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The research reported in this monograph was commissioned by the HTA Programme as project number 03/64/01. The contractual start date was in June 2004. The draft report began editorial review in April 2005 and was accepted for publication in December 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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Abstract

The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review

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Objectives: The aim of this review is to determine the clinical effectiveness and cost-effectiveness of enzyme replacement therapy (ERT) in the treatment of symptomatic Gaucher's disease.

Data sources: Major electronic databases were searched from their inception to August 2003; and updated from January 2003 to July/August 2004.

Review methods: Databases were searched for studies that met the criteria and selected data were extracted and evaluated. Studies were assessed for their relevance to the UK context and the review objective. The bibliographic databases were also searched to identify existing cost studies, economic evaluations and models. A Markov decision model was constructed based on patients moving between states defined by the modified Severity Score Index (SSI). Most of the parameters were derived from the published literature. ERT was assumed to restore patients to full health in the base case.

Results: Sixty-three studies were included, all suggestive of benefit with ERT. However, the way in which the effects translate into patient well-being and survival or the need for services and resources has not been reliably estimated. Quality of life improvements with ERT have been reported. Nonetheless, studies based on the Short Form 36 (SF-36) indicate that patients treated with ERT continue to have reduced health-related quality of life (HRQoL) compared with the general population. No study attached utility values to quality of life measures for ERT-treated patients. Thirty-one studies relevant to the natural history of the disease were found. Sixteen looked at multiple clinical characteristics of a cohort of patients with type I Gaucher's disease. There was considerable within-study and between-study heterogeneity, but all showed that Gaucher's disease was a progressive condition. Some suggested that the disease may become more indolent in adulthood; however, studies were discrepant on this point. Most disease is diagnosed in adulthood, although about one-quarter presented in childhood, these patients having the most severe symptoms and greatest rate of progression. Modelling of natural history was undertaken using the five papers that reported the SSI for each patient, along with patient-level data on age, age at diagnosis, splenectomy status and genotype, to address the question of whether disease stabilises in adulthood and the degree of correlation between phenotype and genotype. Analysis of the available data suggested that disease progression is likely to slow markedly in adulthood and that genotype is a useful predictor of clinical expression of the disease. Five studies looked at quality of life. Data on this topic were also obtained from the registries. The evidence suggests that the vast majority of the clinical characteristics of type I Gaucher's disease have little impact on subjective HRQoL and that therefore for the majority of people with type I Gaucher's disease this may not be a severe condition. Bone and skeletal symptoms contribute most to the morbidity of the disease and can lead to severe pain and immobility. The mean cost per patient treated was approximately £86,000 per annum in England and Wales. The cost per patient varied considerably by dose. Four existing economic evaluations were found, all of which calculated a very high cost per quality-adjusted life-year (QALY). Using the Markov decision model, ERT was assumed to restore patients to full health in the base case. The estimated incremental cost per QALY [incremental cost-effectiveness ratio (ICER)] in the base case ranged from £380,000 to £476,000 per QALY, depending on genotype. Univariate sensitivity analyses examined ERT not restoring full health, more severe

disease progression in the untreated cohort, and only treating the most severely affected patients. These produced ICERs of approximately £1.4 million, £296,000 and £275,000 per QALY, respectively. The base-case unit cost of the drug is £2.975. The unit cost would have had to be reduced ten-fold, to £0.30, to obtain an ICER of £30,000 per QALY. At a unit cost of £1 the ICER would be £120,000 per QALY.

Conclusions: Although ERT for treating the 'average' Gaucher's disease patient exceeds the normal upper threshold for cost-effectiveness seen in NHS policy decisions by over ten-fold, some argue that since orphan drug legislation encouraged the manufacture of Cerezyme, and Gaucher's disease can be defined as an orphan disease, the NHS has little option but to provide it, despite its great expense. More information is required before the generalisability of the findings can be determined. Although data from the UK have been used wherever possible, these were very thin indeed. Nonetheless, even large errors in estimates of the distribution of genotype, genotype–phenotype associations, effectiveness and numbers of patients will not reduce the ICER to anywhere near the upper level of treatments usually considered cost-effective. Further research could help to clarify the many uncertainties that exist. However, although doing so will be of clinical interest, 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. (The possible exception to this would be investigating the most efficient alternative treatment strategies for using ERT in a paediatric population only.) Moreover, if under equity considerations for orphan diseases the NHS feels it is important to provide this drug, regardless of its cost-effectiveness, then refining the precision of the ICER estimate also becomes superfluous.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Allele One of several possible alternatives of a given gene.

Cachexia General weight loss or wasting that can occur during a chronic disease.

Chitotriosidase An enzyme capable of speeding the degradation of chitin, and of molecules that resemble chitin. The function of chitotriosidase in humans is uncertain. Plasma levels of chitotriosidase are commonly greatly elevated in patients with Gaucher's disease.

Chromosome A structure in the nucleus of cells that carries a string-like arrangement of genes; two copies of each chromosome are usually present in each cell, one derived from each parent.

Enzyme A molecule, usually large, that has the ability to speed up the rate at which a particular chemical reaction proceeds in the body.

Eukaryotic Cells that have a fully formed nucleus, or organisms whose cells have a fully formed nucleus (in contrast to bacterial cells, which do not have a fully formed nucleus).

Glucocerebrosidase An enzyme that speeds the degradation of glucocerebroside by splitting off the glucose part, leaving behind a molecule called ceramide. The missing enzyme in Gaucher's disease is acid β-glucocerebrosidase, which belongs to a class of enzymes termed acid β-glucosidases.

Glucocerebroside A type of sphingolipid; part of its structure is contributed by glucose.

Heterozygote The condition where an individual has two different copies of a particular gene, one copy inherited from mother and the other inherited from father.

Homozygote The condition where an individual has two identical copies of a particular gene, one copy inherited from each parent.

Lipid A molecule that has fat-like properties; lipids repel water and associate with other lipids.

Lyophilised Freeze-dried to remove water content.

Lysosome A small structure inside cells that is a major site for degradation of both cellular material and substances taken in from outside the cell. Many thousands exist within a single cell.

Macrophage A type of cell widely distributed in the body that is active in taking up materials from outside the cell and then degrading them. Many start life in the bone marrow, they circulate in the blood as monocytes and come to rest in various tissues and organs where they engage in uptake and degradation of materials.

Necrosis Death of some or all of the cells in an organ or tissue.

Osteoblasts Bone-forming cells found in bone tissue.

Osteoclasts Bone-degrading cells found in bone tissue.

Osteopenia Reduced bone mass, loss of bone cells.

Osteoporosis Loss of bony tissue, resulting in brittle bones that are liable to fracture.

Osteosclerosis Abnormal increase in bone density resulting from poor blood supply, chronic infection or other cause.

continued

Glossary *continued*

Sphingolipid A class of lipid molecule, part of whose structure is contributed by sphingosine.

Sphingolipidoses A group of storage diseases, each characterised by the abnormal accumulation of a particular sphingolipid.

Visceral Concerning the soft internal organs (e.g. liver, spleen, gut, lungs, kidneys, etc.).

List of abbreviations

AEP	auditory evoked potential
BMT	bone-marrow transplantation
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computed tomography
DECT	dual-energy computed tomography
EQ-5D	EuroQol-5Dimensions
ERT	enzyme replacement therapy
GD	Gaucher's disease
GGT	gamma-glutamyltransferase
Hb	haemoglobin
HCG	human chorionic gonadotrophin
HD	high-dose
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICGG	International Collaborative Gaucher Group
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IHQL	Index of Health-related Quality of Life
i.v.	intravenous
LD	low-dose
LSD	lysosomal storage disease
MAE	mean absolute error
MAICER	maximum acceptable incremental cost-effectiveness ratio
MRI	magnetic resonance imaging
NA	not applicable
ND	not determined
NE	not estimated
NIH	National Institutes of Health
NSCAG	National Specialist Commissioning Advisory Group
NR	not reported
ns	not significant
PHT	pulmonary hypertension
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RMSE	root mean square error
RVSP	right ventricular systolic pressure
SD	standard deviation
SE	standard error
SECT	single-energy computed tomography
SF-36	Short Form 36
SF-6D	Short Form 6D
SG	standard gamble
SSI	Severity Score Index
TTO	time trade-off
U	unit

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

Objective

Enzyme replacement therapy (ERT; intravenous imiglucerase) is used in the treatment of people with symptomatic type I and type III Gaucher's disease in order to reduce symptoms of the disease and prevent long-term damage. The aim of this review is to determine the clinical effectiveness and cost-effectiveness of ERT in the treatment of symptomatic Gaucher's disease.

Background

Gaucher's disease

Gaucher's disease is an inherited disorder caused by deficient activity of the enzyme glucocerebrosidase, found mainly in lysosomes. This results in an accumulation of glucocerebroside in the lysosomes of macrophages, predominantly in the reticuloendothelial system. Consequences of this abnormal storage include:

- visceral problems: hepatomegaly, splenomegaly, anaemia and thrombocytopenia causing fatigue, discomfort, infections, bleeding and bruising
- bone problems: pain (acute or chronic) and bone crises, and avascular necrosis
- other problems such as lung disease, impaired growth and delayed puberty.

