectiveness of ERT for MPS1 include the aforementioned open-label study in patients under the age of 5 years who are unsuitable for or have declined an HSCT.[145,148] Other studies include assessment of different ERT dosing regimens[4] and the effect of ERT utilised pre- and post-HSCT.[152–154]

Conclusions from published data on clinical effectiveness of ERT
Only two studies on the effectiveness of laronidase for MPS1 have been undertaken and published on a population of 10 or more patients. The total number of treated patients in these studies is relatively small at 53, and only 43 have been studied in a randomised fashion. The latter, as with most RCTs on rare diseases, is notably an underpowered investigation.

The studies for the most part enrolled patients with moderate to mild disease, and in the RCT the inclusion criteria appear to have selected the more physically able patients.

Assessment of the internal validity of the RCT is somewhat hampered by under-reporting of some methodological elements but on the whole the quality appears to be acceptable.

Outcomes measured in the two studies are a combination of those chosen as likely to reflect readily and rapidly any improvement in patient functional abilities, those related to markers of lysosomal storage, those measuring change in specific disease symptoms and those related to monitoring the safety of the intervention.

Full QoL measurement was not undertaken although elements of one generic instrument were used to assess the effect of treatment on improvement in disability. Hence at present there is no utility-related HRQoL data on which to assess the relative health gain of laronidase treatment.

The RCT was of relatively short duration compared with the duration at which effects of the disease are experienced. Even so, the study demonstrates treatment benefit over placebo for most of the outcomes assessed. Furthermore, improvements in most outcomes are demonstrated after starting ERT in uncontrolled phases of this and the Phase I/II study. However, the total degree of health gain is unclear and may be likely to exceed that demonstrated by treatment-related improvement in health state derived from comparisons to baseline data as patients might have deteriorated further had they not received the treatment. Although the ongoing studies will provide valuable extra data, it is unlikely that they will address this deficit. Therefore, in order to estimate the degree of health gain achieved by ERT, it is necessary to consider what would have happened to these patients had they not received treatment. The next section, therefore, sets out to estimate the natural history of untreated MPS1 disease to prepare the ground from which treatment effect and cost-effectiveness can be reliably modelled.

Natural history of MPS1 disease

Quantity and type of research available
Of 142 potentially useful publications, only 16 met the inclusion criteria [see the section 'Inclusion and exclusion criteria' (p. 13)]. The main characteristics of these studies are summarised in *Table 29*.

Nearly all of the 16 studies reported data on several different MPS syndromes; only five[160,162,164,165,173] were exclusively focused on MPS1. Some studies did not fully disaggregate data for the different MPS1 phenotypes.[162,165,171,173] Of the 346 patients who contributed data, the phenotype of 124 was not defined, 193 were Hurler, 16 Hurler–Scheie and 11 Scheie. Hence the information available from these studies on the more rare phenotypes (Hurler–Scheie and Scheie) is extremely meagre.

Studies documenting multiple manifestations
Three studies[158–160] reported the frequency of many of the major manifestations of MPS1 and

TABLE 29 *Major characteristics of MPS1 natural history publications*

Study	Patient number and subtype	Manifestation studied	Type of study
Leroy (1966)[158] USA	22 MPS1 H 1 MPS1 S	Multiple	All referrals at 1 centre over 30 years
Wraith (1987)[159] Australia	27 MPS1 H	Multiple	Referrals at one centre 1950–86
Alif (1999)[160] Morocco	10 MPS1 H 3 MPS1 HS	Multiple	Survey of affected Moroccan families
Mohan (2002)[161] UK	29 MPS1 H 2 MPS1 S	Cardiovascular (ultrasound)	Retrospective analysis of presentations over 22 years at single specialist centre
Taylor (1991)[162] Canada	24 MPS1 Phenotypes not reported	Cardiovascular (MRI, ultrasound, angiography) subgroup analysis only	Presentations over 18 years at single specialist centre
Wippermann (1995)[163] Germany	12 MPS1 H 6 MPS1 S	Cardiovascular (ultrasound)	Sample from MPS1 patients at three specialist centres (not selected for cardiac problems)
Rose (2002)[164] USA	14 MPS1 H	Cardiovascular (autopsy findings)	Review of autopsy records at single centre 1987–99
Cleary (1995)[165] UK	39 MPS1 H	Presenting signs and features up to 18 months of age	Retrospective review of records of attendees at single specialist centre
Colville (1996)[166] UK	63 MPS1 Phenotypes not reported	First signs observed by parents (questionnaire)	Survey; most families ascertained via UK Society for Mucopolysaccharide Diseases
Leighton (2001)[167]	8 MPS1 H 2 MPS1 HS	Upper airway obstruction and obstructive sleep apnoea	Sample (n = 10) of 75 MPS1 attendees at single specialist centre 1994–6
Walker (1994)[168] UK	13 MPS1 (≥ 2 MPS 1S)	Preoperative assessment and problems with surgical anaesthesia	Case record review of all patients with MPS at single specialist centre 1988–91 identified as having undergone operation/anaesthesia
Peters (1985)[169] USA	26 MPS1 H	Upper airway obstruction: narrowed tracheal diameter from chest X-ray	Review of records at one specialist centre
Bredenkamp (1992)[170] USA	13 MPS1 H	Head and neck complications	Retrospective review of records at three surgical centres 1979–89
Bax (1995)[171] UK	63 MPS1 Phenotypes not reported	Age-related behavioural problems (parental questionnaire)	Most families ascertained via UK Society for Mucopolysaccharide Diseases
Collins (1990)[172] USA	7 MPS1 H 11 MPS1 HS 2 MPS1 S	Optic nerve head swelling and optic atrophy	Review of patient records at single specialist centre for inherited eye diseases
Dumas (2004)[173] USA, UK, France	17 MPS 1 15 MPS 1HS	Functional status (semi-structured interviews)	Patient selection not reported

H, Hurler; HS, Hurler–Scheie; S, Scheie.

one of these inferred typical ages of their onset.[158] They provide a fairly coherent account of MPS1 Hurler phenotype; the outcomes do not overlap significantly with those reported in the remaining studies even though organ systems covered coincide. These three studies are therefore reviewed in this section while remaining studies are reviewed according to disease manifestation in subsequent sections of this review.

One of these three studies included only Hurler phenotype patients,[159] another[158] no Hurler–Scheie and a single Scheie patient. The third study[160] was primarily a genetic investigation of affected Moroccan families and encompassed 10 Hurler and three Hurler–Scheie phenotypes; the genotypes of these patients were unusual in that the relatively rare P533R mutation accounted for 24 of the 26 mutant alleles. Two of the studies[158,159] describe a short lifespan for the Hurler phenotype with deaths mainly associated with cardiac complications and/or pneumonia or respiratory problems [see the section 'mortality' (below)]. The findings reported in these three studies are summarised in *Table 30*. The common features reported for the Hurler phenotype are physical disability affecting joints, mobility and stature; early umbilical and inguinal hernias; and initially slow intellectual development followed, after 1 year of age, by deterioration with increasing age.

Mortality

Two primary studies reported survival in MPS1 disease. The Australian study of Wraith and colleagues[159] reported an average age at death of 6.25 years (range 1.3–10.9) for Hurler phenotype. Leroy and Crocker[158] reported that of 22 Hurler patients they studied over a period of 30 years, three remained alive (aged 2–5 years), seven died at age 1–2 years, six at about 4 years, and six at 7–16 years.

For this report, the Society for Mucopolysaccharide Diseases (UK) made available anonymised information for all 196 MPS1 patients held in their register (to 31 May 2005), which has been maintained since 1981 and contains most, if not all, patients diagnosed in the UK since that time. Of the 196 individuals, 143 were classified as Hurler, 41 as Hurler–Scheie and 12 as Scheie patients. Amongst the 143 Hurler patients, 79 had died and 65 were recipients of BMTs. Of 41 Hurler–Scheie patients, five had died, two had received BMTs and 25 had received ERT. One of the 12 Scheie patients had died and four had received ERT.

The Kaplan–Meier survival curves for all the MPS1 patients and each of the three phenotypes are shown in *Figure 5*.

Appendix 5 shows the estimated 95% CIs for these Kaplan–Meier curves. Strictly patients in receipt of ERT should be censored at commencement of treatment. However, dates of ERT commencement were not available; in practice, because the introduction of ERT for MPS1 disease occurred recently and because a relatively small proportion have received ERT, omission of this censoring is unlikely to change materially the survival curves shown.

The survival of MPS1 Hurler phenotype patients who received and did not receive a BMT is shown in *Figure 6*. Several possible explanations exist for the observed differences in survival. Further analysis of these data is beyond the remit of this report.

Table 31 summarises estimates for median survival and mean age at death. Because of the small numbers and relatively short follow-up, median survival for Hurler–Scheie and Scheie patients has not been reached; for both phenotypes it is reasonable to assume that median survival is beyond 30 years and is greatly prolonged relative to that for patients with the Hurler phenotype.

Cardiovascular manifestations

Four studies[161–164] encompassing 82 patients focused on cardiovascular manifestations. In one of these studies not all phenotypes were specified and findings for only a subgroup were reported.[162] Wippermann and colleagues[163] included 12 Hurler and six Scheie patients and Mohan and colleagues[161] 29 Hurler and two Scheie patients; these studies reported findings from echocardiography examinations. The study of Rose and colleagues[164] was published as an abstract only and reviewed autopsy findings in Hurler patients (n = 14; 12 had received BMT). The results reported for Hurler phenotype in these last three studies are summarised in *Table 32*.

Taylor and colleagues[162] reported that of 24 MPS1 patients, eight developed arterial hypertension, of whom five showed clinical signs of coarctation of the abdominal aorta (strong brachial but weak femoral pulse). Four of the eight were examined by imaging techniques and coarctation was confirmed; three of these were Hurler phenotype and one Scheie phenotype.

TABLE 30 *Results reported in studies of multiple manifestations of MPS1 disease*

Study and patients	Hernia/ hydrocele	Joints/bone dysplasia	Organomegaly	Developmental delay		Cardiac	Respiratory	Growth	Other
Leroy (1966)[158] 22 MPS1 H	8/14 boys by 6 weeks 12/14 boys by 5 months Umbilical hernia common 1–6 years	22/22 kyphosis by 6–12 months 22/22 restricted joint extension by 1 year	22/22 liver by 6–18 months	Sitting alone Standing alone Use of words Toilet never training Learning plateau	Moderate retardation Retarded or never Slow, no sentences Almost achieved By age ~2 years	Murmurs frequent	22/22 nasal discharge and noisy breathing	Dwarfed by 3 years	22/22 corneal clouding by early months Placidity/reduced activity
Alif (1999)[160] 10 MPS1 H 3 MPS1 HS	Not reported	Not reported	Liver: 8/10 H 1/3 HS Spleen: 3/10 H 0/3 HS	Mental delay: 6/10 H 2/3 HS		8/10 H 1/3 HS	Not reported	Height and age reported	Not reported
Wraith (1987)[159] 27 MPS1 H	17/27 inguinal: 8/12 boys. Recur after repair	All had combination of: mental retardation, herniae, bone dysplasia, hepatosplenomegaly and cardiac disease				Valvular disease: majority	Respiratory obstruction: some Infections: frequent	Normal to 1 year All short at >1 year	27/27 corneal clouding

H, Hurler; HS, Hurler–Scheie.

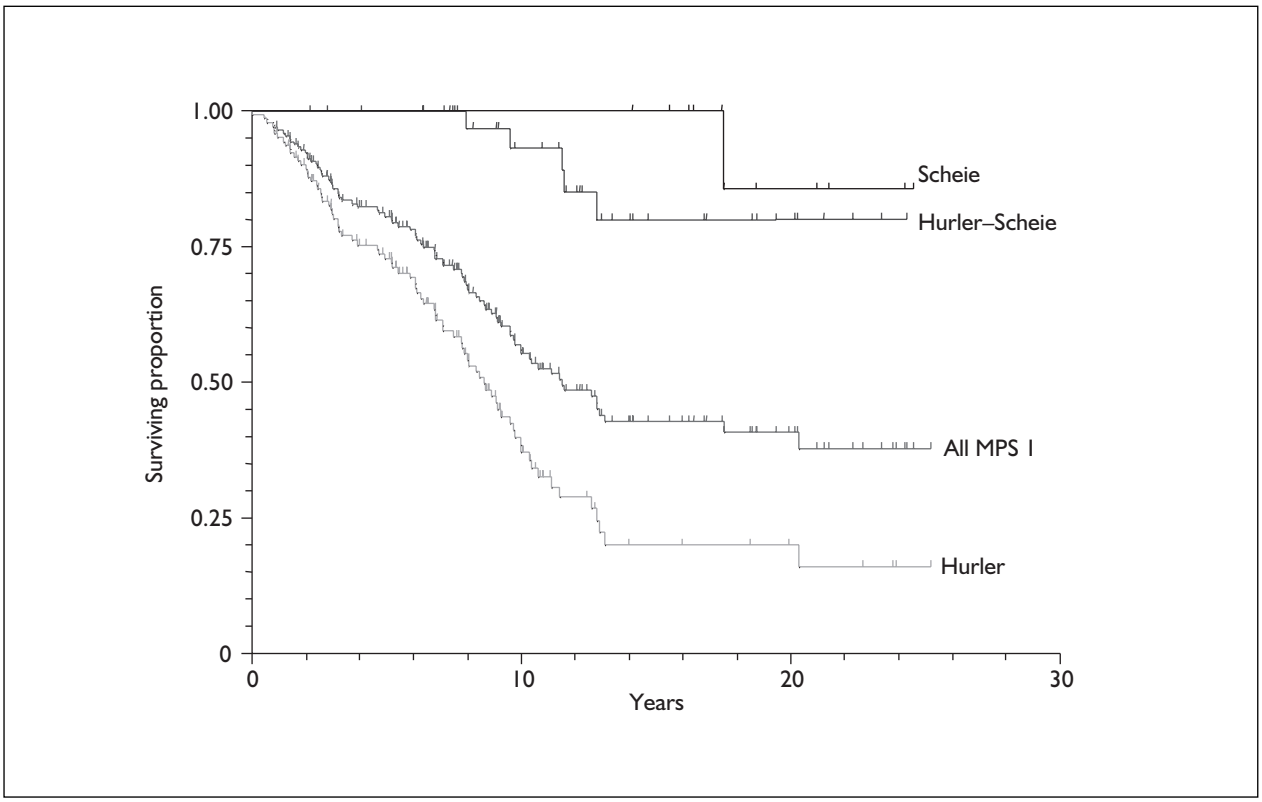

FIGURE 5 *Kaplan–Meier survival curves for UK MPS1 patients (ticks mark censored patients)*