The severity of symptoms and rate of progression vary considerably from patient to patient and range from asymptomatic to severe with early death. The variability is partly related to genotype (over 200 different mutations have been identified). Although, at a population level, different genotypes tend to be associated with certain phenotypes, making it difficult to generalise findings from one country to another, the relationship between genotype and phenotype is not rigid, as background genetics and environment also play a role. Prediction of the clinical course of an individual patient based on genotype alone is uncertain.

Gaucher's disease is classified into three subtypes by clinical features. Type I can present at any age and has predominantly visceral symptoms without neurological effects. Type II causes severe progressive brain disease and death occurs in infancy. Type III presents in childhood and has neurological and visceral symptoms.

Imiglucerase (Cerezyme®) is a recombinant enzyme modified to enhance its uptake into lysosomes. It is given intravenously to replace the defective enzyme and is licensed for use in symptomatic type I disease and to treat the visceral symptoms of type III disease. Intravenous Cerezyme® cannot cross the blood–brain barrier and is not effective for neurological manifestations.

Prevalence

Over 90% of affected individuals have type I Gaucher's disease. It is rare, affecting between 1 in 40,000 and 1 in 60,000 individuals. There are thought to be around 250 people affected in England and Wales. Type III is even rarer, affecting less than 1 in 100,000 individuals. The focus of this report is mainly type I Gaucher's disease.

The NHS

This technology is already widely used in the NHS as patients with significant clinical symptoms have had access to the therapy following the recommendations of the National Specialist Commissioning Advisory Group. Current provision of ERT is said to cost the NHS in England and Wales around £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.

Methods

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 to estimate the likely clinical effectiveness and cost-effectiveness of ERT.

Scoping searches were performed to identify existing reviews and health technology assessments and to inform the development of the review protocol. Broad search strategies were used so that publications on effectiveness, natural history of the disease, and prevalence and incidence would be captured. References from searches of MEDLINE, Cochrane Library, EMBASE and CINAHL from their inception to August 2003 were obtained from an existing Reference Manager database that was compiled for a previous rapid review. The searches were then updated from January 2003 to July/August 2004.

Terms for β-glucocerebrosidase were added to the updated searches to identify references that may have been missed previously. Searches were also made for ongoing and completed but unpublished studies on major research registers.

Data on type of disease, method and period of ascertainment, population and prevalence rates were extracted from included studies. A data extraction form was developed based on the range of symptoms of type I Gaucher's disease described in literature reviews and highlighted in discussions with clinical experts and Genzyme, the manufacturers of Cerezyme. Data on study characteristics, quality and results reported were extracted into tables by one reviewer and checked by another. 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 or probably cohort or case–control designs, the quality assessment was performed using quality recommended criteria. For other studies the following broad criteria were used, based on factors that influence the generalisability of findings reported in case-series. Where the number of patients assigned was the same as the number analysed it was assumed that withdrawals did not occur and thus were accounted for, even in the absence of an explicit statement by the authors. 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.

As most effectiveness studies were not controlled, to estimate the extent to which the outcomes observed were the results of ERT, it was important to consider what would have happened to the patients in the absence of ERT. Thus, the relevance of prevalence and natural history studies were assessed for their relevance to the UK context and the review question.

The bibliographic databases were also searched to identify existing cost studies, economic evaluations and models. To be included in the review, studies had to analyse the treatment of Gaucher's disease in terms of both the costs and effectiveness. There were no language exclusions.

Evidence about effectiveness

Number and quality of studies

Primary studies of any design, reporting at least ten patients, were included. Sixty-three studies were included. Only one RCT compared ERT with usual treatment. This was a well-designed study, but underpowered (29 patients randomised to three arms) because of poor recruitment. One other RCT compared recombinant imiglucerase with the placenta-derived predecessor alglucerase and thus only provided before and after data on the effectiveness of ERT. The rest of the studies were of moderate quality at best and none had reliable comparator data.

Direction of evidence

All studies are suggestive of benefit with ERT.

Summary of benefits

The one relevant RCT showed a potentially beneficial effect in two haematological surrogates (haemoglobin and platelet levels) and, to a lesser extent, on hepatomegaly. The other studies consistently demonstrated improvements in haematological parameters and in hepatomegaly and splenomegaly. Most measures of disease involvement on average tended to return towards normal in the majority of patients after about 1 or more years of treatment. For organomegaly and haemoglobin the rates and extent of response appeared greater the more abnormal the pre-ERT condition. Platelet levels appeared to improve more slowly and to a lesser degree the more severe the initial thrombocytopenia. Liver size in most cases approached 1.2 times that expected for body weight. Spleen enlargement appeared to reduce to between five and ten times normal in most patients.

The effect of ERT on skeletal involvement also appeared to be positive in terms of pain, bone crises and fracture rate, but the quantitative evidence for these benefits was extremely weak. There was some evidence that ERT may exacerbate the depletion in bone density; thus, caution is needed in interpretation of results and careful monitoring is required.

The way in which all of these effects translate into patient well-being and survival or the need for services and resources has not been reliably estimated.

Quality of life improvements with ERT have been reported. Nonetheless, studies based on the Short Form 36 (SF-36) indicate that patients treated with ERT continue to have reduced health-related quality of life (HRQoL) compared with the general population. No study attached utility values to quality of life measures for ERT-treated patients.

Natural history

Benefit from treatment probably exceeds the health gain demonstrated by before and after studies, because Gaucher's disease is a progressive condition and future deterioration may be prevented. Therefore, to be able to determine the full extent of health gain from treatment it was necessary to review the natural history of untreated Gaucher's disease to estimate the health loss prevented.

Thirty-one studies relevant to the natural history of the disease were found. Sixteen looked at multiple clinical characteristics of a cohort of patients with type I Gaucher's disease. There was considerable within-study and between-study heterogeneity, but all showed that Gaucher's disease was a progressive condition. Some suggested that the disease may become more indolent in adulthood; however, studies were discrepant on this point. Most disease is diagnosed in adulthood, although about one-quarter presented in childhood, these patients having the most severe symptoms and greatest rate of progression.

Modelling of natural history was undertaken using the five papers that reported the Severity Score Index (SSI) for each patient, along with patient-level data on age, age at diagnosis, splenectomy status and genotype, to address the question of whether disease stabilises in adulthood and the degree of correlation between phenotype and genotype. Analysis of the available data suggested that disease progression is likely to slow markedly in adulthood and that genotype is a useful predictor of clinical expression of the disease.

Quality of life

Five studies looked at quality of life. Data on this topic were also obtained from the registries. The evidence suggests that the vast majority of the clinical characteristics of type I Gaucher's disease have little impact on subjective HRQoL and that therefore for the majority of people with type I Gaucher's Disease this may not be a severe condition. Bone and skeletal symptoms contribute most to the morbidity of the disease and can lead to severe pain and immobility.

Economic evaluation

Costs

The mean cost per patient treated was approximately £86,000 per annum in England and Wales. The cost per patient varied considerably by dose.

Cost per quality-adjusted life-year

Four existing economic evaluations were found, all of which calculated a very high cost per quality-adjusted life-year (QALY). The most recently published report was from 1996, therefore, a *de novo* economic model was developed. A Markov decision model was constructed based on patients moving between states defined by the modified SSI. Most of the parameters were derived from the published literature. ERT was assumed to restore patients to full health in the base case. The estimated incremental cost per QALY [incremental cost-effectiveness ratio (ICER)] in the base case ranged from £380,000 to £476,000 per QALY, depending on genotype.

Sensitivity analyses

Univariate sensitivity analyses examined ERT not restoring full health, more severe disease progression in the untreated cohort, and only treating the most severely affected patients. These produced ICERs of approximately £1.4 million, £296,000 and £275,000 per QALY, respectively. The base-case unit cost of the drug is £2.975. The unit cost would have had to be reduced ten-fold, to £0.30, to obtain an ICER of £30,000 per QALY. At a unit cost of £1 the ICER would be £120,000 per QALY.

Limitations of the calculations (assumptions made)

The evidence for effectiveness is generally based on studies that are not of a robust design. Such designs tend to exaggerate apparent treatment effects and are therefore unlikely to have contributed to the high estimate of the ICER.

Because of the weak evidence base, several substantial assumptions were required to produce an estimate of the cost-effectiveness (wherever possible assumptions that favour ERT were chosen). These assumptions are:

- that SSI categorisation identifies states that are different in relation to HRQoL from each other

- that within each of the 'mild', 'moderate' and 'severe' categories of SSI patients have a comparable HRQoL
- that ERT returns patients to full health
- that people on treatment have normal life expectancy
- that the natural history shows slowing of disease progression in adulthood.

Conclusion

Other important issues regarding implications

Although ERT for treating the 'average' Gaucher's disease patient exceeds the normal upper threshold for cost-effectiveness seen in NHS policy decisions by over ten-fold, some argue that since orphan drug legislation encouraged the manufacture of Cerezyme, and Gaucher's disease can be defined as an orphan disease, the NHS has little option but to provide it, despite its great expense.

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, these were very thin indeed. Nonetheless, even large errors in estimates of the distribution of genotype, genotype–phenotype associations, effectiveness and numbers of patients will not reduce the ICER to anywhere near the upper level of treatments usually considered cost-effective.

Recommendations for further research

Further research could help to clarify the many uncertainties that exist. However, although doing so will be of clinical interest, 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. (The possible exception to this would be investigating the most efficient alternative treatment strategies for using ERT in a paediatric population only.) Moreover, if under equity considerations for orphan diseases the NHS feels it is important to provide this drug, regardless of its cost-effectiveness, then refining the precision of the ICER estimate also becomes superfluous.