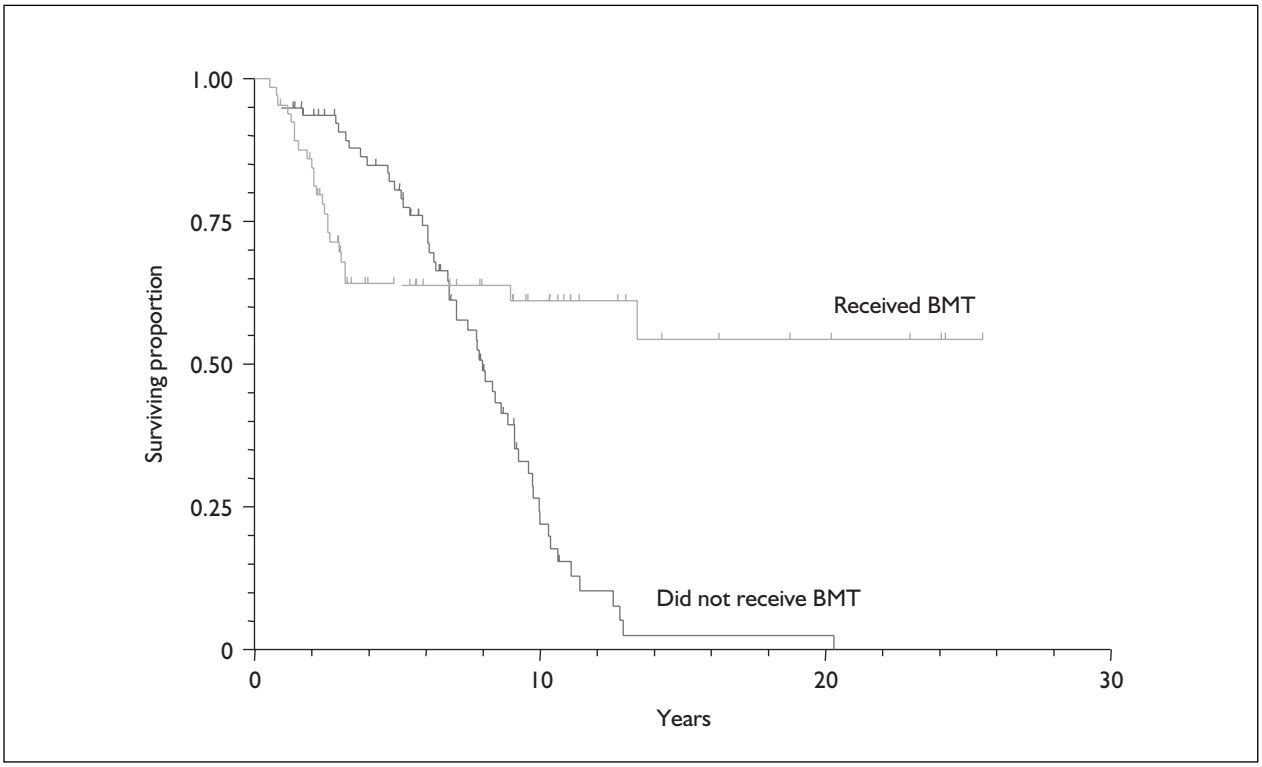

FIGURE 6 *Kaplan–Meier survival curves for Hurler patients who received or did not receive a bone marrow transplant (ticks mark censored patients)*

TABLE 31 *Survival of MPS1 phenotypes estimated from Kaplan–Meier survival analysis*

	Median survival (years)	95% CI median survival	Mean survival time (years)	95% CI mean survival time
MPS1 (all)	11.6	9.5 to 13.7	14.6	13.0 to 16.1
Hurler	8.7	7.6 to 9.7	10.5	8.8 to 12.2
Hurler–Scheie	Cannot estimate	Cannot estimate	21.6	19.3 to 24.0
Scheie	Cannot estimate	Cannot estimate	1 death only	Cannot estimate
Hurler BMT	Cannot estimate	Cannot estimate	15.6	12.5 to 18.8
Hurler no BMT	8.0	7.0 to 8.9	7.9	7.0 to 8.8

The results reported for eight Scheie patients in the other two studies are summarised in *Table 33*.

From these studies, it is clear cardiac disease develops at an early age in Hurler syndrome; although mentioned as a cause of death, the lack of a published systematic analysis of cause of death in these patients means that its contribution to mortality is difficult to gauge. The data for the other phenotypes are so meagre that few conclusions can be drawn other than that similar symptoms are observed to the Hurler phenotype but in patients of greater age on average.

Respiratory manifestations

Three studies[167–169] focused on respiratory complications in MPS1. Walker and colleagues[168] reported that problems were commonly encountered at preoperative anaesthesia for MPS patients; data were not disaggregated for syndromes or MPS1 phenotypes. It was also remarked that four Hurler patients out of 13 MPS1 patients exhibited obstructive sleep apnoea. Peters and colleagues[169] examined records of chest X-rays and of one autopsy and reported that tracheal diameter was narrowed in three of 26 MPS1 Hurler patients. Leighton and colleagues[167] conducted a detailed investigation of obstructive sleep apnoea in a cross-sectional study design of 26 patients representative of the 75 MPS patients seen at a single specialist centre. Of the 26 patients eight were Hurler and two were Hurler–Scheie phenotype. This study comprised data from parental sleep diaries (estimates of difficulties in waking, restless sleep, cessation of breathing during sleep) and from objective ward monitoring of respiratory movement, percentage arterial oxygen saturation, pulse rate, heart rate and video sound monitoring. The results reported for some of these measures are summarised in *Table 34*. The authors concluded that all 10 MPS1 patients exhibited either moderate or severe obstructive sleep apnoea. Likely sequelae that have been attributed to obstructive sleep apnoea include behavioural problems and learning difficulties.

Presenting signs and symptoms

Two studies reported on early signs and symptoms exhibited by patients with MPS1. The study of Cleary and Wraith[165] was based on retrospective analysis of clinical records. It details the frequency of 12 signs and symptoms observed at presentation during the first 18 months of life for 39 Hurler patients attending a single specialist centre; mean age at diagnosis was 9.4 months and the most common presenting features were Gibbus deformity (16/39) and recurrent ear, nose and throat infections (15/39), followed in order by skeletal abnormality (9/39), inguinal hernia (9/39), umbilical hernia (7/39), feeding problems (7/39), failed screening hearing test (6/39), recurrent chest infections (5/39), large head (5/39), developmental delay (4/39) and hepatosplenomegaly (3/39).

The second study, by Colville and Bax,[166] was based on responses to a questionnaire sent to families of 63 MPS1 patients classified only as "Hurler/Scheie". The response rate was unclear but appeared to be 81% (51/63). The child's appearance was the most commonly reported sign that alerted parents to problems, followed by repeated infections, clumsiness and stiffness or hernias.

Head and neck complications

Bredenkamp and colleagues[170] performed a retrospective review of case records of 43 MPS patients who attended three specialised surgical centres in the USA to determine the frequency of head and neck involvement and of surgical procedures performed. Thirteen patients were classified as Hurler phenotype. The results reported are summarised in *Table 35*; they clearly indicate common involvement of head and neck complications and the necessity for surgical interventions in Hurler patients. However, the

TABLE 32 *Cardiovascular manifestations reported in Hurler phenotype*

Study and patients	Mean age (years)	Hypertrophy	Mitral valve involvement		Aortic valve involvement		Ejection fraction	Coronary artery stenosis
			Regurgitation	Wall thickening or stenosis or prolapse	Regurgitation	Wall thickening or stenosis		
Mohan (2002)[161] 29 MPS1 H	Not reported	9/29 left ventricular hypertrophy (7 mild)	11/29 (10 mild, 1 moderate 0 severe)	12/29	2/29 (1 mild, 1 moderate, 0 severe)	5/29	6/29 abnormal	Not reported
Wippermann (1995)[163] 12 MPS1 H	3.8 (range 1–6.6)	Not reported	10/12 (4 mild, 4 moderate, 1 severe)	12/12 (2 mild, 10 marked)	4/12, (3 mild, 1 moderate, 0 severe)	6/12 (5 mild, 1 marked)	Not reported	Not reported
Rose (2002)[164] 14 MPS1 H	2.8 (range 0.5–17)	13/14 heart heavier than normal	Heart valve involvement: Absent: 1/14 Mild: 5/14 Severe: 8/14				Not reported	Grade I: 1/14 Grade II: 0/14 Grade III: 4/14 Grade IV: 9/14

H, Hurler.

TABLE 33 *Cardiovascular manifestations reported in Hurler–Scheie and Scheie phenotypes*

Study and patients	Mean age (years)	Hypertrophy	Mitral valve involvement		Aortic valve involvement	
			Regurgitation	Wall-thickening or stenosis or prolapse	Regurgitation	Wall-thickening or stenosis
Mohan (2002)[161] 2 MPS1 S	Not reported	Not reported	1/2 (1 mild, 0 moderate, 0 severe)	1/2	1/2 (1 mild, 0 moderate, 0 severe)	Not reported
Wippermann (1995)[163] 6 MPS1 S	20.5 (range 18.5–29.1)	Not reported	6/6 (3 mild, 3 moderate, 0 severe)	6/6 (0 mild, 6 marked)	5/6 (3 mild, 2 moderate, 0 severe)	6/6 (1 mild, 5 marked)

S, Scheie.

TABLE 34 *Results from overnight monitoring of MPS1 patients' % arterial O_2 saturation*

	Mean (SD) % arterial O_2 saturation	Mean (SD) dips/hour below 92% arterial O_2 saturation	Mean (SD) % time at <92% arterial O_2 saturation
'Normal'	>96	<0.7	~0
MPS1 H (n = 8)	90 (5.84)	33.7 (25.7)	44.3 (39.5)
MPS1 HS (n = 2)	94 (range 92.5–95.5)	13.1 (range 7.7–18.5)	25.3 (range 15.8–34.9)

H, Hurler; HS, Hurler–Scheie.

TABLE 35 *Head and neck complications and surgical procedures in Hurler patients*

Middle ear effusion	Middle ear pressure equalisation tubes[a]	Airway obstruction	Tonsillectomy and adenoidectomy[a]	Tracheostomy[a]	Rhino-sinusitis
10/13	6/13	7/13	5/13	3/13	5/13

[a]Surgical procedure.

possibility of selection bias exists since patients with greater involvement may have been referred more frequently to the specialised centres.

Collins and colleagues[172] retrospectively reviewed medical records for 108 MPS patients who attended a single specialist centre for hereditary eye diseases in the USA. MPS1 patients were classified as Hurler (n = 7), Hurler–Scheie (n = 11) and Scheie (n = 2). This study reported the frequency per eye of optic nerve head swelling and optic atrophy. Both outcomes were absent in the two Scheie patients. Of 14 eyes of Hurler patients eight (57%) showed swelling and two (14%) optic atrophy. Nine (43%) of 21 eyes of the 11 Hurler–Scheie patients exhibited swelling and four eyes (19%) optic atrophy. The possibility of selection bias exists since those patients with eye involvement may have been referred more frequently to the specialised eye disease clinic.

Behavioural problems

Bax and Colville[171] reported the results from a survey by questionnaire of behavioural problems in 258 MPS patients. Sixty-three patients were classified as "Hurler/Scheie" (mean age 6.7 years, SD 7).

It is evident from the text that the majority of the MPS1 patients were of the Hurler phenotype but

TABLE 36 *Behaviour problems reported in MPS1 patients*

	Frequency				Frequency		
Abilities	**0–4 years old**	**5–9 years old**	**0–9 years old**	**Behaviour**	**0–4 years old**	**5–9 years old**	**0–9 years old**
Able to walk	16/25 (64%)	12/24 (50%)	28/49 (57%)	Sleep problems	29/49 (59%)	16/25 (64%)	12/24(49%)
Able to speak in sentences	7/25 (28%)	9/24 (36%)	16/49 (33%)	Destructive	4/49 (8%)	1/25 (4%)	3/24 (13%)
Toilet trained	3/25 (12%)	5/24 (21%)	8/49 (16%)	Cannot settle	20/49 (41%)	12/25 (48%)	8/24 (33%)
				Fearful	18/25 (72%)	14/24 (58%)	32/49 (65%)
				Faddy	1/25 (4%)	4/24 (17%)	5/49 (10%)

that some Hurler–Scheie phenotype patients were included. Unfortunately, the numbers of each were not reported and it is evident from the text that profound differences exist between results for each, for example, "as a group their language abilities were quite poor although there were notable exceptions, presumably those with the milder Hurler/Scheie phenotype, who were fluent speakers, keeping up with their peers at school". The failure to disaggregate data by phenotype and the unknown proportions of each phenotype limit the utility of the reported findings. The response rate appeared to be 78% (49/63); the findings presented in this paper are summarised in *Table 36*.

A separate publication[166] based on this survey reported on parentally observed first signs and symptoms of disease [see the section 'Presenting signs and symptoms' (p. 66)].

Functional status

One study, published in abstract form only, reported the results from a yet to be validated semi-structured interview tool to determine self-care, mobility and caregiver assistance in 17 MPS1 patients.[174] Most (88%) were clinically diagnosed as Hurler–Scheie phenotype and the mean age of the sample was 17.7 years (range 7–35). The frequency of patients' reported functional difficulties were dressing 87%, bathing and grooming 70%, feeding 59% and toileting tasks 47%. Walking devices were used by 41% and some care assistance was required by 88%.

Summary of natural history studies

It is clear from the natural history publications reviewed here that the rarity of MPS1 has resulted in an almost complete absence of authentic longitudinal cohort studies that describe disease progression and that previous descriptions of the disease have been largely based on information gleaned from personal experience, case series and occasional surveys of small numbers of patients. In the absence of substantial and robust new evidence, it is unlikely that further systematic analysis would add materially to the breadth or precision of analyses embodied in published narrative reviews.[4,23]

The information available from the reviewed papers on the more rare Scheie and Hurler–Scheie phenotypes was particularly sparse and so fragmentary that, on the basis of this information, no coherent description of disease progression can be constructed. The greater quantity and quality of information on Hurler patients presented in the reviewed papers is consistent with the description of a "condition with expression in intellectual deficit, changes in body configuration and specific visceral chemical pathology"[158] and associated with curtailed life expectancy. Manifestations of this severe phenotype documented in these studies include:

- retardation: both mental and motor with gains reaching a plateau followed progressive deterioration
- characteristic faces: flat nose, coarse features, enlarged head
- hepatomegaly and splenomegaly
- restriction of joint extension (elbows and other joints) without spasticity
- characteristic radiological changes: spine, skull metacarpals, etc.
- cloudiness of the cornea
- kyphosis
- early appearance of inguinal and umbilical hernias
- upper airway obstruction and sleep apnoea
- hirsuitism.

Registry data provided by the Society for Mucopolysaccharide Diseases (UK) allowed the construction of Kaplan–Meier survival curves for MPS1 and for the three different phenotypes From these curves, the median survival for MPS1 patients as a whole and for the Hurler phenotype appears to be about 11.5 and about 8.6 years, respectively. The survival of MPS1 patients as a whole merely reflects the greater proportion of Hurler individuals, and considerable differences between phenotypes are obvious. No comparable analyses were found in the literature. It is clear that access to good-quality registry data in which patients have been followed over several decades is the most likely source to provide added value in our understanding of the natural history of MPS1 and of other rare diseases.

Economic analysis: MPS1 disease

Review of quality of life in MPS1 disease

To model the cost-effectiveness of ERT treatment in MPS1 disease, information on the utility-based QoL of MPS1 patients is crucial. Without this information, we are unable to estimate the likely QALY gain as a result of treatment with ERT.

Our review of the published literature failed to identify any study that reported the QoL of MPS1 patients within a utility format.

Existing economic analyses of treatments for MPS1 disease

One economic evaluation was identified that investigated the cost-effectiveness of BMT for children with Hurler syndrome.[175] This economic evaluation was reported as an abstract. The evaluation used data derived from a consortium of 25 institutions based in the USA and Canada to build a model that compared transplantation with no transplantation using discounted, QALY expectancy as the outcome measure. To estimate the health state utilities required to calculate the QALY gain from transplantation, the authors conducted a threshold analysis to determine the level of utility necessary to change the direction of the decision from not transplanting to transplanting. A related and unrelated donor model was created and, as one would expect, the transplantation decision is usually optimal when using reasonable estimates of the BMT state utilities relative to the non-BMT states. It is clear from the analysis that the result is sensitive to the assumed QoL of the post-BMT state. Although this analysis attempts to estimate the QALY gain from transplantation and reports the results accordingly, the utility estimates are in essence 'guesstimates' and are not based on any real data collected within the 25 institutions involved, and the study therefore offers little evidence to inform a cost-effectiveness model of ERT for MPS1 disease.

Modelling the cost-effectiveness of ERT for MPS1 disease

The objective of an economic analysis is to estimate the cost-effectiveness of ERT in the management of MPS1 disease compared with standard supportive care. To fulfil this objective, it is necessary to consider and understand the progression of disease had the patients not received ERT treatment (the natural history).

To apply an accurate costing analysis to the progression of MPS1, information on the rate and severity of each of the clinical manifestations is required over a period of time. In addition, information is required on the impact of ERT on the rate and severity of each clinical manifestation and any subsequent alteration in symptomatic treatment. The natural history and clinical effectiveness review [see the sections 'Clinical effectiveness' (p. 52) and 'Natural history of MPS1 disease' (p. 61)] were unable to identify any information to this effect, hence it is not possible to estimate accurately the costs of the disease.

Information on the mortality effects of the disease and the impact of ERT upon patient mortality is also required. ERT for MPS1 disease is a new and emerging treatment, which has had marketing approval only since 2003, and therefore there are no long-term data on the likely mortality benefits.

Disease manifestations inevitably have a huge impact on the QoL of the patient. An understanding is required of the relationship between each clinical manifestation and the QoL of the patients, to allow the calculation of QALYs with and without ERT treatment. This review did not identify any study that reported the QoL of patients in a utility format.

Given the lack of data on the clinical manifestations of the disease over time and the lack of data on patient mortality, alongside a situation where there is no information on utility-based QoL of MPS1 patients, it was clearly not sensible to develop a cost-effectiveness model of ERT treatment for the disease. The model would have to consist of many assumptions using 'guesstimates' that would be based on no published evidence whatsoever, leading to an incremental cost per QALY result that would effectively be meaningless. For any decision-analytic modelling to be undertaken, comprehensive and longitudinal information, including utility-based QoL, is required. Given the rarity of the disease, a (national) patient registry may be the only source of such information.

ERT drug costs

Although it was not possible to provide a comprehensive modelling exercise to estimate the cost-effectiveness of ERT, an estimate of the likely cost associated with prescribing laronidase is possible. This estimate cannot include treatment-related mortality or QoL effects.

The current price of Aldurazyme is £460.35 + VAT per vial and each vial contains 100 U/ml of laronidase.[124] Therefore, the cost of the drug alone for treating a patient weighing 70 kg would be approximately £335,134 per year and the cost of treating a child weighing around 20 kg would be £95,752 per year.

According to the registry maintained by the Society for Mucopolysaccharide Diseases (UK), there are currently 41 live MPS1 Hurler–Scheie and Scheie patients in England and Wales. Three are less than 5 years old and the ages of the remainder range up to 24 years. If all were to be treated with laronidase then, assuming their body weight conforms to the average by age, the annual cost to the NHS would be about £5.1 million (see Appendix 6).

Chapter 6
Discussion

Emerging ERT for other LSDs

This report was commissioned along with that for Gaucher's disease to assess the clinical and cost-effectiveness of licensed ERTs for LSDs, namely imiglucerase (Cerezyme) for Gaucher's disease, galactosidase alfa and beta (Replagal and Fabrazyme) for Fabry's disease and laronidase (Aldurazyme) for MPS1.

When this report was in the final stages of being compiled, it was announced that the US Food and Drug Administration had granted marketing approval for the use of galsulfase (Naglazyme; BioMarin Pharmaceuticals) in the treatment of MPSVI Maroteaux–Lamy syndrome. It is probably only a matter of time before this drug is licensed in the EU.

Searches of commercial pharmaceutical R&D pipeline databases (PharmaProjects, R&D Insight, Adis International) revealed that there are other ERTs for LSDs in development.

Idursulfase is currently undergoing Phase III investigation for the treatment of MPSII Hunter syndrome.[176] Full results of the study are due in late 2006. Algulcosidase alfa for Pompe's disease is also in Phase III investigation.

Non-ERT treatments under investigation include the substrate inhibitor miglustat, which is in Phase III development for Niemann–Pick disease and Tay Sachs disease and Phase II investigation for Fabry's disease.

Should these products be licensed, it is probable that commissioning decisions will need to be made about their utilisation within the NHS. At present within England and Wales this falls under the auspices of NSCAG, as it is responsible for treatments for LSDs within the six designated treatment centres until at least April 2007.

Feasibility and future research

A number of substantial assumptions have been required to produce an estimate of the cost-effectiveness of ERT in Fabry's disease. Where assumptions have been made, attempts were made to ensure that these tend to favour rather than detract from the value of ERT. A similar exercise was not possible for MPS1 owing to the absence of meaningful QoL data and the very limited data available on the natural history of the disease and the effects of laronidase on the progress of the disease.

A strength of this report is that the authors have tried to identify all published data that could inform this review, including all study designs. However the quality and quantity of published data on effectiveness were poor or moderate at best. Therefore, an unusual step in a systematic review was taken to try to obtain and analyse primary observational data that had been routinely collected by clinicians.

Two disease registries exist on patients with Fabry's disease, the Fabry Outcome Study supported by TKT Europe 5S and the International Fabry's disease registry supported by Genzyme Corporation. It is clear that there is a willingness and ability to collect data on patients with Fabry's disease within the global clinical community. Interactions between the clinical community, patients and methodologists to ensure that the most important information is collected could lead relatively rapidly to a more robust evidence base. However, although such patient registries have potential to inform the health technology appraisal of treatments, the value of such registries is limited by the quality of the data collection and analyses that are applied.

The FOS has been designed "by the expert FOS Advisory Group as a European multicenter, open-label survey of enzyme replacement therapy with Replagal in patients with Fabry disease".[177] The objectives of the database are, among others, to "enhance our understanding of the natural history of Fabry's disease, including intra- and interfamilial variation, and to provide high-quality data and analyses to drive improvements in Fabry's disease treatment".

Unfortunately, it was not possible to gain access to the data held within FOS for the purposes of this review owing to the time required to approve

access. The structure of the FOS database requires that all participating clinical investigators make the decisions concerning the use and publication of FOS data. It became clear that for access to be granted approval was required from the FOS management board, the European FOS board and all members of the Executive board. Naturally, since membership of these boards is widespread, the opportunities for all to discuss access were limited. At the time of writing the next opportunity for the European FOS board to meet is November 2005 (personal communication). It also appears clear that owing to the complexity and nature of the dataset, the analysis would have to be conducted by the FOS management team, which would require considerable resources on their part. Therefore, for the FOS dataset to be used to achieve the objectives stated above, communication needs to begin well in advance, at least 12 months before start of a project. Discussion should also occur concerning the likely resource impact upon the FOS management team who are required to conduct all analyses on the raw data. It is clear from the natural history review [see the section 'Natural history of Fabry's disease' (p. 30)] within this report that the published data reporting the natural progression of Fabry's disease is limited. Therefore, there is no, or very little, knowledge of how the rate and severity of the multiple clinical manifestations of Fabry's disease progress over time or of the correlation between these manifestations. The FOS represented one source of data potentially useful to contribute to the understanding of the natural history of the disease and indeed the impact of ERT upon the natural progression. Appendix 4 describes a modelling exercise that would have been undertaken had full access to the FOS database been achieved within the time frame.

For future research using the FOS database to be feasible, it is clear that a greater length of time is required.

As with the FOS above, it became clear at an early stage that the timescale for accessing data in the second Fabry's registry, the International Fabry's Registry, and the recently launched International MPS1 registry (also supported by Genzyme), would be longer than that available. This was in part informed by our previous experience of attempting to access data held in the International Gaucher's Registry.[1]

All these registries rely on voluntary submission of data by participating clinicians, hence there are bound to be questions around the selectivity of the patient sample that they contain and the completeness of the data on individual patients. Furthermore, these registries were only established at the time marketing approval was granted and therefore will contain limited data, if any, on the natural history of untreated patients. Through previous experience of the Gaucher's International Registry, it is also apparent that even after more than 12 years of data collection such registries may not contain meaningful longitudinal data owing to incomplete data ascertainment.[1]

For MPS1, the authors of this report were fortunate to be able to access readily anonymised data held by the Society for Mucopolysaccharide Diseases (UK), a UK registered charity, which appears to have identified and obtained at least minimal data on most, if not all, diagnosed UK MPS1 patients born since the early 1980s. The Society seems very proactive in following and engaging with patients and carers and further developing their data collection process to monitor progression of disease in patients. Access to the dataset was readily obtained and requests for specific data, which could be analysed by the authors, were quickly dealt with. Owing to the length of existence of the data collection exercise and the strength of patient ascertainment, it may contain the best opportunity available to assess the natural history of MPS1 in the absence of ERT. Owing to the time available during this review, analyses were only possible on data on prevalence and mortality. Data on the latter will be invaluable in assessing the effect of ERT in coming years. Although the dataset contains many key data, it does have limitations and there are two dimensions that the society should be encouraged to develop. As there are currently no major data on the QoL of MPS1 patients, the society and the contributing clinicians should begin to measure this parameter using a utility-based instrument. However, it is acknowledged that there is an issue with utilising such a measure in children. Second, as far as possible, the society should continue to expand the collection of data related to disease progress so that the impact of ERT can be better measured. This should include major clinical events and interventional procedures and the adoption of a validated severity score index, should one be developed.

Given the above, it is nevertheless very unlikely the ICER could be brought down by the orders of magnitude required to make ERT an efficient use of health service resources by current thresholds. Therefore, from the single perspective of informing health policy commissioning decisions,

whatever the findings of such research, they are likely to be redundant. If the NHS decides that it is important to provide ERT regardless of its cost-effectiveness, then refining the precision of the ICER estimate becomes unnecessary.

On the other hand, in view of the extremely high cost of ERT, further research could lead to evidence-based changes in practice that might generate considerable savings or lead to more effective treatment regimes for patients. Focused efforts in the following main areas might be particularly rewarding:

1. Fabrazyme and Replagal have been licensed for the treatment of Fabry's disease at vastly different recommended dosages yet with approximately the same high cost per patient. Although both are claimed to be effective, this very large dose discrepancy implies that either there are subtle differences between the products or that the clinical effect achieved may be sub-optimal with one or the other and/or that beyond a certain point dose level is superfluous to effect. A head-to-head comparison of products could address these uncertainties. Such an investigation avoids ethical issues around withholding an effective treatment from patients that are sometimes levelled at placebo comparisons.
2. There is an issue about whether or not the patients used in the various clinical trials were actually the best patients to judge the effectiveness and cost-effectiveness of ERT. Patients may have been enrolled not because they were representative of the disease but because they possessed manifestations that allow measurability of an improvement in the primary outcome. For example, in the RCT on laronidase for MPS1 the outcomes (FVC or 6-minute walking distance) were chosen by the need to demonstrate an effect of treatment in the short term in a slowly progressing disease. Furthermore, the patients were chosen by their ability to perform the outcome measure. In reality, both more and less severely affected patients were probably excluded from this study, leading to some uncertainties around the generalisability of findings. Further research on wider populations would be welcomed, as would identification of any subgroups of patients that may be particularly responsive or unresponsive to treatment. The data registries already in existence may contain sufficient numbers of patients and follow-up information for such analysis to begin to be undertaken.
3. An extension of the above would be to identify if there are treatment strategies that could be developed, particularly for severely affected paediatric patients, that might meet current standards of efficiency within the NHS.
4. A contentious area is the treatment of mildly symptomatic and/or asymptomatic patients with (low-dose) ERT to prevent overt symptoms/disease and reduce residual disease burden and associated costs. This will remain a contentious issue without supporting evidence.
5. The following should also be encouraged:
   (a) the development and validation of a disease severity index for MPS1 and the continued development and validation of the MSSI for Fabry's disease
   (b) the general collection of QoL data in a utility format.