Chapter 1

Aim of the review

Gaucher's disease is a rare inherited condition, classified as a lysosomal storage disease. Its presentation can range from very mild to life-threatening. It is caused by an enzyme deficiency resulting from mutation in the gene coding for the lysosomal enzyme glucocerebrosidase. Before the development of enzyme replacement therapy (ERT), treatment was supportive and directed at the pathological sequelae of the illness. ERT aims to replace the defective or missing enzyme with a functional protein that is infused into the bloodstream and taken up into cellular lysosomes. The aim of this review is to determine the clinical effectiveness and cost-effectiveness of ERT in the treatment of symptomatic Gaucher's disease.

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.

Lysosomal storage diseases 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.[1] A considerable variety of pathologies can develop from this and the clinical manifestations of many lysosomal storage diseases were described long before the discovery of lysosomes. Many lysosomal storage diseases 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 neurological as well as peripheral symptoms.

The underlying cause of most lysosomal storage diseases is mutation in a gene coding for a lysosomal enzyme leading to a deficiency in the functional activity of the enzyme.[1] 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 may lead to potentially toxic products.

Treatments for lysosomal storage diseases

Four treatment strategies that directly address the underlying cause of the disease have been suggested for lysosomal storage diseases:[2,3]

- ERT
- enzyme enhancement therapy
- substrate reduction therapy[4]
- 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 thus have the potential to benefit patients with neuronopathic manifestations of lysosomal storage disease. 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 lysosomal storage disease. Engraftment of genetically modified stem cells carrying functional genes represents one approach. Delivery systems for effective gene therapy are in development. Only ERT and substrate reduction therapy modalities have been licensed in Europe for treatment of subpopulations of patients with Gaucher's disease.

Gaucher's disease

Clinical, pathological and molecular aspects of Gaucher's disease have been the subject of numerous reviews.[5–8] Gaucher's disease is an autosomal panethnic lysosomal storage disease caused by a deficiency in lysosomal β-glucocerebrosidase activity leading to an accumulation of the cerebroside glucosylceramide. It is the most common lysosomal storage disease.

Nature of the disease

The enzyme deficiency results from mutation in the lysosomal acid β-glucosidase gene mapped to

1q21(a region on chromosome 21), or extremely rarely from mutation in the prosaposin gene coding for a lysosomal protein activator (saposin C) of acid β-glucosidase.[8] Glycolipid is stored in the lysosomes of various tissues and cells, but especially in macrophages. When engorged with lipids these are known as Gaucher cells and their presence is a hallmark of the disease. Most of the stored material is of exogenous origin and derived from membrane fragments of phagocytosed blood cells rather than cell-specific sphingolipid biosynthesis. The potentially toxic deacylated degradation product of glucocerebroside has also been detected.

Gaucher cells are distributed in organs where macrophages reside especially in the spleen, liver, bone marrow and lymph nodes, but also lungs, skin, eyes, kidney, heart and, in rare cases, the nervous system. Gaucher cells and other sites of storage lead to widespread multisystem pathologies by incompletely understood mechanisms. The combination of disease manifestations in individual patients is heterogeneous, so that Gaucher's disease has been subdivided into three major types (see *Table 1*), of which type I is by far the most common. Major manifestations observed in patients with Gaucher's disease, sourced from reviews, are summarised below.

Bone disease

Detectable skeletal involvement is probably present in virtually all patients with Gaucher's disease type I, but the type and degree of severity are highly variable and can be asymptomatic. Skeletal symptoms may occur at any time in life. Skeletal manifestations are major determinants of morbidity,[5,9,10] and encompass generalised osteopenia with osteoporosis, focal deformities (e.g. Erlenmeyer flask deformity of the distal femur), bone lesions of various types including lytic lesions, osteosclerosis, and pathological fractures, occurring at various sites, especially the femoral head and neck but also humeri, vertebral bodies, tibiae, ribs, pelvis and others. Normal cell residents of bone marrow become progressively replaced by Gaucher cells, but where they abut trabecular and cortical surfaces there may be no extra signs of bone pathology. It is thought that Gaucher cells may directly or indirectly alter cytokine balance, which then affects the function of osteoclasts and osteoblasts. Bone involvement may be associated with fluctuating chronic and/or acute bone pain. Gaucher bone crises are described as "acute excruciating episodic bone pain".[11] They tend to be recurrent, may last for 1 week to several weeks, are characterised by severe pain often unrelieved by narcotics, and are associated with local signs of redness, swelling, warmth and tenderness around the affected bone. They are often accompanied by fever. Patients who have sustained severe bone involvement may be wheelchair bound.

Splenic disease

Phagocytic cells in the spleen accumulate storage products. Clinical evidence of splenic disease is present in at least 95% of patients with type I disease.[5] Splenomegaly develops with hyperplasia of connective tissue; in extreme cases the spleen may enlarge as much as 75-fold and can account for up to 15–25% of body weight. Fibrosis may allow massive enlargement with only a small risk of spontaneous rupture; but the enlarged spleen is at risk of rupture from blunt trauma with potential serious consequences. Episodes of splenic infarction are accompanied by abdominal pain and risk of coincidental infection. Splenomegaly may contribute to lung compression, irritation of the diaphragm and abdominal distension, which promotes feelings of satiety. The enlarged spleen correlates with low blood counts and anaemia, and contributes to a tendency to bleed and bruise and greater susceptibility to infection. Splenectomy is followed by rapid increases in erythrocytes and platelets.

Hepatic disease

Accumulation in Kupffer cells results in liver enlargement.[5] About 80–90% of type I patients have hepatomegaly; the liver can be up to four times its normal size, but enlargement is less extreme than that of the spleen. Infrequent developments of liver disease include cirrhosis, portal hypertension and oesophageal varices. Nearly half of patients with type I disease exhibit moderately elevated serum aminotransferase levels potentially indicative of compromised liver function. Hepatic infarction can occur, with similar symptoms to splenic infarction (fever and pain). Liver enlargement and consequent abdominal distension may contribute to feelings of satiety and discomfort.

Haematological manifestations

Anaemia, thrombocytopenia and leucopenia are common presenting features of type I Gaucher's disease. They are usually associated with an enlarged spleen that provides greater than normal splenic blood flow with inappropriate sequestration and destruction of blood cells. Splenectomy leads to rapid improvements. If transfusion-dependent anaemia develops, a vicious cycle of transfusion and splenic enlargement may

follow.[5] In splenectomised patients infiltration of bone marrow by Gaucher cells and displacement of normally resident cells results in haematological manifestations. Haematological involvement contributes to patient fatigue, and a tendency to bleed and bruise.

Pulmonary manifestations

Post-mortem examination has revealed that all types of Gaucher's disease can involve the lungs. Although abnormal pulmonary function can be detected in many patients, symptomatic or clinically significant lung involvements are rare. Serious lung disease appears to be associated mainly with children who exhibit a severe course of the disease and can encompass changes to lung vasculature with pulmonary hypertension, infiltration by Gaucher cells, and severe hypoxia. Pulmonary involvement is thought to develop via several pathophysiological mechanisms.

Neuronopathic manifestations

Neuronopathic manifestations are characteristic of type III disease and include oculomotor abnormalities and myoclonic seizures. Several subdivisions of type III have been proposed (see next section).

Clinical presentation and classification of Gaucher's disease

Three major clinical subtypes of Gaucher's disease have been delineated; their characteristics are outlined below and are summarised in *Table 1*. It is generally thought that the classification is an operational one and describes what is probably an underlying biological continuum.

Type I (or non-neuronopathic) Gaucher's disease is the most common form affecting around 1 in 40–60,000 individuals.[12] Although also known as adult Gaucher's disease, it can present in childhood. A wide range of clinical signs and symptoms (with the exception of neurological effects) manifests in type I Gaucher's disease. The most frequent initial sign is enlargement of the spleen and/or liver. Presentation of visceromegaly in a child of 6 months may progress to impair mobility, growth, posture and appetite. Haematological effects include thrombocytopenia, leading to an increased tendency for bleeding and bruising, leucopenia, leading to decreased immune function and recurrent infections, and reduction in haemoglobin levels, manifested as chronic fatigue. Hypermetabolism and cachexia may be present.

Skeletal symptoms may occur at any time in life, and represent the greatest morbidity of type I Gaucher's disease. Initially, effects may be very mild and progress very slowly. Joints and bone-covering tissue become degenerated and painful. Progressive reduction in bone density leads to curvature of the bones, spontaneous fractures, widening of bones along the knee joint. The latter flaring, rather than the normal rounded shape of thigh bones at the knee, called Erlenmeyer flask deformity, is revealed by X-ray in more than 50% type I patients with Gaucher's disease. Bone crises or necrosis can lead to permanently reduced mobility. Growth retardation with associated delay in onset of puberty, pain and poor physical strength are observed in children. Type I patients exhibit a broad spectrum of disease severity, ranging from very mild to highly debilitating.