Data collection registries

As the number of ERTs for LSDs and other rare and ultra-rare diseases is likely to increase, encouraged by the orphan drug legislation, commissioning decisions will have to be made once the ERTs have been given marketing approval. It is imperative that the issues raised in undertaking this Health Technology Assessment (and that on Gaucher's diseases[1]) are addressed in order to aid future assessments of clinical and cost-effectiveness. The key recommendations are outlined below.

As the volume and quality of literature available on the natural history of a given disease in the absence of ERT are likely to be limited, it is imperative that evidence gathering begins as early as possible. It would not be unreasonable to suggest that a registry should be created and data collection commence at the latest at the time an application for orphan drug status is made.

Such a data collection exercise should be proactively managed to ensure as complete an ascertainment of diagnosed patients in a defined general population as possible in order to minimise selection bias. Ideally this should be undertaken at the national level for the UK.

The data collected should include all-important clinical parameters including HRQoL utilising a utility-based instrument. Parameters related to utilisation of health care resources should also be collected.

Once entered into the registry, patients should be proactively followed up to ensure that the registry contains complete patient-level data.

As there will almost certainly be a need for primary analyses of registry data as part of any assessment of the clinical and cost-effectiveness of ultra-orphan drugs, formal procedures for requesting patient level data should be in place.

Access to suitably anonymised data from patient registries should be made available in a timely fashion to independent researchers for analysis. A necessary commitment of such open access should be to submit the results of such analysis to transparent peer review. The access arrangements operated by data archives such as that run by the Economic and Social Research Council in the UK provide one model for such arrangements.

Pharmaceutical companies currently support the large international registries. Should they not be willing to encourage or support registries adhering to the recommendations above, then the registries may have to be funded from other sources.

With regard to other research, it is important to note that the monopoly position of ERT treatments should not be used as an excuse to stifle important research on alternative interventions. For example, trials of miglustat, an oral substrate reduction therapy, in Gaucher's disease were restricted by the argument that it was not ethical to enrol patients in the trial of the drug unless they could not tolerate or were inappropriate for treatment with imiglucerase (Cerezyme®) because it would have deprived patients of an ethical treatment. This subsequently led to a limited license for miglustat. We believe that the stated ethical principle is erroneous and can be demonstrably shown to not have been applied in other areas of clinical research and drug development. This is particularly pertinent as miglustat is currently in Phase II development for Fabry's disease.

Finally, it may be pertinent to undertake an assessment of the development and production costs of ERT.

Conclusion

Despite limited evidence, there is little doubt that ERT is effective to some extent in the treatment of most symptoms of Fabry's disease and MPS1.

The precise degree of health gain produced is uncertain in both diseases because of limited comparative studies, information about the diseases prior to the introduction of ERTs, long-term follow-up to ascertain any effect on morbidity and mortality and, in the case of MPS1, the absence of measurement of QoL in a utility format.

Although beneficial to patients, treatment is very expensive. It costs on average £85,000 per year for each 50-kg patient with Fabry's disease and £95,000 (£335,000) for each child (adult) with MPS1. Treatment is life-long. Therefore, although lifetime treatment with ERT will produce a health gain, it does so at an extremely high cost. The estimated ICER for Fabry's disease is around £252,000 per QALY, which is well above thresholds that are normally considered acceptable to the NHS. For comparison, the ICER for ERT for Gaucher's disease is over £300 per QALY. Thus far it has not been possible to calculate an ICER for MPS1 owing to the lack of sufficient data.

Although the authors have undertaken a wide review of the published literature and also sought unpublished data from registries, there remain many uncertainties and assumptions within the effectiveness data and economic model for Fabry's disease. In fact, a more detailed economic analysis for Fabry's disease was planned based on the data that should be available from the FOS registry if time and access permitted. However, when the high cost of annual treatment is considered, for a condition that is for most patients not life threatening in the short term, it is immediately apparent that the ICER estimates are almost certainly of the right order. Moreover, wherever possible in the base case of the economic model, assumptions were chosen which favoured treatment. In fact, all treated patients were assumed to experience normal health. Hence the true ICER is probably higher than that stated above.

The extremely high price of ERTs is usually attributed to the fact that the diseases are rare, but it cannot be ignored that orphan drug legislation usually gives companies a monopoly position in the treatment of a disease. The legislation may act to keep prices high by deterring competition, which may also deter purchasers from using standards for assessing cost-effectiveness that they would normally apply. It is of interest that the annual prices per patient of both ERTs for Fabry's disease (Replagal and Fabrazyme) are not dissimilar even though the doses of the ERTs are vastly different.

With new ERTs of LSDs in development, we believe that it is important that these are tested in well-designed trials and that for each disease existing ERTs are not utilised as a barrier to the development of these and non-ERT treatments.

To permit the evaluation of the clinical and cost-effectiveness of emerging ERTs, it is vital that disease registries are established as early as possible, ideally prior to the development of an ERT. These should have as far as possible a comprehensive ascertainment of diagnosed patients. The remit of the registries should be to collect sufficient data to ascertain the natural history of the disease and the effect of ERT on this natural history in order to compensate for the limited data in the published literature. The data should include HRQoL in a utility format. All registries should allow timely access to anonymised patient data for the purpose of health technology assessment and the advancement of patient care.

Acknowledgements

Many people generously shared their time, expertise and data with us during the production of this report. We are extremely grateful to them. The views expressed in this report, however, are those of the authors and should not be interpreted as representing the views of those who helped us.

We would particularly like to thank the following: Dr Ed Wraith (Royal Manchester Children's Hospital), Dr Atul Mehta (the Royal Free Hospital), Christine Lavery MBE and Maureen Cummins [The Society for MPS Diseases (UK)], Dr Alec Miners, Dr Amanda Burls, Genzyme Therapeutics and Transkaryotic Therapies Inc.

We would also like to thank the following for statistical advice and/or assistance with components of the economic modelling: Josie Sandercock, Dr Nicola Cooper, Lily Yao, Sue Jowett and Professor Stirling Bryan.

Contribution of authors

Martin Connock (Systematic Reviewer) located and extracted natural history data, reviewed natural history literature, contributed to writing background and prevalence sections, analysed survival data, wrote sections of the report and commented on drafts of the report. Ariadna Juarez-Garcia (Health Economist) constructed and analysed the cost-effectiveness model, wrote sections of the report, reviewed the quality of life literature, located and extracted data relating to economic evaluation and commented on drafts of the report. Emma Frew (Health Economist) contributed to the development of the Fabry's cost-effectiveness model, located and extracted data relating to economic evaluation, reviewed the quality-of-life literature, wrote sections of the report, commented on drafts of the report and identified and liaised with collaborators. Anke Mans (Systematic Reviewer) extracted data, reviewed and wrote sections on prevalence of Fabry's disease and clinical effectiveness of enzyme replacement therapy in Fabry's disease and commented on drafts of the report. Janine Dretzke (Systematic Reviewer) contributed to clinical effectiveness, natural history and prevalence sections for Fabry's disease. Anne Fry-Smith (Information Specialist) devised and implemented the bibliographic database searches and wrote the sections on literature searches. David Moore (Research Analyst) coordinated the report, developed the protocol, identified and liaised with collaborators, undertook the clinical effectiveness and prevalence review of MPS1, directed the clinical effectiveness, natural history and prevalence review of Fabry's disease, wrote sections of the report, commented on drafts of the report and edited the final report.

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Appendix 1

Search strategies for primary studies

Fabry's disease

Database: MEDLINE (Ovid) 1966 to July week 5 2004

1. fabry$.mp. (1582)
2. fabry disease.mp. (1246)
3. alpha galactosidase a deficiency.mp. (29)
4. alfa galactosidase a deficiency.mp. (0)
5. ceramide trihexosidase deficiency.mp. (1)
6. fabrazyme.mp. (7)
7. agalsidase beta.mp. (26)
8. alfa galactosidase beta.mp. (0)
9. alpha galactosidase beta.mp. (69)
10. recombinant human alfa galactosidase.mp. (0)
11. recombinant human alpha galactosidase.mp. (11)
12. recombinant human a galactosidase.mp. (0)
13. a galactosidase a deficiency.mp. (0)
14. replagal.mp. (6)
15. agalsidase alfa.mp. (25)
16. agalsidase alpha.mp. (2)
17. alfa galactosidase alfa.mp. (0)
18. alpha galactosidase alpha.mp. (79)
19. or/1-18 (1710)

Database: EMBASE (Ovid) 1980 to week 32 2004

1. fabry$.mp. (1121)
2. fabry disease.mp. (993)
3. alpha galactosidase a deficiency.mp. (24)
4. alfa galactosidase a deficiency.mp. (0)
5. ceramide trihexosidase deficiency.mp. (0)
6. fabrazyme.mp. (74)
7. agalsidase beta.mp. (70)
8. alfa galactosidase beta.mp. (0)
9. alpha galactosidase beta.mp. (46)
10. recombinant human alfa galactosidase.mp. (0)
11. recombinant human alpha galactosidase.mp. (3)
12. recombinant human a galactosidase.mp. (7)
13. a galactosidase a deficiency.mp. (95)
14. replagal.mp. (64)
15. agalsidase alfa.mp. (74)
16. agalsidase alpha.mp. (9)
17. alfa galactosidase alfa.mp. (0)
18. alpha galactosidase alpha.mp. (84)
19. or/1-18 (1286)

Database: CINAHL (Ovid) 1982 to August week 1 2004

1. fabry$.mp. (12)
2. fabry disease.mp. (6)
3. alpha galactosidase a deficiency.mp. (1)
4. alfa galactosidase a deficiency.mp. (0)
5. ceramide trihexosidase deficiency.mp. (0)
6. fabrazyme.mp. (0)
7. agalsidase beta.mp. (0)
8. alfa galactosidase beta.mp. (0)
9. alpha galactosidase beta.mp. (0)
10. recombinant human alfa galactosidase.mp. (0)
11. recombinant human alpha galactosidase.mp. (0)
12. recombinant human a galactosidase.mp. (0)
13. a galactosidase a deficiency.mp. (1)
14. replagal.mp. (0)
15. agalsidase alfa.mp. (0)
16. agalsidase alpha.mp. (0)
17. alfa galactosidase alfa.mp. (0)
18. alpha galactosidase alpha.mp. (0)
19. or/1-18 (12)
20. from 19 keep 1-12 (12)

Database: Cochrane Library (CENTRAL) Issue 3 2004

#1.fabry* 70
#2.FABRY DISEASE single term (MeSH)13
#3.(alpha next galactosidase next deficiency)3
#4.(alfa next galactosidase next deficiency)0
#5.(ceramide next trihexosidase next deficiency)0
#6.fabrazyme2
#7.(agalsidase next beta)2
#8.(alfa next galactosidase next beta)0
#9.(alpha next galactosidase next beta)0
#10.(recombinant next human next alfa next galactosidase)0
#11.(recombinant next human next alpha next galactosidase)1
#12.(recombinant next human next galactosidase)0
#13.(galactosidase next deficiency)10
#14.replagal 0
#15.(agalsidase next alfa)4
#16.(agalsidase next alpha)1
#17.(alfa next galctosidase next alfa)0
#18.(alfa next galctosidase next alpha)0
#19.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)78

Database: Science Citation Index (Web of Science) 1981–2004

#1. TS=fabrys

#2. TS=alpha galactosidase a deficiency
#3. TS=alfa galactosidase a deficiency
#4. TS=ceramide trihexosidase deficiency
#5. TS=fabrazyme
#6. TS=agalsidase beta
#7. TS=alfa galactosidase beta
#8. TS=alpha galactosidase beta
#9. TS=recombinant human alfa galactosidase
#10. TS=recombinant human alpha galactosidase
#11. TS=recombinant human a galactosidase
#12. TS=a galactosidase a deficiency
#13. TS=replagel
#14. TS=agalsidase alfa
#15. TS=agalsidase alpha
#16. TS=alfa galactosidase alfa
#17. TS=alpha galactosidase alpha
#18. #1 OR #2 OR#3 OR #4 OR #5 OR #6 OR#7 OR#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 Or #15 Or #16 OR #17

DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED; Timespan=1981-2004

MPS1 disease

Database: MEDLINE (Ovid) 1966 to July week 5 2004

1. mps-1.mp. (73)
2. mps1.mp. (78)
3. mps-I.mp. (139)
4. mpsI.mp. (18)
5. mucopolysaccharidosis type I.mp. (101)
6. mucopolysaccharidosis type 1.mp. (6)
7. mucopolysaccharidosis I.mp. (720)
8. mucopolysaccharidosis 1.mp. (8)
9. aldurazyme.mp. (1)
10. iduronidase.mp. (376)
11. laronidase.mp. (5)
12. hurler$.mp. (650)
13. hurler-scheie.mp. (87)
14. hurler scheie.mp. (87)
15. scheie.mp. (196)
16. or/1-15 (1275)

Database: EMBASE (Ovid) 1980 to week 32 2004

1. mps-1.mp. (55)
2. mps1.mp. (41)
3. mps-I.mp. (116)
4. mpsI.mp. (26)
5. mucopolysaccharidosis type I.mp. (96)
6. mucopolysaccharidosis type 1.mp. (6)
7. mucopolysaccharidosis I.mp. (62)
8. mucopolysaccharidosis 1.mp. (6)
9. aldurazyme.mp. (26)
10. iduronidase.mp. (236)
11. laronidase.mp. (28)
12. hurler$.mp. (565)
13. hurler-scheie.mp. (69)
14. hurler scheie.mp. (69)
15. scheie.mp. (119)
16. hurler syndrome/ (459)
17. scheie syndrome/ (98)
18. or/1-17 (846)

Database: CINAHL (Ovid) 1982 to August week 1 2004

1. mps-1.mp. (0)
2. mps1.mp. (0)
3. mps-I.mp. (2)
4. mpsI.mp. (13)
5. mucopolysaccharidosis type I.mp. (1)
6. mucopolysaccharidosis type 1.mp. (0)
7. mucopolysaccharidosis I.mp. (2)
8. mucopolysaccharidosis 1.mp. (0)
9. aldurazyme.mp. (0)
10. iduronidase.mp. (1)
11. laronidase.mp. (0)
12. hurler$.mp. (3)
13. hurler-scheie.mp. (0)
14. hurler scheie.mp. (0)
15. scheie.mp. (0)
16. or/1-15 (19)
17. from 16 keep 1-19 (19)

Database: Cochrane Library (CENTRAL) Issue 3 2004

#1.mps-11
#2.mps-i0
#3.mpsi0
#4.mps10
#5.(mucopolysaccharidosis next type next i)0
#6.(mucopolysaccharidosis next type-1)0
#7.(mucopolysaccharidosis next i)3
#8.mucopolysaccharidosis-10
#9.MUCOPOLYSACCHARIDOSIS I single term (MeSH)2
#10.aldurazyme1
#11.iduronidase1
#12.laronidase1
#13.hurler*5
#14.hurler-scheie2
#15.(hurler next scheie)2
#16.scheie54
#17.(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)58

Database: Science Citation Index (Web of Science) 1981–2004

#1. TS=(mps-1)
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#3. TS=(mps-I)
#4. TS=mpsI
#5. TS=(mucopolysaccharidosis type I)
#6. TS=(mucopolysaccharidosis type 1)
#7. TS=(mucopolysaccharidosis I)
#8. TS=(mucopolysaccharidosis 1)
#9. TS=aldurazyme
#10. TS=iduronidase
#11. TS=laronidase
#12. TS=hurler*
#13. TS=hurler-scheie
#14. TS=hurler scheie
#15. TS=scheie
#16. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 DocType=All document types; Language=All languages

Appendix 2

Tables for effectiveness of ERT for Fabry's disease

Data from the relevant studies are given in *Tables 37–44*.

TABLE 37 *Pain-related outcomes: RCTs and non-comparative extensions*

Study (design) Enzyme	Period studied	Outcome measured	Results: ERT	Results: Placebo	Results: Difference (*p*-value)
Eng (2001)[45] (RCT)	5 months	**Short-form McGill Pain Questionnaire (scores 0 to 45)**			ERT – comparator
Fabrazyme		Mean decrease in scores	*n* = 29	*n* = 29	
		Total pain	3.9	4.7	–0.8 (ns)
		Sensory	3.0	3.2	–0.2 (ns)
		Visual analogue scale	1.0	1.5	–0.5 (ns)
		Affective	1.0	1.5	–0.5 (ns)
		Present pain intensity	0.7	0.5	0.2 (ns)
Wilcox (2004)[49] (non-comparative extension of Eng[45])	36 months	**McGill Pain Questionnaire scores**	"Remained low throughout extension study"		
Fabrazyme		**Pain medication use** Number of patients stopping medications by end of period	5 of 34		Not stated
Schiffmann (2001)[42] (RCT)	6 months	**Brief Pain Inventory scores (0–10) (mean ± SE)**			–1.9 vs –0.7
Replagal		Worst pain	*n* = 14	*n* = 12	Greater decrease in
		Baseline	6.2 ± 0.46	7.5[c]	ERT group from
		Month 6	4.3 ± 0.73	6.8[c]	baseline over 24 weeks ($p = 0.02$)
		Overall severity	*n* = 14	*n* = 12	–1.1 vs –0.7
		Baseline	3.8 ± 0.44	5.4 ± 0.45	(ERT vs placebo)
		Month 2	3.1 ± 0.54	5.2 ± 0.67	Greater decrease in
		Month 4	3.3 ± 0.67	5.2 ± 0.59	ERT group from
		Month 6	2.7 ± 0.54	4.7 ± 0.65	baseline over 24 weeks ($p = 0.02$)
		Pain-related QoL	*n* = 14	*n* = 12	–1.1 vs –0.6
		Baseline	3.2 ± 0.55	4.8 ± 0.59 (SE)	Greater decrease in
		Month 2	3.2 ± 0.61	4.1 ± 0.71	ERT group from
		Month 4	2.8 ± 0.67	4.6 ± 0.75	baseline over
		Month 6	2.1 ± 0.56	4.2 ± 0.74	24 weeks ($p = 0.05$)
		Number of patients able to discontinue medication by week 8	*n* = 11 4	*n* = 12 0	4 ($p = 0.03$)

continued

TABLE 37 *Pain-related outcomes: RCTs and non-comparative extensions (cont'd)*

Study (design) Enzyme	Period studied	Outcome measured	Results		
			ERT	**Placebo**	**Difference (*p*-value)**
Schiffmann (2003)[53] (non-comparative extension of Schiffmann[42])	24 months	**Brief Pain Inventory scores**			
		Overall severity	*n* = unclear[a]	*n* = 10[b]	No differences between groups
		Month 6	4.3[c]	6.9[c]	
		Month 24	5.0[c]	4.5[c]	
Replagal		Additional number of patients able to discontinue medication during extension	2		

[a] On ERT for months 0–24.
[b] On ERT for months 6–24.
[c] Estimated from graph.

TABLE 38 *Pain-related outcomes: uncontrolled studies*

Study (design) Enzyme	Period studied	Outcome measured	Results			
			Before ERT (baseline)	**After treatment with ERT**	**Difference (*n*)**	***p*-Value (before vs after)**
Hoffmann (2005)[62] (same study as Beck[43])[a]	2 years	**Mean Brief Pain Inventory scores**			(Differences calculated)	
		Worst pain				
		Baseline	5.1			
Replagal		*1 year*		4.6	–0.5 (*n* = 41)	ns
		2 years		4.0	–1.1 (*n* = 20)	<0.05
		Least pain				
		Baseline	2.1			
		1 *year*		2.1	–0.0 (*n* = 41)	ns
		2 *years*		1.9	–0.8 (*n* = 20)	ns
		Average pain				
		Baseline	4.1			
		1 *year*		3.5	–0.6 (*n* = 41)	ns
		2 *years*		2.5	–1.6 (*n* = 20)	<0.05
		Pain now				
		Baseline:	2.9			
		1 year		2.5	–0.4 (*n* = 41)	ns
		2 years		1.6	–1.3 (*n* = 20)	<0.05
Dehout (2004)[58] (non-comparative before–after)	6 months	**Abdominal pain** Number of patients with abdominal pain severity score of	*n* = 11	*n* = 11		
Replagal		0 (*no pain*)	1	4		For improvement in pain severity <0.02
		1 (*mild*)	2	5		
		2 (*moderate*)	4	1		
		3 (*severe*)	3	1		
		4 (*very severe*)	1			

continued

TABLE 38 *Pain-related outcomes: uncontrolled studies (cont'd)*

Study (design) Enzyme	Period studied	Outcome measured	Results			
			Before ERT (baseline)	**After treatment with ERT**	**Difference (*n*)**	***p*-Value (before vs after)**
		Number of patients with abdominal pain frequency score of 0 (*never*) 1 (*rarely*) 2 (*monthly*) 3 (*weekly*) 4 (*daily*)	*n* = 11 1 1 2 3 4	*n* = 11 4 4 1 1 1		For improvement in pain frequency <0.02
Guffon (2004)[60] (retrospective non-comparative before–after) Fabrazyme	Mean of 18 months	**Pain in extremities on scale of 1–10** (1 = none; 10 = strong) Severity: (*mean* ± *SD*)	4.69 ± 3.11	2.25 ± 1.69	(Differences calculated) –2.44 (*n* = 16)	0.012. Patients on treatment for ≥24 months reported fewer episodes than patients treated for <24 months
		Number of pain crises per month (mean ± SD)	4.38 ± 7.46	2.21 ± 7.23	–2.17 (*n* = 17)	0.019
		Duration of pain crises (hours) (mean ± *SD*)	8.69 ± 13.19	2.98 ± 6.48	–5.71 (*n* = 16)	0.097
Hilz (2004)[61] (before–after case series) Fabrazyme	18–23 months	**Neuropathic pain (total symptom score, TSS) (mean ± SD)**	1.76 ± 1.97	0.83 ± 1.53	(Difference calculated) –0.93 (*n* = 11)	0.038
Eng (2001)[59] (non-comparative dose escalation) Fabrazyme	5 infusions every 48 h or 2-weekly (variable doses)	**Short-form McGill Pain Questionnaire**	Overall pain and present pain intensity scores improved with all doses (p = 0.03 and 0.004 respectively) (no further details given)			
Cianciaruso (2003)[56] (non-comparative before–after) Fabrazyme	1 year (ongoing at time of report)	**Number and intensity of painful crises**	In the 4 treated patients for whom results were available, the intensity and number of pain crises were reduced (no further details)			

[a] Different results reported in Beck and colleagues;[43] according to author (Mehta A, University College London, personal communication, 2005) results in Hoffmann and colleagues[62] are correct.

TABLE 39 *Renal function outcomes*

Study (design) Enzyme	Period studied	Outcome measured	Results: ERT	Results: Comparator	Results: Change (before vs after ERT)
Schiffmann (2001)[42] (RCT)	6 months	Mean fraction of normal glomeruli[a] (%)	*n* = 12	*n* = 9	(*p*-Value for difference between groups)
		At baseline	39.9 ± 6.6 (SE)	59.6 ± 6.8 (SE)	
Replagal		*At week 24*	48.0 ± 8.9	43.6 ± 10.1	8.1 vs –16 (*p* = 0.01)
		Mean inulin clearance (ml/min/1.73 m^2)	*n* = 13	*n* = 11	
		At baseline	77.2 ± 5.57	90.9 ± 12.07	
		At week 24	71.0 ± 4.47	71.5 ± 9.66	–6.2 vs –19.5 (*p* = 0.19)
		Mean creatinine clearance (ml/min/1.73 m^2)	*n* = 13	*n* = 11	
		At baseline	92.7 ± 6.2	100.6 ± 12.2	
		At week 24	94.8 ± 7.7	84.5 ± 10.6	2.1 vs –16.1 (*p* = 0.02)
Wilcox (2004)[49] (non-comparative extension of Eng[45])	36 months		(in ERT/ERT and placebo/ERT groups)		
		Mean SCr (mg/dl)			
		At entry to extension	0.8 and 0.9 (*n* = 49)		Remained normal in both groups
Fabrazyme		*At 36 months*	0.9 and 1.0 (*n* = 48)		
		Mean GFR (ml/min/1.73 m^2)			
		At 36 months	129.5 and 107.1		Remained normal in both groups
		Mean GFR in patients with low GFR (<90 ml/min/1.73 m^2)	(all patients combined)		Not reported
		At start of RCT	68.6 ± 19.65 (SD)		
		At 36 months	79.6 ± 6.27		
Baehner (2003)[55] (non-comparative before–after study)	17–41 weeks	Mean creatinine clearance (ml/min/1.73 m^2)	Range of mean values: 65–73		"Creatinine clearance remained stable throughout study"
Replagal					
Beck (2004)[43] (non-comparative before–after study)	Up to 56 months	GFR (ml/min/1.73 m^2) (only analysed in patients with baseline GFR <90 ml/min/1.73 m and >18 years old)			
Replagal		*In patients with baseline GFR 60–90:*			
		At baseline:	70 (*n* = 57)		
		At 1 year	73 (*n* = 57)		ns (before vs after)
		At 2 years	72 (*n* = 30)		
		In patients with baseline GFR 30-60[a] baseline:	42 (*n* = 26)		
		At 1 year	44 (*n* = 26)		ns (before vs after)
		At 2 years	45 (*n* = 18)		

continued

TABLE 39 *Renal function outcomes: uncontrolled studies (cont'd)*

Study (design) Enzyme	Period studied	Outcome measured	Results		
			ERT	Comparator	Change (before vs after ERT)
Cianciaruso (2003)[56] (non-comparative dose-finding study) Fabrazyme	1 year (ongoing at time of study)	Proteinuria	Not reported		In 2 of the 4 patients for whom results were available, proteinuria was reduced (no further details)
Eng (2001)[59] non-comparative dose-finding study) Fabrazyme	48 h to 2 weeks (5 infusions only)	Renal magnetic resonance imaging	Not reported		"Unchanged"

[a] Glomeruli without mesangial widening or sclerosis.
[b] Not start of extension phase.
[c] 3 patients with GFR <30 were included in this group.
SCr, serum creatinine.