TABLE 1 *Clinical subtypes of Gaucher's disease*

Clinical feature	Type I	Type II	Type IIIa	Type IIIb	Type IIIc
Onset	Childhood/adulthood	Infancy (<1 year)	Childhood (>10 years)	Childhood (<5 years)	Childhood (2–20 years)
Hepatosplenomegaly	+ to +++	± to +	± to +	+++	+
Bone disease	+ to +++	–	–	+++	–
Cardiac valvular disease	–	–	–	–	+++
Progressive brain disease	–	+++	+	–	±
Oculomotor apraxia	–	+	+	+	+
Corneal opacities	–	NT	NT	NT	+
Survival	6–80+ (mean 60) years	< 3 years	2nd to 4th decade	2nd to 4th decade	2nd to 4th decade
Ethnic predilection	Ashkenazi Jewish	Panethnic	Northern Swedish	Panethnic	Panethnic

Table based on Beutler and Grabowski (1995)[8] and Cox and Schofield (1997).[5]
NT, not formally tested; + signs refer to degree of involvement; –, lack of involvement.

Type II Gaucher's disease is also known as acute neuronopathic Gaucher's disease, and formerly as Infantile Gaucher's disease. In addition to symptoms of the type I disease such as extensive visceral involvement, it presents severe neurological effects, and initially manifests in babies after the first few months of life. Type II is a rapidly progressive disease. Children do not usually survive beyond 2 years old. It is very rare (affecting less than 1 in 100,000) and does not appear to be concentrated within a particular ethnic group.[12]

Type III Gaucher's disease is intermediate in severity between types I and II. Also known as chronic neuronopathic Gaucher's disease and formerly as Juvenile Gaucher's disease, it is characterised by neurological effects that are less pronounced and more slowly progressive than those of type II. It presents in childhood. Those surviving adolescence frequently reach their thirties or forties. Like type II, it is very rare.

Type III has been divided into three subtypes. Type IIIc presents with mild non-progressive neuronopathic symptoms (oculomotor apraxia), with slight splenomegaly (but no hepatomegaly or skeletal effects), and characteristic progressive thickening and calcification of cardiac mitral and aortic valves.[13] Cranial scans reveal dilatation of the lateral ventricles.

Type IIIa patients present with mild to moderate hepatosplenomegaly with slowly progressive deterioration of the nervous system. Neurological effects include myoclonic seizures[14] and dementia.[15]

Type IIIb patients have severe hepatosplenomegaly, often with oesophageal varices. The major neurological effect is horizontal supranuclear gaze paresis.[15]

The Zimran Severity Score Index

To categorise the clinical severity of Gaucher's disease for research purposes, Zimran proposed a Severity Score Index (SSI) in 1989.[16] Described as "an objective determination of the disease phenotype", the Zimran SSI attempted to gauge the severity of disease in patients with differing spectra of disease. The original SSI proposed by Zimran in 1989[16] included age at diagnosis as a criterion for determining severity score. The primary objective of the study was to explore the correlation between genotype and phenotype. The severity scoring system combined cytopenia, spleen, liver and bone disease states with age at diagnosis and two treatment criteria (splenectomy and joint replacement) into a single index. The index score ranged from 0 to 30 (lower numbers being better health). Disease states scoring below 10 were described as mild, disease states between 11 and 25 were classified as moderate, and a disease state scoring over 25 was classified as severe. Modifications to the score were proposed by Zimran in 1992.[17] The adjustments involved the inclusion of abnormal liver function tests and the use of scans to establish the presence of bone disease, and ensured that aggressive bone disease, even in the absence of any visceral disease, will generate a similar score to a patient with substantial visceral disease; for example, a splenectomised patient with leucopenia, anaemia and thrombocytopenia plus massive hepatomegaly would score 9, as would a patient with necrosis or pathological fractures, with chronic bone pain with signs on a scan. CNS involvement was also added (scoring 20), allowing the application of the revised scale, at least in principle, to all types of Gaucher's disease. The age criterion was excluded. Neither the SSI nor the modified SSI has ever been validated but they have been widely used by others. Features of the modified SSI include scoring of current health severity, not expected progression (hence the omission of age at diagnosis), incorporation of correlations between symptoms (e.g. splenectomy and blood parameters), allowance for full impact of bone involvement, allowance for the impact of a fuller range of symptoms (e.g. inclusion of pulmonary hypertension), and no allowance for growth retardation or delayed puberty in children. Although the modified SSI includes up to 20 points for neurological involvement, it can still score between 0 and 28 on non-neurological symptoms, allowing comparisons of severity across individuals with type I Gaucher's disease. Details of the scoring on the modified 1992 Zimran SSI are given in *Table 2*, as the scores are measured in many studies and are reported in the results sections of this review.

Genotype–phenotype

About 200 different disease-causing mutations have been identified in the glucocerebrosidase gene mapped to 1q21.[8] Exchange with a nearly adjacent pseudogene has been identified as the source of some mutant sequences.[18] The frequency of some of the more common mutations has been determined in several geographically dispersed and general populations. Four mutations that have been frequently identified in symptomatic patients are N370S, L444P, 84GG and IVS2. The latter two are null mutations incapable of forming enzymes

TABLE 2 *Zimran's 1992 SSI*

Clinical feature		Score
Cytopenia	Unsplenectomised	1
	If splenectomised	
	Leucopenia	1
	Anaemia	1
	Thrombocytopenia	1
Splenomegaly	None	0
	Mild	1
	Moderate	2
	Massive	3
Splenectomy		3
Hepatomegaly	None	0
	Mild	1
	Moderate	2
	Massive	3
Liver function tests	Normal	0
(GOT, alkaline phosphatase, LDH, GGT)	Some abnormal	1
	All abnormal	2
Clinical signs of liver disease		4
CNS involvement		20
Other organ involvement		4
(lungs, kidneys, etc.)		
	Bones: choose one from each category	
Objective	No signs/symptoms	0
	X-ray or scan signs	1
Subjective	No pain	0
	Mild/occasional pain	2
	Chronic pain (not related to fractures)	3
Fractures	None	0
	Post-traumatic	1
	Aseptic necrosis or pathological fractures	5

GGT, gamma-glutamyltransferase; GOT, glutamic oxalacetic transaminase; LDH, lactate dehydrogenase.

that are likely to be associated with severe phenotype. No homozygotes or compound heterozygotes of two null mutations have ever been identified.[8] Many mutations are rare, whereas some others are detected at moderate frequency (e.g. R463C and R496H mutations are generally associated with mild effects; V394L and D409H generally have severe effects).

Combinations of alleles result in variation in enzyme activity and stability. There is extensive heterogeneity between patients in the severity and nature of their symptoms that is thought to depend on not only β-glucocerebrosidase genotype, but also genetic background and environmental factors. However, broad generalisations can be made:[8] presence of an N370S allele apparently precludes neuronopathic disease (i.e. is associated with type I Gaucher's disease only); the L444P allele is associated with neuronopathic forms of the disease and homozygosity for L444P is characteristic of the Swedish Norrbottnian population of type IIIa patients; however, homozygosity has been observed in type I patients from elsewhere[5] and also in type II disease. Homozygosity for the D409H mutation is apparently responsible for the rare type IIIc form of the disease.

Mutation frequency in UK patients has been the subject of a few studies. Walley and colleagues 1993[19] screened 26 non-Jewish UK patients and two obligate carriers for two common mutations (N370S and L444P); the N370S mutation accounted for 26% of the 54 alleles, the L444P for 35%. Hatton and colleagues[20] analysed 46 British and Irish patients (30 type I, 24 type II, four type III) for 10 mutations. Although the N370S mutation was mostly associated with mild disease, three type I patients carrying one N370S allele had childhood-onset disease. All four type III patients were homozygous for L444P.

Diagnosis of Gaucher's disease

Until recently, diagnosis was based primarily on clinical observation and invasive assessment of

bone marrow for the presence of Gaucher cells. Misdiagnosis was an issue, as pseudo-Gaucher cells have been described in other diseases such as chronic granulocytic lymphoma, Hodgkin's disease and thalassaemia. Sensitive tests that use fluorescent artificial substrate and measure glucocerebrosidase (acid β-glucosidase) activity in leucocytes or skin fibroblasts obtained from the patient provide a definitive diagnosis of Gaucher's disease.[21] Glucocerebrosidase activity between 0 and 30% of normal values is confirmatory of the presence of the disease. In populations where there is a high prevalence of the disease caused by a relatively small number of mutations (e.g. Ashkenazi Jews) DNA testing can provide a useful aid to diagnosis. DNA analysis is also useful for identifying asymptomatic homozygotes and carriers in close relatives of affected individuals. Potential lack of awareness of Gaucher's disease among physicians may lead to delayed diagnosis.

Measurement of plasma chitotriosidase (released by glucocerebroside-laden macrophages) demonstrates several thousand-fold elevation above normal in nearly all symptomatic patients and has been suggested to indicate total body Gaucher cell load. Serial measurements are used to assess disease progression.[22] However, elevated chitotriosidase activity, although more moderate, can occur, rarely, in other macrophage-involved pathologies. About 6% of the general population, including symptomatic patients, are homozygous for a mutation in the chitotriosidase gene, which results in very low detected plasma chitotriosidase activity.[21,22] Neurological symptoms in Gaucher's disease are usually diagnosed by auditory evoked potentials (PEPs), neuropsychometry and eye movements.[21]

Historical therapy

Traditional management of Gaucher's disease has comprised multiple interventions ranging from palliative care to surgery. In severe cases, blood transfusions, haematopoietic stem cell transplantation, splenectomy, bone-marrow transplantation and orthopaedic surgery have been performed to alleviate the gross effects of the disease.[21,23] However, surgical interventions generally carry a relatively high mortality risk and for Gaucher's disease patients the tendency to bleed may increase risk.[24] There is also a possibility of a low therapeutic effect or the acceleration of disease at other sites.[21] For example, type III Norrbottnian Gaucher's disease has been reported to exacerbate following partial or total splenectomy.[24,25] Less radical interventions include bed rest, analgesia, anti-inflammatory agents and occasionally hyperbaric oxygen.