TABLE 40 *Heart function outcomes*

Study (design) Enzyme	Period studied	Outcome measured	Results		
			ERT	Comparator	p-Value for difference
Schiffmann (2001)[42] (RCT) Replagal	6 months	QRS complex duration (ms) Mean change ± SE	(*n* not reported) –2.4 ± 3.90	(*n* not reported) 3.6 ± 1.17	0.047 (between groups)
Baehner (2003)[55] (non-comparative before–after study) Replagal	Up to 55 weeks (~13 months)	QRS complex duration (ms) Mean change ± SE *At week 13* *At week 27* *At week 41*	 –5.5 ± 2.96 (*n* = 15) –8.7 ± 2.60 (*n* = 11) –3.6 ± 1.83 (*n* = 5)		 0.086 (vs baseline) 0.007 0.121
		Left ventricular mass index (g/m^2) Mean change ± SE *At week 13* *At week 27* *At week 41*	 –5.5 ± 5.9 (*n* = 15) –23.0 ± 5.7 (*n* = 11) –25.2 ± 8.1 (*n* = 7)		 0.372 0.003 0.039
Beck (2004)[43] (non-comparative before–after study) Replagal	17–56 months	Mean ventricular wall thickness (mm) *At baseline* *At 1 year* *At 2 years*	 14 12 (*n* = 52) 10 (*n* = 7)		 <0.05 (vs baseline) <0.05
		Left ventricular mass indexed to height >50 $g/m^{2.7}$ *At baseline* *At 1 year* *At 2 years*	 65 (60 for 2-year group) 50 (*n* = 52) 40 (*n* = 17)		 <0.05 <0.05

continued

TABLE 40 *Heart function outcomes (cont'd)*

Study (design) Enzyme	Period studied	Outcome measured	Results		
			ERT	**Comparator**	**p-Value for difference**
Weidemann (2003)[64] (non-comparative before–after study)	12 months	Left ventricular wall thickness (mm)			
		Mean ± SE	*n* = 10		
		At baseline	13.8 ± 0.6		
Fabrazyme		*At 12 months*	11.8 ± 0.6		<0.05 (vs. baseline)
		Myocardial mass (g)			
		Mean ± SE	*n* = 10		
		At baseline	201 ± 18		
		At 12 months	180 ± 21		<0.05
		Peak systolic strain rate (radial function) (s^{-1})			
		Mean ± SE	*n* = not reported		
		At baseline	2.8 ± 0.2		<0.05
		At 12 months	3.7 ± 0.3		
		Peak systolic strain rate (longitudinal function) (s^{-1})			
		Mean ± SE	*n* = not reported		
		At baseline	1.1 ± 0.1		<0.05
		At 12 months	1.4 ± 0.1		
Eng (2001)[59] (non-comparative dose-finding study)	48 h to 2 weeks (5 infusions only)	ECG, echocardiogram	Not reported		"Remained unchanged"
Fabrazyme					

TABLE 41 *Neurological outcomes*

Study (design) Enzyme	Period studied	Outcome measured	Results: Before/after or ERT/placebo	Results: Difference (Diff.) *p*-Value
Schiffmann (2003)[53] (non-comparative before–after extension of RCT Schiffmann[42])	3 years	**Sensory abnormalities** Temperature sensation in extremities	Mean change estimated from graphs (*n* up to 25 but not reported for outcome)	"Significant changes from baseline"
		Cold sensation threshold in foot	ERT/ERT and placebo/ERT	
		Warm sensation threshold in foot	3 and 2 1 and 3	
Replagal				
Guffon (2004)[60] (retrospective non-comparative before–after study)	Mean 18.7 months (range: 6–29)	**Sensory abnormalities** Heat tolerance on scale of 1–10 (no details given) (mean ± SD)	*n* = 17 2.76 ± 1.64/5.76 ± 1.92	0.002
Fabrazyme				
Hilz (2004)[61] (before–after case series)	18–23 months	**Sensory abnormalities** Vibratory detection thresholds at first toe[a] (mean ± SD)	*n* = 22 15.5 ± 3.5/14.3 ± 4.1	Diff. 1.2 <0.05
Fabrazyme		Cold detection threshold	19.8 ± 11.1/19.9 ± 10.2	Diff. –0.1 ns
		Heat-pain perception threshold, 0.5[b]	22.3 ± 6.7/19.4 ± 1.3	Diff. 2.9 <0.01
		Heat-pain perception threshold, 5.0[c]	27.3 ± 5.6/22.5 ± 2.3	Diff. 4.8 <0.01
Hajioff (2003)[46] (RCT)	6 months	**Hearing** Median high-frequency hearing loss (dB ISO)	ERT: *n* = 14 ears, –5[d] Placebo: *n* = 16 ears, –3.3[d]	Diff.1.7 ns
Replagal				
Hajioff (2003)[46] (open-label extension)	24 months	**Hearing** "Improvement in median high-frequency hearing loss (dB ISO)"[e]		
Replagal		*At 18 months*	2.1, *n* = 20 ears	0.02
		At 30 months	4.9, *n* = 20 ears	0.004
Hajioff (2003)[54] (further extension of open-label phase, with addition of 8 men and 2 women; non-comparative before–after)	Extension to 42 months (new patients had ERT for 6–30 months)	**Hearing** "Improvement in median high-frequency hearing loss (dB ISO)"[e]		
		At 18 months	1.5, *n* = 26 ears	0.07
		At 30 months	5.0, *n* = 24 ears	0.006
		At 42 months	4.0, *n* = 20 ears	0.01
Replagal				

continued

TABLE 41 *Neurological outcomes (cont'd)*

Study (design) Enzyme	Period studied	Outcome measured	Results: Before/after or ERT/placebo	Results: Difference (Diff.) *p*-Value
Conti (2003)[57] (noncomparative before–after study) Replagal	6 months (n = 8) 12 months (n = 4)	**Hearing** Hearing loss	Unchanged except unilateral worsening in 1 patient associated with vertigo (time point not reported)	Not reported
		Audiological evaluation	Unchanged except mild unilateral improvement in 1 patient and unilateral progression in 1 patient	Not reported
Eng (2001)[59] (non-comparative dose escalation) Fabrazyme	5 infusions every 48 h or 2-weekly (variable doses)	**Fatigue**	Patients anecdotally reported less fatigue	Not reported
Guffon (2004)[60] (retrospective non-comparative before–after study) Fabrazyme	Mean 18.7 months (range 6–29)	**Fatigue on scale of 1–10 (mean ± SD)**	n = 17 5.53 ± 2.85/3.71 ± 2.37	0.046
		Psychological status on scale of 1–10 (mean ± SD)	5.82 ± 2.70/8.12 ± 1.45	0.005
		Frequency of physical exercise on scale of 1–10 (mean ± SD)	2.47 ± 1.66/4.47 ± 2.70	0.007

[a] Vibratory detection thresholds were in the normal range in all patients throughout the study.
[b] Perception of beginning discomfort
[c] Perception of intermediate pain severity
[d] Results taken from graph; numbers are switched around in text of article but "greater decline" stated for treatment group.
[e] This (and the graphs) implies an increase in hearing loss (or decrease in hearing), but the authors suggest in the text that improvement in hearing occurred.

TABLE 42 *Other outcomes*

Study (design) Enzyme	Period studied	Outcome measured	Results: ERT	Results: Comparator	Results: *p*-Value for difference
Schiffmann (2001)[42] (RCT)	6 months	**Body weight** Change (kg) (Mean ± SD)	(*n* not reported, up to 14) 1.5 ± 0.6	(*n* not reported, up to 12) –1.4 ± 1.3	0.02
Replagal					
Eng (2001)[45] (RCT and open-label extension)	5 months placebo-controlled phase	**Renal endothelial (GL-3)** % of patients free of GL-3 in	*n* = 29 20/29 patients (69%)	*n* = 29 0/29 patients (0%)	<0.001
		Improved	6/29 (21%)		
Fabrazyme		Unchanged	2/29 (7%)		
		Plasma GL-3 (ng/μl)	Median decrease from 13.6 to 0 (from graph)	Median decrease from 13.2 to 10.6 (from graph)	0.001
		Heart GL-3 Mean (± SD) change in score for microvascular endothelial deposit	–0.6 ± 0.7	–0.2 ± 0.8	<0.001
		Skin GL-3 Mean (± SD) change in score for microvascular endothelial deposit	–2.1 ± 0.7	–0.1 ± 1.0	<0.001
	6 months open-label extension	**Plasma GL-3** (ng/μl)	Median decrease remained at 0 (from graph)	Median decrease from 10.6 to 0 (from graph)	Not reported
Thurberg (2002)[47] (same trial as Eng[45])	11 months total	**GL-3 clearance from multiple kidney cell types**	*n* = 21–24	*n* = 17–25	(For placebo-controlled phase)
		Vascular endothelial cells	92–100%	100%	<0.001
		Mesangial cells	100%	90%	<0.001
		Interstitial cells	100%	78%	<0.001
		Arterial endothelial cells	96%	87%	<0.001
		Tubular epithelium	50%	78%	Not reported
		Podocytes	18%	23%	Not reported
Thurberg (2004)[48] (same trial as Eng[45] with extension to 30 months)	30 months	**GL-3 clearance from multiple dermal cell types**	*n* = 3–19	*n* = 5–21	Not reported
		Complete clearance from capillary endothelial cells maintained in	89%	85%	
		Reduction in score in vascular smooth muscle cells and perineurium	33–61%	60–75%	
Schiffmann (2001)[42] (RCT)	6 months	**Plasma GL-3**	*n* = 14	*n* = 11	
		At baseline	12.14 ± 0.907	10.96 ± 1.087	
		At week 24	5.58 ± 0.536	10.19 ± 1.271	
Replagal		*Change*	–6.56 ± 0.751	–0.77 ± 0.497	0.005

continued

TABLE 42 *Other outcomes (cont'd)*

Study (design) Enzyme	Period studied	Outcome measured	Results ERT	Comparator	*p*-Value for difference
Baehner (2003)[55] (non-comparative before–after study)	Up to 55 weeks	**Plasma GL-3** *At week 13* *At week 27*	*n* = 15 "Decreased from baseline" (data not shown)		0.029 ns
Replagal					
Eng (2001)[59] (non-comparative dose-escalation study)	Up to 10 weeks	**Plasma GL-3** *At baseline*	*n* = 15 17.1 ± 12.8		"Decreased in dose-dependent manner"; *p* not reported
Fabrazyme		**Diaphoresis**	Patients anecdotally reported an increased ability to sweat		Not reported
Schiffmann (2003)[53] (non-comparative before–after extension of RCT Schiffmann[42])	3 years	**Diaphoresis** *n* = 17 Acute change in sweat response to iontophoresed acetylcholine (measured once after an ERT infusion at end of study)	Improved 24–72 h after ERT infusion, returned to pre-infusion level after 7 days		Not reported
Replagal					
Dehout (2004)[58] (non-comparative before–after study)	6 months	**Diarrhoea** Number of patients with diarrhoea frequency score of	*n* = 11		
Replagal		0 (never) 1 (rarely) 2 (monthly) 3 (weekly) 4 (daily)	5/8 0/2 1/0 3/0 2/1		Not reported
Guffon (2004)[60] (retrospective non-comparative before–after study)	Mean 18.7 months (range 6–29)	**Bowel movements** Number of bowel movements per day (mean ± SD)	*n* = 15 3.28 ± 2.77/2.51 ± 2.31		0.058
Fabrazyme					

TABLE 43 *Improvements in Mainz Severity Score Index*[a]

Category	Score before/after (interquartile range)	Median reduction in score (range)
General score (maximum = 18)	8.5 (6–11)/6.5	2 (1–3)[b]
Renal score (maximum = 18)	4 (4–8)/4	0 (0–2)
Cardiovascular score (maximum = 20)	8 (1–14)/6	2 (0–4)[b]
Neurological score (maximum = 20)	11 (9–13)/8	3 (2–5)[b]
Total score (maximum = 76)	32 (26–41)/23	9 (6–12)[b]

[a] Before–after study; duration = 12 months; enzyme = Replagal; *n* = 39
[b] $p < 0.001$. Data taken from Whybra and colleagues.[22]

TABLE 44 *Adverse events*

Study (design) Enzyme	Adverse events	Results (*p*-value compared with control) ERT	Comparator	Comments
Eng (2001)[45] (RCT and non-comparative extension)	Events occurring in ≥ 10% of ERT patients	*n* = 29	*n* = 29	"No significant changes from baseline in echocardiogram, ECG or other safety assessments were observed in either group after week 20 of the double-blind study or after 6 months of the open-label study"
	Rigors (number of patients)	14 (*p* = 0.004)	0	
	Fever	7 (*p* = 0.024)	1	
	Headache	5 (*p* = ns)	2	
Fabrazyme	Chills	4 (*p* = ns)	0	
	Pain related to Fabry's disease	3 (*p* = ns)	1	
	Hypertension	3 (*p* = ns)	0	"Although not considered to be related to [ERT] therapy, skeletal pain was the only other adverse event that occurred more frequently among enzyme-treated patients during the double-blind study (*p* = 0.02)"
	Renal function	"Did not change substantially from baseline, *p* = 0.19"		
	Infusion-associated reactions (mild to moderate) occurred in	34 of 58 (59%)		Reducing infusion rate, giving preventive medications, or both, controlled these reactions
	Withdrawal	1		Patient had positive skin test to ERT after 8th infusion, treatment was discontinued
	IgG seroconversion	51 of 58 patients (88%)		Seroconversion did not affect primary or secondary efficacy end-points
Wilcox (2004)[49] (non-comparative extension of Eng[45])	Incidence of cardiovascular events "at time of this report"	5 of 58 (9%)		
	Infusion reactions			
	At month 18	26 of 57 (46%)		
Fabrazyme	*At month 24*	16 of 56 (29%)		
	At month 30	11 of 52 (21%)		
	At month 36	7 of 47 (15%)		
Schiffmann (2001)[42] (RCT)				"The vast majority of adverse events (e.g. constipation, abdominal pain crisis, hearing loss) were symptoms that are typically observed in patients with Fabry disease and were not thought to be related to the study drug"
Replagal				
	Infusion reaction in	8 of 14 (57%)	None reported	Infusion reactions controlled with antihistamines and low-dose corticosteroids, subsequently tapered. All patients continued and subsequent reactions were generally milder
	IgG seroconversion	3 of 14 (21%)		
Hajioff (2003)[46] (RCT)	Infusion reaction (fever and chills)	1 of 7		Premedication with hydrocortisone given to patient for next 3 infusions, subsequently none given, with no further reaction
Replagal				

continued

TABLE 44 *Adverse events*

Study (design) Enzyme	Adverse events	Results (p compared with control) ERT	Comparator	Comments
Baehner (2003)[55] (non-comparative before–after study) Replagal				"One patient, with atrial fibrillation, died as a result of postoperative thromboembolic complications" "An analysis of the adverse events largely revealed events that would be expected to occur in patients with Fabry disease, such as hearing loss. There were no apparent adverse effects related to agalsidase alfa administration on vital signs, clinical laboratory tests, physical examinations or electrocardiograms. None of the patients in this study experienced an infusion reaction or developed anti-agalsidase alfa antibodies at any time"
Beck (2004)[43] (non-comparative before–after study) Replagal	Infusion-related reactions occurred in Mean time between starting ERT and first reaction Serious adverse events occurred in Withdrawal because of infusion-related reaction	37 of 314 (12%) 12.1 months ± 11.1 (SD) 38 of 314 (12%) 1		Reaction: fever, malaise, skin rash. Responded to slowing or temporarily cessation of infusion, or paracetamol, hydrocortisone or antihistamine Serious events: stroke, TIA, arrhythmias, renal disorder, vertigo, sudden deafness; none considered to be related to treatment
Eng (2001)[59] (non-comparative dose escalation) Fabrazyme	Hypersensitivity reactions in Antibody development in	At least 4 (number unclear) 8 of 15 (53%)		"The most common adverse event was a transient mild-to-moderate increase in BP"
Schiffmann (2000)[63] (non-comparative before-after study) Agalsidase alfa (human fibroblast)				"No untoward effects occurred; no patient developed antibodies by day 28 postinfusion"

Appendix 3

Data set of Miners and colleagues

Dr A Miners allowed access to the dataset used within the paper by Miners and colleagues.[116] The dataset contained information for a total of 46 patients and the following information was available for each individual:

Marital status
General health – hypertension
General health – heart attack
General health – heart failure
General health – diabetes
General health – angina
General health – cancer
General health – renal
General health – other
Gastrointestinal symptoms
Chest pains
Stroke
Problems with irregular heart beat
Problems with vision loss
Problems with swollen ankles
Currently receiving dialysis and awaiting transplant
Undergone renal transplant
EQ5D mobility
EQ5D self care
EQ5D usual activities
EQ5D pain
EQ5D anxious/depressed
VAS score
EQ5D health state
EQ5D utility
SF-36 – physical functioning
SF-36 – physical limitations
SF-36 – pain score
SF-36 – general health score
SF-36 – energy score
SF-36 – social functioning score
SF-36 – mental limitation score
SF-36 – physical summary score
SF-36 – mental summary score

Table 45 provides a summary of the individuals within the dataset with respect to the age of the patient and the clinical manifestations of the disease.