ERT for Gaucher's disease

Glucocerebrosidase in a form suitable for intravenous administration has been developed to replace the deficient enzyme in patients with Gaucher's disease. The enzyme was originally extracted from human placenta and sequentially treated with exoglycosidases to expose mannose residues on the surface of the protein so as to increase targeting and incorporation into macrophages via their mannose receptor. This was initially undertaken by Brady and co-workers at the National Institutes of Health (NIH) laboratories[26] and the enzyme later mass produced by Genzyme Corporation and subsequently marketed as Ceredase® (alglucerase); it was licensed in the USA and European Union (EU) (1991 and 1994, respectively) for long-term use in patients with a confirmed diagnosis of type I Gaucher's disease who exhibit severe manifestations of the disease. However, the use of Ceredase was limited by the finite availability of acceptable placentae and the possibility, however small, of the transmission of infective agents.

A recombinant form of glucocerebrosidase, imiglucerase (Cerezyme®), has been developed by Genzyme Corporation to overcome these issues. Cerezyme® has received licensing approval in the USA (November 1994) and in Europe (1998). It was originally licensed in the EU for use by specialists as long-term therapy for adults and paediatrics with confirmed diagnosis of type I Gaucher's disease who exhibit clinically significant manifestations of the disease resulting in one or more of the following signs or symptoms:

- anaemia (low number of red blood cells)
- bleeding tendency due to low platelet count
- spleen or liver enlargement
- bone disease.

The EU licence has, since 2003, been extended to include treatment for non-neuronopathic symptoms of type III Gaucher's disease.

Imiglucerase has now replaced Ceredase for virtually all patients, with over 200 patients with Gaucher's disease in the UK receiving ERT.

Cerezyme is produced by genetically engineered Chinese hamster ovary cells that carry multiple copies of the human gene for glucocerebrosidase. It is purified from the culture medium and then treated in the same way as Ceredase to uncover

mannose residues. The amino acid sequences of the two proteins are identical except at position 495, where arginine is present in Ceredase but histidine in Cerezyme. *In vitro* studies indicate that this amino acid substitution has no effect on catalytic activity. The carbohydrate structures of the two differ because these are added by enzyme systems that differ between human and hamster. Limited supplies of Ceredase are said to be still available, but nearly all therapy now uses Cerezyme.

Vials of 200 units (U) and 400 U of Cerezyme provide lyophilised powder containing 212 and 424 U of imiglucerase together with citrate buffer constituents, mannitol and non-ionic surfactant Polysorbate 80. Small amounts of cross-linked gelatine polypeptides may also be present. The powder is reconstituted in sterile water at 40 U ml^{-1}. The appropriate dose for a patient is diluted to 100–200 ml with isotonic saline and administered by intravenous infusion over 1–2 hours followed by a flush of 50 ml. Home treatment is common and well tolerated.

Genzyme's Cerezyme product leaflet recommends that doses be individualised, the range suggested being 2.5 U kg^{-1} three times a week to 60 U kg^{-1} every 2 weeks, corresponding to 30–120 U kg^{-1} a month. Thus, at the high dose of 60 U kg^{-1} one infusion for a 70-kg adult requires 4200 U which can be assembled from 10 × 400-U vials plus 1 × 200-U vial.

In type III Gaucher's disease, the recommended starting dose for children is the same as that for type I patients.[27] However, doses of 120 U kg^{-1} every 2 weeks have been given.[28] Adult doses for type III disease are not stated as the patients present earlier in life and as yet not many treated individuals would have reached adulthood.

Intravenously administered glucocerebrosidase is cleared rapidly from the circulation; if enzyme delivery to desired target cells is to be maintained over a long period then, in theory, continuous exposure at a concentration that appropriately matches the affinity of receptors on these target cells may represent an ideal situation. Large doses of enzyme administered across large time intervals are less likely to satisfy these conditions and may lead to loading of therapeutically irrelevant cells that may possess low-affinity/high-density receptors. Thus, in theory, as expounded by Beutler and colleagues,[8] a high frequency of administration coupled with an adequate dose level may be expected to be a more pharmokinetically efficient, if less convenient, treatment regimen that could be associated with considerable cost savings.

Other specific treatments for Gaucher's disease

A substrate reduction therapy for Gaucher's disease has recently been licensed in Europe for those mild to moderately affected patients unsuitable for ERT or for whom ERT is not a therapeutic option. The active ingredient, miglustat (also termed Zaveska®, Vevesca and OGT 918), is *N*-butyldeoxynojirimycin, a piperidine sugar analogue (imino sugar analogue of glucose) that inhibits glucosylceramide synthase, the first enzyme in the biosynthetic pathway of glycosphingolipids. A trial of miglustat reported reduced organomegaly and small haematological improvements after 12 months of therapy.[29] Results from extension of the trial to 36 months have been reported.[30,31]

Monitoring patients with Gaucher's disease

The National Specialist Commissioning Advisory Group (NSCAG) has produced guidelines for the treatment and assessment of patients with type I Gaucher's disease.[32] The International Collaborative Gaucher Group (ICGG)[33] has made minimum recommendations for monitoring ERT-treated and non-ERT-treated adult patients with type I disease, and similar recommendations for paediatric patients have been published.[34] Comprehensive serial monitoring of all clinically relevant aspects of the disease according to a recommended schedule is suggested. Assessments encompassed in the recommendations are physical examination, patient-reported quality of life, haemoglobin and platelet count, visceral and skeletal involvement with specified radiological techniques, and biomarkers. Recommended frequency of monitoring is greater for ERT patients and monitoring of ERT patients is adjustable according to improvement towards therapeutic goals or the development of significant clinical complications.

Current service provision

Since 1997, 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. NSCAG has provided diagnosis and management advice for adults and children with Gaucher's disease and recommends that all newly diagnosed patients should be referred to one of the four designated units (see below) to determine the correct

treatment. Once treatment is established it can be carried out on a shared-care basis with the patient's local doctor.

Thus, in England and Wales all patients currently have the right to have access to one of the four expert centres which are designated to run services for patients with Gaucher's disease. Two are for children, Great Ormond Street (under Dr Ashok Vellodi) and the Royal Manchester Children's Hospital (under Dr Ed Wraith), and two are for adults, Addenbrooke's Hospital (under Dr Tim Cox) and Royal Free Hospital (under Dr Atul Mehta).

Until recently, prescriptions for Cerezyme in England and Wales were automatically funded by primary care trusts or their predecessors, the Health Authorities, by convention rather than mandate, often under a risk-sharing arrangement. However, in 2004 at least one region in England decided against funding Cerezyme treatment for further patients with Gaucher's disease.[35] From 1 April 2005 NSCAG took on responsibility for commissioning policy on Gaucher's disease in England (Austin D, West Midlands Specialist Services Agency; personal communication, 2005) and consequent costs will fall on local purchasers whether they can afford it or not. Health Commission Wales, the body responsible for specialist services in Wales, which is part of Welsh Assembly Government, is producing its own policy because of concerns over escalating costs.

EU orphan drug legislation states, "…patients suffering from rare conditions should be entitled to the same quality of treatment as other ...".[36] Some argue that this obliges health services to pay for any effective therapy for a rare disease, but this could lead to adoption of therapies unconstrained by their cost-effectiveness. Moreover, this statement refers to research issues rather than reimbursement.

Burden to the NHS

The current costs of Cerezyme are £595 per 200-U vial and £1190 per 400-U.[37] Prices are in UK pounds.

The annual drug cost of treating a 5-kg infant and a 70-kg adult with Cerezyme at the recommended dose of 60 U kg^{-1} every 2 weeks is £30,000 and £325,000, respectively. However, clinicians individualise (lower or raise) doses, especially for adults. According to expert opinion the current average cost per adult patient is approximately £90,000 per annum and the average cost per patient in England and Wales around £86,000 per annum.

Estimating the financial cost to the NHS is difficult because of the uncertainty around the prevalence rates, and lack of information about the distribution of treated patients and doses. Assuming a dose of 60 U kg^{-1} every 2 weeks and that there are about 200 patients in the UK receiving ERT, this would give a burden for drug cost to the NHS of £6 million to £65 million depending on the distribution of patients' weights. Expert opinion is that ERT is currently costing the NHS £20 million per annum. This is consistent with the mean cost per patient cited and the rough number of patients known to be on treatment (over 200). Recent changes to the Cerezyme licence mean that the number of patients treated may increase as type III patients are now covered, although, according to the Gaucher Association, most are already being treated off-licence.

If ERT prolongs life in those who would otherwise have succumbed to the disease before reaching maximal adult weight, it is likely that over time the annual drug cost will shift upwards.

Chapter 3
Methods

Introduction

This review addressed the following questions:

- What is the prevalence of Gaucher's disease?
- What is the clinical effectiveness of ERT for Gaucher's disease?
- What is the natural history of Gaucher's disease?
- What is the cost-effectiveness of ERT for Gaucher's 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 to estimate the likely clinical effectiveness and cost-effectiveness of ERT.

Search strategies

Scoping searches

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

Primary studies

Broad search strategies were used so that publications on effectiveness, natural history of the disease, and prevalence and incidence would be captured.

References from searches of MEDLINE, Cochrane Library, EMBASE and CINAHL from their inception to August 2003 were obtained from an existing Reference Manager database that was compiled for a previous rapid review.[38]

The searches were updated from Jan 2003 to 2004 using the following bibliographic databases:

- MEDLINE (Ovid) 2003 to July week 5 2004
- EMBASE (Ovid) 2003 to week 32 2004
- CINAHL (Ovid) 2003 to July week 5 2004
- Cochrane Library (CENTRAL) 2004 Issue 3
- Science Citation Index (SCI) (Web of Knowledge) 1981 to August 2004.

Terms for β-glucocerebrosidase were added to the updated searches to identify references that may have been missed previously. Searches on these terms were run in the databases for the period of the original searches. The full search strategies are provided in Appendix 1.

Ongoing and completed but unpublished studies

The following sources were searched on 17 August 2004:

- National Research Register 2004 Issue 3, http://www.update-software.com/National/search.htm. The same strategy for searching CENTRAL as above was used.
- Clinical Trials.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 MEDLINE.

Inclusion and exclusion criteria

References were placed in an electronic bibliographic database and categorised by

- whether secondary or primary research and whether purely biological/biochemical in intention
- presumed study design
- 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 and 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 3*.

TABLE 3 *Inclusion criteria*

Criterion	Incidence/prevalence	Natural history of disease	Effectiveness
Study design	Primary study	Any primary study conducted before adoption of ERT[a] with at least ten patients	Any primary study with at least ten patients
Population	People with Gaucher's disease type I or III		
Intervention/ comparator	Not relevant	Not ERT, none or other (e.g. before and after study with non-ERT treatment)	Different ERT or none (i.e. before and after study with ERT) or other (e.g. imino sugar therapy, transplant therapy, splenectomy therapy)
Outcomes	Prevalence or incidence of Gaucher's disease	Any clinical or patient-relevant outcome (e.g. QoL, symptoms, fractures, clinical signs, spleen size, liver size, haematological parameters, disease markers, frequency of other interventions such as pain relief, splenectomy, bone-marrow transplantation)	

[a] The adoption of ERT will not necessarily be contemporaneous in all states or regions.
QoL, quality of life.

Studies were excluded from the review if they only reported biochemical/biological outcomes.

Data extraction

Data were extracted by one reviewer and 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 type I Gaucher's disease described in literature reviews[39] and highlighted in discussions with clinical experts and Genzyme, the manufacturers of Cerezyme.

Clinical effectiveness

Data on study characteristics, quality and results reported were extracted into tables by one reviewer and checked by another.

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 or probably cohort or case–control designs, the quality assessment was performed using quality recommended criteria.[40] For other studies the following broad criteria were used, based on factors that influence the generalisability of findings reported in case-series:

- Were eligibility criteria explicit?
- Was the sample source/selection described?
- Were the patients assembled at the 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 stated?
- Were reasons for withdrawals stated?

Where the number of patients assigned was the same as the number analysed it was assumed that withdrawals did not occur and thus were accounted for, even in the absence of an explicit statement by the authors. 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.

As most effectiveness studies were not controlled, to estimate the extent to which the outcomes observed were the results of ERT, it was important to consider what would have happened to the patients in the absence of ERT. Thus, 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 [Database of Abstracts of Reviews of Effectiveness (DARE)] 2004 Issue 3
- Cochrane Library [NHS Economic Evaluation Database (EED)] Issue 3 2004
- Health Economic Evaluation Database (HEED) July 2003
- MEDLINE (Ovid) 1966 to July 2004
- EMBASE (Ovid) 1980 to August 2004.

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

Chapter 4
Results

Search results

Existing systematic reviews

Two existing reviews were identified. The first was published in 1996 by the Wessex Institute of Public Health Medicine. This was a rapid review on Ceredase in the treatment of type I Gaucher's disease.[41] The report concluded that Ceredase is beneficial, but of high cost, and that more work was needed to determine the optimum dose. Most of the included studies in this report were of uncontrolled trials with a limited number of cases, and the maximum follow-up period appears to have been 2 years.

The second, an unpublished rapid review written in 2004,[38] was produced at the request of a local NHS agency to inform local commissioning policy. This report concluded that Cerezyme is beneficial, but that even with optimistic assumptions the incremental cost–utility exceeds £200,000 per quality-adjusted life-year (QALY). This report provided a foundation for sections of the present report.

Primary studies: number and types of studies identified

After removal of duplicate references, the literature search yielded 4430 references (*Figure 1*). Of these, 331 were judged to be potentially relevant for the prevalence, natural history or effectiveness reviews, of which 83 satisfied the inclusion criteria for the effectiveness review.

Prevalence

Gaucher's disease is rare and the exact prevalence of the condition is unknown. No published primary studies were found reporting on the prevalence of Gaucher's disease in the UK but there were studies performed in other national populations. Findings in the 14 publications that satisfied inclusion criteria are summarised in *Table 4*. Several of the studies report numbers of cases detected, but are unclear about the size of the denominator population.[42–45] The best conducted studies and those most relevant to the UK would appear to be the Dutch,[46] Portuguese[47] and Australian[48] studies.

The Australian population was described as mainly of British extraction with significant contribution from other European countries and to a lesser extent Asian countries. None of the three studies disaggregated type III Gaucher's disease from type II data. The Dutch and Portuguese studies reported rates for early (aged <15 years) and late (aged >15 years) diagnosed patients. Assuming similarity between the UK population and those in