TABLE 45 *Summary statistics of data from Miners and colleagues dataset*

	N	Value
Mean age	45	35 years
Gastrointestinal symptoms	41	53%
Chest pains	42	48%
Stroke	39	13%
Problems with irregular heart beat	42	43%
Problems with vision loss	40	18%
Problems with swollen ankles	41	61%
Currently receiving dialysis and awaiting transplant	41	7%
Undergone renal transplant	41	7%
General health – hypertension	43	14%
General health – heart attack	44	7%
General health – heart failure	44	2%
General health – diabetes	44	0%
General health – angina	44	9%
General health – cancer	44	0%
General health – renal	44	9%
Total sample size	46	

The data contained the patient-specific SF-36 domain scores which made it possible to convert these scores into the SF-6D (Short Form with six attributes) preference-based measure of health (and thus to obtain utility values for the QoL of each patient). To estimate the SF-6D health state classification from the SF-36 values we used the methodology and programme by Brazier and colleagues.[118] *Figure 7* displays the distribution of these SF-6D scores; the population mean is equal to 0.63 with an SD of 0.16.

The results of univariate analysis of each clinical variable against EQ5D and SF-6D are shown in *Table 46*.

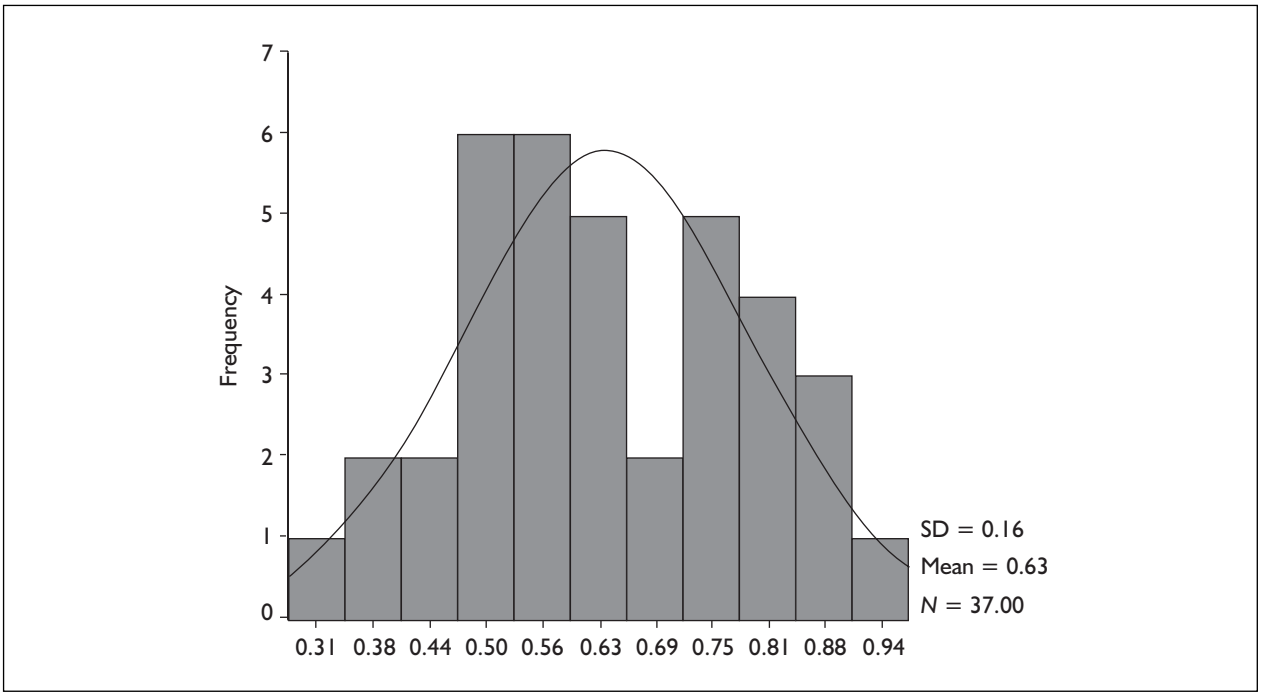

FIGURE 7 *Distribution of SF-6D preference-based measure of health*

TABLE 46 *Univariate analysis of each of the clinical variables against SF6D and EQ5D*

	EQ5D		SF6D	
Variable	**Coefficient**	**Significance**	**Coefficient**	**Significance**
Age	1.67×10^{-2}	0.007	-6.32×10^{-3}	0.026
Gastrointestinal symptoms	-7.52×10^{-2}	0.534	-4.27×10^{-2}	0.452
Chest pains	–0.102	0.390	-4.77×10^{-2}	0.392
Stroke	–0.282	–1.895	–0.127	0.112
Problems with irregular heart beat	-9.45×10^{-2}	0.453	-1.69×10^{-2}	0.771
Problems with vision loss	-3.26×10^{-2}	0.836	-2.22×10^{-2}	0.784
Problems with swollen ankles	–0.320	0.010	–0.143	0.014
Currently receiving dialysis and awaiting transplant	–0.165	0.488	-7.57×10^{-2}	0.529
Undergone renal transplant	–0.160	0.515	-8.23×10^{-2}	0.467
General health – hypertension	–0.134	0.448	1.579×10^{-2}	0.843
General health – heart attack	–0.158	0.468	–0.208	0.208
General health – heart failure	-3.60×10^{-2}	0.922	-5.85×10^{-2}	0.0723
General health – angina	–0.298	0.114	–0.109	0.200
General health – renal	-9.84×10^{-2}	0.608	-6.42×10^{-2}	0.456

Appendix 4

Example of economic analyses on ERT for Fabry's disease

Introduction

The objective of an economic analysis is to estimate the cost-effectiveness of ERT in the management of Fabry's disease compared with standard supportive care.

In order to estimate the degree of health gain achieved by ERT, it is necessary to consider what would have happened to patients had they not received treatment. Therefore, the natural history of untreated Fabry's disease needs to be understood in order to facilitate reliable modelling of the health gain attributed to ERT treatment. Fabry's disease is a complex disease with multiple clinical manifestations appearing at variable time points during the lifetime of a patient. Deficient activity of the enzyme α-gal A affects many tissues and organs and signs and symptoms include neuropathic pain, angiokeratoma (dermatological lesions), renal failure, heart failure, fever, vomiting, gastrointestinal problems, corneal lesions and hypertension, to name just a few. All of these manifestations inevitably have a huge impact on the QoL of the patient.

The following section describes a modelling exercise that would have been undertaken had access to patient data registries and/or other data sources been achieved within the time frame of this report.

Structure of decision model

The MSSI provides a framework in which Fabry's disease progression can be described.[22] The MSSI is composed of four sections, general, neurological, cardiovascular and renal signs and symptoms of the disease. The MSSI can be divided into severity bands of mild (<20), moderate (20–40) and severe (>40) to reflect the severity of the disease.[22] The MSSI is discussed in detail in the section 'Mainz Severity Sore Index' (p. 5).

Markov models are typically used to simulate the progression of patients through a disease. Progression of Fabry's disease could have been modelled using the MSSI where health states are defined according to the stage of progression along the severity score scale. Over time, as patients present with a greater number of signs and symptoms of the disease, they will progress along the MSSI.

To facilitate this modelling exercise, an understanding of the relationship between MSSI and the QoL of patients is crucial to allow the reliable calculation of QALYs. No published evidence exists that directly estimates the relationship between the MSSI and the QoL of patients. Estimating this relationship is not straightforward as, given the design of the MSSI, a severity score can be reached from the development of a whole range of signs and symptoms. For example, a severity score of 10 can be reached by a patient presenting with characteristics such as Fabry's facial appearance, severe tinnitus, mild vertigo and chronic acroparesthesia, whereas another patient with a severity score of 10 may have evidence of renal dysfunction but with no other symptoms. Clearly, the QoL of both patients will be very different. The MSSI score therefore needs to be validated in terms of its contribution to the QoL of the patients.

Of the registries of data on patients with Fabry's disease, the FOS database contains information on the year of diagnosis of Fabry's disease, signs and symptoms of the disease, treatment, demographic details and family history for each patient.[69] In addition, the QoL of the patient is recorded using the EQ5D instrument. To use the MSSI to structure the progression of the disease, it would have been useful to use the data in the FOS database to estimate the relationship between the QoL of the patients (as measured by the EQ5D) and the MSSI. One would expect a negative relationship – as the SSI increases, the QoL decreases, but validating the MSSI in this way would have been a useful exercise. In addition, understanding the relationship between each of the signs and symptoms and QoL would also have been crucial. This analysis would check that the

weight attached to each sign and symptom to contribute to the MSSI score would be similar to the contribution to the EQ5D score. For example, the presence of cornea verticillata is not given a high score within the MSSI, therefore we would expect a minor impact of this symptom upon QoL.

Once the MSSI had been validated in terms of the QoL, it would have been possible to have adopted a conventional Markov modelling approach using the MSSI to structure the disease, to estimate the cost effectiveness of ERT treatment for Fabry's disease.

Appendix 5

Survival curves for MPS1 patients

The Society for Mucopolysaccharidosis Diseases (UK) has maintained a registry of UK MPS1 patients from 1981 to the present. The Society made available anonymised information suitable for calculation of Kaplan–Meier survival curves. Kaplan–Meier curves were constructed using Stats Direct software. The results are shown in *Figures 8–12* with censored patients denoted by tick marks and 95% CIs also represented. These data are summarised in *Figures 5* and *6* in the section 'Mortality' (p. 63). The anonymised data underpinning these figures are available in electronic form on request.