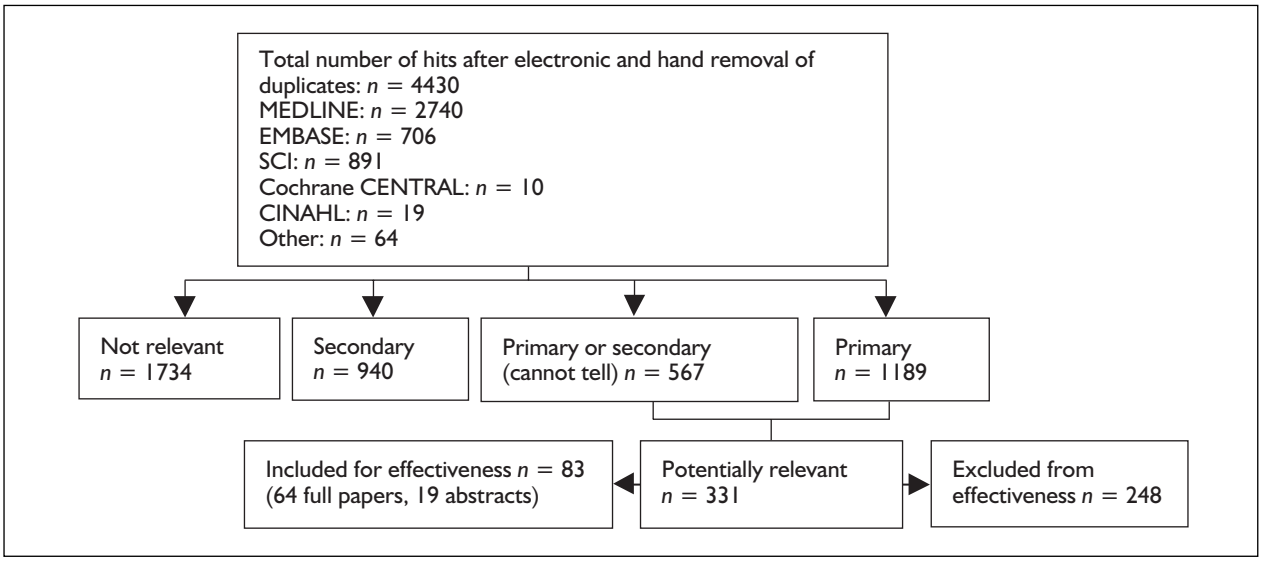

FIGURE 1 *Flowchart of study identification*

TABLE 4 *Prevalence studies of Gaucher's disease*

Study	Output and method	Ascertainment period	Prevalence (*n*/100,000)	
Poorthuis, 1999,[46] Netherlands	Birth prevalence (records from clinical genetic centres) (no. of enzyme-confirmed diagnoses in period/no. of live births in same period)	1970–1996	All types Types II and III Type I early[a] Type I late[b]	1.16 0.26 0.26 0.64
Meikle, 1999,[48] Australia	Birth prevalence (patient referral records, national referral laboratory) (no. of enzyme-confirmed diagnoses/no. of live births in same period)	1980–1996	All types	1.75
Pinto, 2004,[47] North Portugal	Birth prevalence (referrals to national laboratory for diagnosis of LSDs) [no. of enzyme-confirmed diagnoses/no. of live births between the birth years of the oldest and youngest patients (birth period)]	1982–2001	All types Types II and III Type I early[a] Type I late[b]	1.35 0.55 0.30 0.50
Dionisi-Vici, 2002,[49] Italy	Disease 'incidence' [incidence proportion] (case reports in paediatric reference centres, $n = 23$, in Italy) (no. of diagnoses[c] in persons up to 17 years of age/no. of live births in same period)	1985–1997	All types	2.48
Ozkara, 2004,[50] Turkey	Birth 'incidence'[d] (referrals for enzymic analysis at national centre) (no. of cases/no. of live births in same period)	1997–2000	Type II and III	0.45
Applegarth, 2000,[51] Canada	Disease 'incidence' (referrals to central pediatric provincial laboratory) (no. of enzyme-confirmed cases/no. of live births in same period)	1972–1996	All types	0.39
Czartoryska, 1994,[42] Poland	Number detected (national clinics for paediatric referral)	1975–1993	NA	
Michelakakis, 1995,[45] Greece	Number detected (national clinic for referral)		NA	
Goldblatt, 1979,[52] South Africa[e]	Minimum prevalence (nationwide survey) (no. detected/no. of total population)	7 years	Type I	0.5
Swart, 1987,[53] South Africa[f]	Minimum prevalence (referrals to central hospital) (no. detected/no. of total population)	1971–1984	Type I	0.4
Fried, 1973,[54] Israel	Minimum prevalence (study of hospital records)	?–1966	All types	10
Coelho, 1997[44] Brazil and others	Number detected (referrals to specialist diagnostic laboratory)	1982–1995	NA	
Krasnopolskaya, 1993,[43] USSR	Number detected (referrals to specialist diagnostic laboratory)	1982–1992	NA	
Giraldo, 2000[55]	National survey by questionnaire	1993–1999	NE	

[a] Diagnosed at age <15 years.
[b] Diagnosed at age >15 years.
[c] Postnatal diagnoses only.
[d] With neurological symptoms.
[e] Afrikaner population.
[f] Cape coloured population.
LSD, lysosomal storage disease; NA, not applicable; NE, not estimated.

these three studies, their consistency of methods and results allows approximate estimations for the UK.

About 25% of the 59.6 million UK population is under 15 years old;[56] assuming rates of diagnosed type I Gaucher's disease from Dutch and Portuguese studies to be approximately in the range 0.26–0.30 and 0.5–0.64 per 100,000 for people aged less than 15 years and over 15 years, respectively, one would expect about 39–45 and 223–286 diagnosed cases in the UK in these age

groups, giving a total of 262–331 cases. On a pro rata basis, England and Wales would encompass 87% of these (228–288). This estimate is not inconsistent with quoted figures for the UK.

The UK Gaucher's Association knows of 264 patients with Gaucher's disease in the UK, 24 of whom have type III disease. Under 200 (about 190) of these currently receive ERT (Lewis S, Gaucher's Association, London: personal communication, 2005). There are four NSCAG-designated Gaucher's centres in England and Wales and these see a few more patients than the 264 patients the Association knows about, but because of data protection and confidentiality laws, information cannot be exchanged with the Gaucher's Association (Lewis S, Gaucher's Association, London: personal communication, 2005). The Dutch study reported 70 type I diagnoses in 26 years from 1970 to 1996. Taking the Dutch population at midpoint (1983) as approximately 14.7 million (from 2004 population 16.4×10^6, growth 0.51% per annum:[57] $N=N_0 \exp -0.0051t$), then about 0.183 new diagnoses were made per year per million population. Pro rata extrapolation to England and Wales yields 9.5 new diagnoses of type I Gaucher's disease per year. Applying the same calculation to the Australian figures yields approximately 13 new diagnoses per year.

Gaucher's disease is well known to have unusually high prevalence in the Jewish Ashkenazi population; Fried[54] estimated a prevalence of 1 in 10,000.

Frequency studies of disease-causing mutations in the gene for glucocerebrosidase have been reported for those diagnosed with Gaucher's disease[19,20] and general populations; these indicate that, at least for some mutations such as N370S, many asymptomatic individuals exist who are mutant at both alleles but never come to the attention of medical services for Gaucher's disease-related manifestations.[8] This, together with the large number of identified different disease-causing mutations, means that these studies are of little use in estimating the overall numbers of diagnosed cases, their severity and the consequent requirements for service provision. It is clear that with rare exceptions (e.g. homozygosity for the D409H and for the L444P) the allelic combination of mutations in an individual is not predictive of disease severity and that unidentified factors of genetic background and/or environment are influential for the clinical course of the disease.

Clinical effectiveness

Quantity and quality of research available

Number of studies

Of 331 potentially useful papers, 83 fulfilled inclusion criteria for effectiveness and 248 were excluded. Many of the primary studies that were considered not to fulfil inclusion criteria were case studies or small case series reporting on members of a single kinship. See Appendix 2 for details of excluded studies and reasons for exclusion. Of the 83 included papers, 19 were abstracts for which no full study was found. These were subsequently excluded as there was insufficient detail for them to be of use. These excluded abstracts are listed in Appendix 3. One included study was published in two separate full papers,[58,59] leaving a total of 63 included studies (shown in *Table 5*).

One relevant ongoing trial was identified.[60] This is an international open-label Phase I/II trial of a new ERT produced by Transkaryotic Therapies (TKT) Inc. that is infused at a dose of 60 IU every 2 weeks for 40 weeks. This glucocerebrosidase is a human gene product generated in a human cell line. Outcomes include haematological parameters and organomegaly measures. The trial started in July 2004 with recruitment reported at 12 type I patients.

Study designs and characteristics

Because study description in many publications was brief or absent, determining the study design and study characteristics was imprecise. In most instances it was difficult to determine whether a study was prospective or retrospective. From most reports it was not possible to distinguish between case series and uncontrolled trials. Brief details of the included studies are listed in *Table 5*. An electronic copy detailing the full data extraction for all studies is available from the authors on request.

Only two RCTs were identified, by Grabowski and colleagues[61] and Schiffmann and colleagues.[28] The Grabowski trial only compared the effectiveness of the placental enzyme Ceredase with the recombinant enzyme Cerezyme. This trial was thus not designed to demonstrate the effectiveness of ERT, but merely the comparative effectiveness of two ERTs. The follow-up in this study was 9 months with 15 patients in each arm. The Schiffmann trial is the only study identified that compared ERT with a concurrent, randomised, control arm with no ERT. This trial randomised 29 patients into three groups receiving vitamin D

TABLE 5 *Major characteristics of included studies*

Study	Study design	Population *n*	Follow-up	Outcome measure; ERT	Comment; multiple or control group
RCTs					
Grabowski, 1995,[61] USA	RCT	30 (15 per arm)	9 months	Hb; Plt; Liv; Spl; ab; Ceredase vs Cerezyme	Randomised comparison; all +ERT
Schiffmann, 2002,[28] USA	RCT	29	24 months	Bone density; Ceredase/Cerezyme	Randomised comparison; + and –ERT groups
Case–control or cohort-like studies					
Brautbar, 2004,[63] Israel	Retrospective Cohort?	79 ERT 149 no ERT	≥ 2 years	Antibody levels; NR	Control group no ERT; + and –ERT groups
Kaplan, 1996,[69] USA	Retrospective Cohort? Before–after	99, 54 ERT; children	2–3 years on ERT	Growth; Ceredase	Control group no ERT; + and –ERT groups
Vlieger, 2002,[64] Netherlands	Case–control-like Retrospective	19 long-term on ERT; 22 no ERT; 46 non-GD controls	NA	MRI bone-marrow involvement; NR	Control group non-GD; + and –ERT groups
Case series with a comparison group					
Alfonso, 2003,[70] Spain	Prospective? Case series Before–after	54 ERT 16 no ERT	1.5 years	SSI, serum lipids, Liv; Spl; Ceredase/Cerezyme	+ and –ERT groups
Beutler, 1995,[71] USA	Retrospective Case series Before–after	45	Mean 63.7 months, median 61 months	Hb; Plt; Liv; Spl; Skel; Growth; Ceredase?	+ and –ERT groups
Cohen, 1994,[66] Israel	Retrospective Matched comparison	32 ERT 27 no ERT	2–36 months	HCG levels; Ceredase	Control age matched no ERT; + and –ERT groups
Dayan, 2003,[65] Israel	Retrospective Matched study Case series	65 (36 ERT) 65 controls (non-GD)	0	Saliva output; NR	Control healthy volunteers
Dweck, 2002,[72] Israel	Retrospective Case series Before–after	56 (33 received ERT, 12 of whom no ERT then ERT, 23 never ERT)	3–9 years	Hb; Plt; Liv; Spl; Skel; Growth; ERT NR	+ and –ERT groups
Elstein, 1996,[73] Israel	Retrospective Case series Before–after	14 (bone complications)	≥ 2 years	Skel; Ceredase/Cerezyme	+ and –ERT groups
Elstein, 2004,[74] Israel	Retrospective Case series	17 ERT 26 no ERT	NR (~9 months?)	Pregnancy outcomes; Cerezyme (implied)	+ and –ERT groups; GD and pregnancy