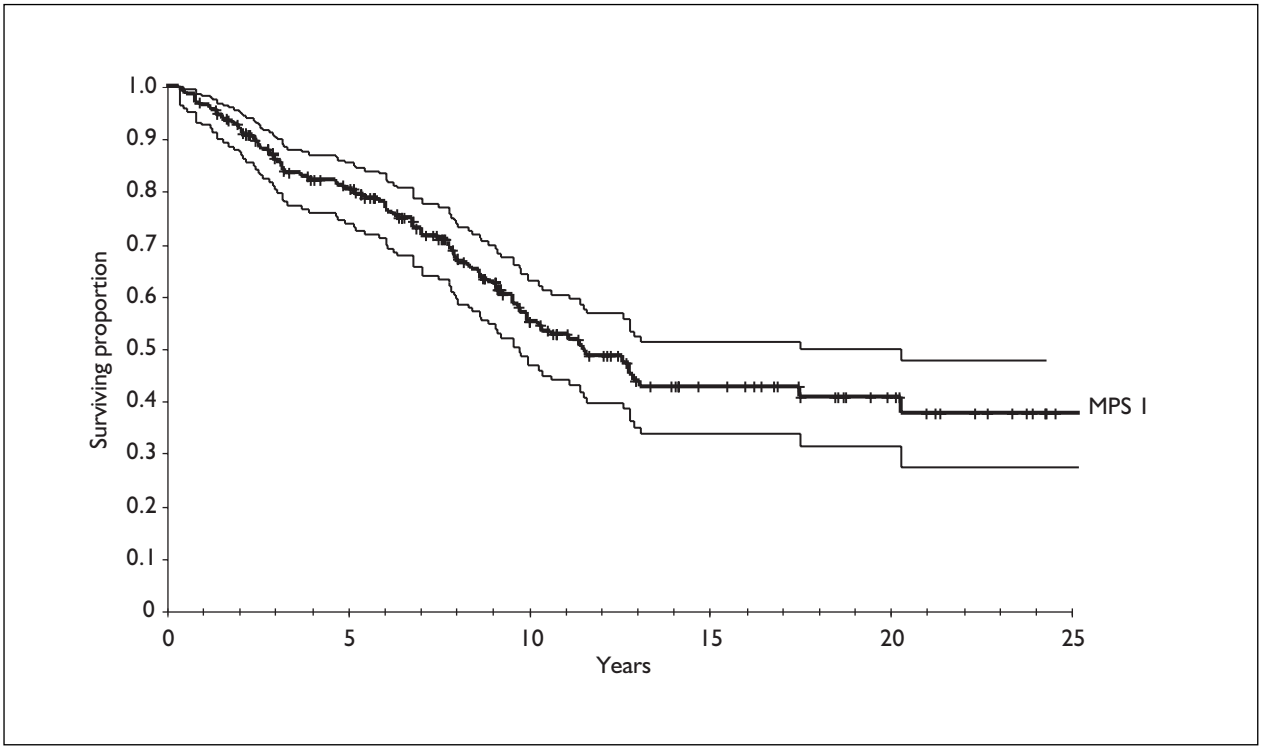

FIGURE 8 *Kaplan–Meier survival curves for all MPS1*

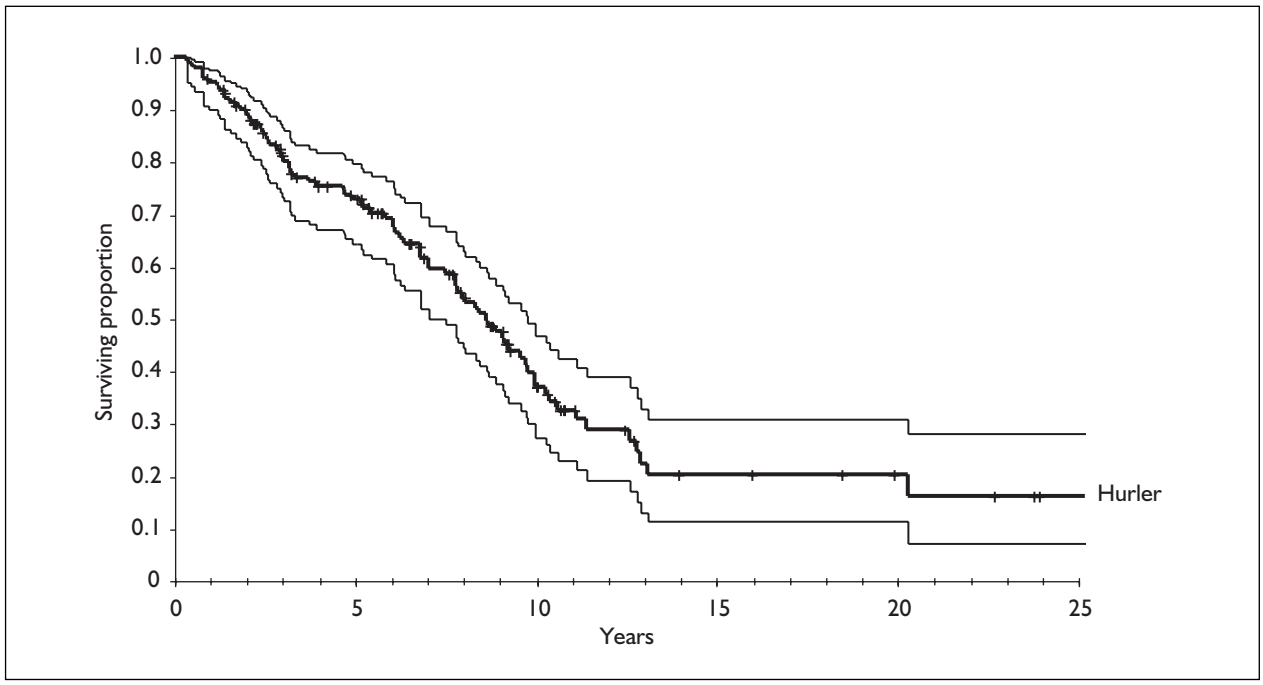

FIGURE 9 *Kaplan–Meier survival curves for Hurler syndrome*

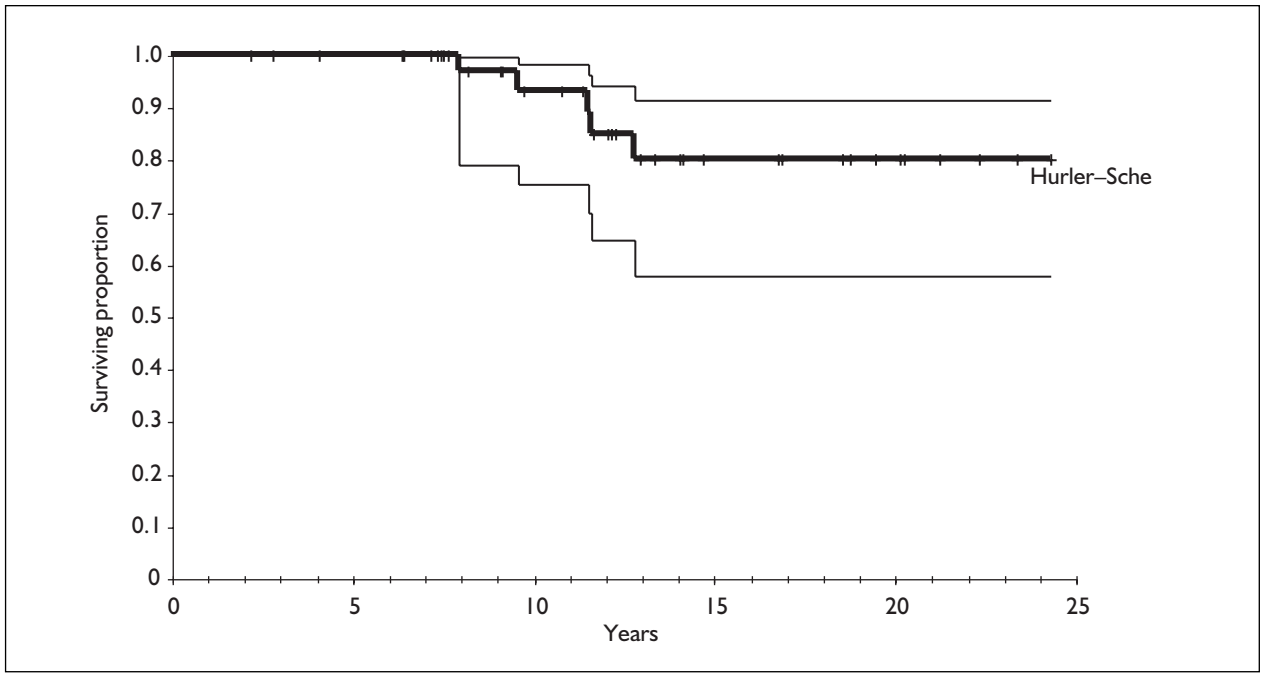

FIGURE 10 *Kaplan–Meier survival curves for Hurler–Scheie syndrome*

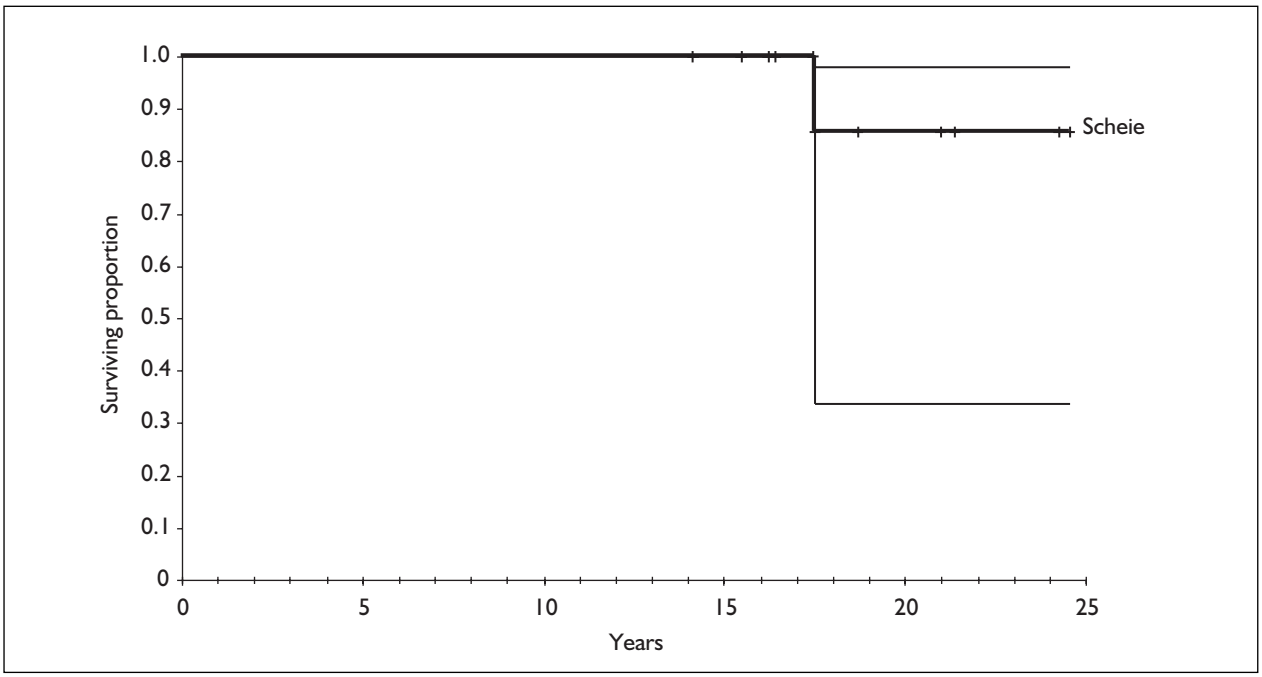

FIGURE 11 *Kaplan–Meier survival curves for Scheie syndrome*

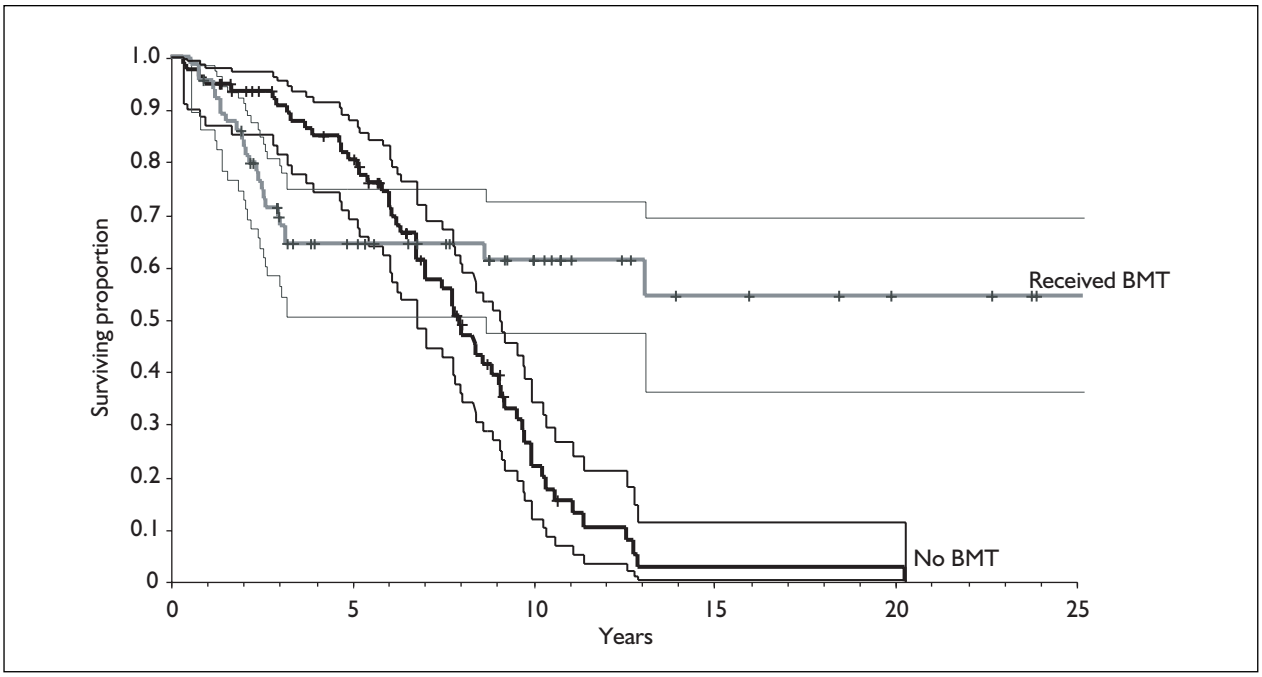

FIGURE 12 *Kaplan–Meier survival curves for Hurler syndrome with and without bone marrow transplant*

Appendix 6

Cost of treating MPS1 in England and Wales

Anonymised patient data were supplied by the Society for Mucopolysaccharide Diseases (UK) *(Table 47)* Weights for MPS1 patients were calculated from standard general population growth charts and assuming that MPS1 patients conform to these age-related profiles.

TABLE 47 *Distribution of Hurler–Scheie and Scheie patients by age and projected ERT cost*

Current age (years)	No. alive in England and Wales	Mean normal weight (kg)	Units required per infusion	Vials required per week	Whole vials required per week	Cost per week 1 vial = £460.35 (£)	Cost per year (£)
2	2	14	1400	2.8	3	1381.05	72159.86
4	1	18.55	1855	3.71	4	1841.4	96213.15
6	2	22.8	2280	4.56	5	2301.75	120266.4
7	3	25.95	2595	5.19	6	2762.1	144319.7
8	0	28.95	2895	5.79	6	2762.1	144319.7
9	3	32.65	3265	6.53	7	3222.45	168373
10	1	36.5	3650	7.3	8	3682.8	192426.3
11	2	42.05	4205	8.41	9	4143.15	216479.6
12	4	46.55	4655	9.31	10	4603.5	240532.9
13	1	52.55	5255	10.51	11	5063.85	264586.2
14	4	56.35	5635	11.27	12	5524.2	288639.5
15	1	61.1	6110	12.22	13	5984.55	312692.7
16	3	65	6500	13	13	5984.55	312692.7
17	2	65	6500	13	13	5984.55	312692.7
18	2	65	6500	13	13	5984.55	312692.7
19	1	65	6500	13	13	5984.55	312692.7
20	3	65	6500	13	13	5984.55	312692.7
21	3	65	6500	13	13	5984.55	312692.7
22	0	65	6500	13	13	5984.55	312692.7
23	1	65	6500	13	13	5984.55	312692.7
24	3	65	6500	13	13	5984.55	312692.7
Total					*211*	*97133.85*	*5075244*

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We look forward to hearing from you.

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ISSN 1366-5278