continued

TABLE 5 *Major characteristics of included studies (cont'd)*

Study	Study design	Population *n*	Follow-up	Outcome measure; ERT	Comment; multiple or control group
Giraldo, 2000,[55] Spain	Retrospective Case series Before–after	155 (114 clinical data; 94 at start of ERT)	Up to 4 years on ERT	Hb; Plt; Liv; Spl; QoL; Ceredase/Cerezyme	+ and –ERT groups; Spanish Registry survey
Hollak, 2001,[75] Netherlands	Retrospective Case series Before–after	12 ERT 9 no ERT	≥ 4 years	Bone-marrow fat fraction; Ceredase/Cerezyme	+ and –ERT groups
Ida, 1999,[76] Japan	Retrospective Case series Before–after	(35); 12 ERT, 2 BMT	≥ 1 year of ERT	Skel; NR	+ and –ERT groups (and 2 BMT patients); follow-up from time of bone involvement, many years in some cases
Kauli, 2000,[77] Israel	Retrospective Case series Before–after	57, 36 ERT; children	1–7 years ERT	Hb; Plt; Liv; Spl; growth; Ceredase/Cerezyme	+ and –ERT groups
Mariani, 2003,[78] Italy	Retrospective Case series Before–after	74; 31 ERT	NR	^{99m}Tc scintigraphic imaging; Ceredase/Cerezyme	+ and –ERT groups
Mistry, 2002,[79] USA	Retrospective Case series Before–after	134 screened for PHT; 9 PHT, 8 ERT	Mean (range) 1–12 (4.6) years	Pulmonary hypertension (asymptomatic/severe life-threatening); Ceredase/Cerezyme	+ and –ERT groups; few patients, rare study on ERT effect on pulmonary hypertension
Murray, 1991,[80] USA	Retrospective Case series Before–after	12 ERT, 11 no ERT; 54 non-GD controls	Unclear	Immune response to therapy; Ceredase	+ and –ERT groups; probably superseded by subsequent studies. Ceredase no longer used
Richards, 1993,[67] USA	Retrospective Before–after	262	3–36 months ERT	Immunological response; Ceredase	Control healthy volunteers
Terk, 2000,[81] USA	Retrospective Case series Before–after	42; 32 ERT, 10 no ERT	12–56 months	MRI bone marrow; Liv; Spl; Ceredase/Cerezyme	+ and –ERT groups
Case series with no comparator group					
Altarescu, 2000,[82] USA	Prospective Case series Before–after	12 start HD, 32 start LD	12 months	Hb; Plt; Liv; Spl; Ceredase	No control group; 10 of the 32 were reported in 1993 in a previous paper; have looked back to select patients. Given different doses and then analysed the results?

continued

TABLE 5 *Major characteristics of included studies (cont'd)*

Study	Study design	Population *n*	Follow-up	Outcome measure; ERT	Comment; multiple or control group
Altarescu, 2001,[83] USA	Retrospective Case series Before–after	21	2–8 years, median 3.5	Hb; Plt; Liv; Spl; growth; Ceredase/Cerezyme	No control group; type III patients
Barton, 1991,[84] USA	Prospective Case series Before–after	12	9–12 months	Hb; Plt; Liv; Spl; Skel; Ceredase	No control group
Beck, 1997,[85] Germany	Retrospective Case series Before–after	13 (6 children)	≥ 12 months	Hb; Plt; Liv; Spl; growth; Ceredase	No control group
Belmatoug, 1995,[86] France	Retrospective Case series Before–after	26 with Skel involvement	Mean (range) 14 (6–24) months	Skel; Ceredase	No control group
Bembi, 1994,[87] Italy	Prospective? Case series Before–after	9 type I, 3 type III	12–24 months	Hb; Plt; Liv; Spl; Skel; growth; Ceredase	No control group
Bembi, 2002,[88] Italy, USA, Germany	Retrospective Case series Before–after	10	3–9 years	Skel; Cerezyme?	No control group
Caubel, 2003,[89] France	Retrospective Case series Before–after	14 type I, 3 type III	1 year	SSI; Hb; Plt; Liv; Spl; Skel; growth; Ceredase/Cerezyme	No control group
Cohen, 1998,[90] Israel	Retrospective Case series Before–after	10	15–54 months	Skel; Ceredase	No control group
Damiano, 1998,[91] USA	Retrospective Case series Before–after	254	1–48 months	QoL; NR	No control group
Ehlen, 1995,[92] Germany	Retrospective Case series Before–after	18	18 months	Hb; Plt; Liv; Ceredase	No control group
Elstein, 1998,[93] Israel	Retrospective Case series Before–after	28	6–24 months	Hb; Plt; Liv; Spl; Cerezyme	No control group; 10 patients from Zimran[121]

continued

TABLE 5 *Major characteristics of included studies (cont'd)*

Study	Study design	Population *n*	Follow-up	Outcome measure; ERT	Comment; multiple or control group
Elstein, 2000,[94] Israel	Retrospective Case series Before–after	15	31–91 months, mean 56.2, median 54	Hb; Plt; Liv; Spl; Ceredase/Cerezyme	No control group; withdrawal of ERT effect; patients self-selected, e.g. personal reasons
Fallet, 1992,[95] USA	Prospective? Case series Before–after	11	2–12 years pre ERT, 6–12 months on ERT	Hb; Plt; Liv; Spl; Skel; Ceredase	No control group
Figueroa, 1992,[96] USA	Retrospective Case series Before–after	14	6 months	Hb; Plt; Liv; Spl; Ceredase	No control group (authors compare with literature results of HD effects)
Giraldo, 2000[97] Spain	Prospective? Case series Before–after	84	>6 months	QoL SF-36 for 57 responders; NR	No control group
Hayes, 1998,[98] USA	Retrospective Case series Questionnaire	16 (13 ERT)	ERT for >6 months	QoL; Ceredase	No control group
Hollak, 1997,[99] Netherlinds	Prospective? Case series Before–after	12	6 months	Hb; Plt; Liv; Spl; REE; Ceredase	No control group, except for REE
Hollak, 1995,[100] Holland	Prospective? Case series Before–after	25	6–18 months	Hb; Plt; Liv; Spl; Ceredase	No control group
Hollak, 1997[101] Holland	Prospective? Case series Before–after	30	12 months	Hb; Plt; Liv; Spl; Coag; Ceredase	No control group
Ida, 2001,[102] Japan	Retrospective Case series Before–after	13 ERT (children)	>3 years on ERT, Ceredase	Hb; Plt; growth; Ceredase	No control group
Lorberboym, 1997[103] USA	Prospective? Case series Before–after	40, 37 ERT	Mean 31.6 months on ERT	Bone marrow changes; Spl; Liv; Ceredase	No control group
MacKenzie, 1998,[104] Canada	Retrospective Case series Survey/questionnaire	25	NR	NR, no quantitative outcome data	No control group

continued

TABLE 5 *Major characteristics of included studies (cont'd)*

Study	Study design	Population *n*	Follow-up	Outcome measure; ERT	Comment; multiple or control group
Magnaldi, 1997,[105] Italy	Retrospective Case series Before–after	26 ERT (22 type I); 20 non-GD controls	≥ 1 year of ERT	Bone marrow; Ceredase	No control group
Masek, 1999,[106] USA	Prospective Case series Survey/questionnaire	37, 25 on ERT	≤ 2 years	QoL; Ceredase	No control group
Olsen, 2003,[68] UK	Retrospective Case series Before–after	24 type I or III children; 21 ERT, 14 evaluated	Unclear	Bone-marrow changes by MRI; Cerezyme	No control group
Pastores, 1993,[107] USA	Retrospective Case series Before–after	33	6–24 months on ERT	Hb; Plt; Liv; Spl; Skel; immune response; Ceredase	No control group
Patlas, 2002,[108] Israel	Retrospective Case series Before–after	103 children; 48 ERT	≤ 4.5 years	Liv; Spl; Ceredase/Cerezyme	No control group
Patlas, 2002,[109] Israel	Retrospective Case series Before–after	100 ERT	2–7 years	Liv; Spl; Ceredase/Cerezyme	No control group; some patients same as in ref. 108?
Perez-Calvo, 1997,[110] Spain	Retrospective Case series Before–after/survey	34	0.5–3 years on ERT	Hb; Plt; Liv; Spl; Ceredase	No control group
Poll, 2001,[58,59] Germany	Retrospective Case series Before–after	30	Mean 36 months	Bone-marrow changes by MRI; Ceredase/Cerezyme	No control group; two publications report identical results
Poll, 2002,[111] Germany	Retrospective Case series Before–after	30	Mean 36 months	Bone-marrow changes by MRI; Hb; Plt; Liv; Spl; Cerezyme	No control group; are these same 30 patients as ref. 59
Rice, 1996,[62] USA	Retrospective Before–after	39; 32 type I, 21 ERT	NR	Hb; Plt; Liv; Spl; Ceredase	No control group; very few quantitative data
Rosenberg, 1999,[112] USA	Retrospective Case series Before–after surveillance	1122	≤ 18 months	Immunological response; Ceredase/Cerezyme	No control group

continued

TABLE 5 *Major characteristics of included studies (cont'd)*

Study	Study design	Population *n*	Follow-up	Outcome measure; ERT	Comment; multiple or control group
Rosenthal, 1995,[113] USA	Prospective? Case series Before–after surveillance	12	42 months	Skel; Ceredase	No control group
Schaison, 2002,[114] France	Retrospective Before–after	108	Variable	Liv; Spl; Hb; fatigue; pain; Ceredase/Cerezyme	No control group
Verderese, 1993,[115] USA	Prospective? Case series Before–after questionnaire	12	6 months	Symptom score; Ceredase	No control group
Weinreb, 2002,[116] USA	Retrospective Case series Before–after Gaucher Registry	1028	2–5 years	Hb; Plt; Liv; Spl; Ceredase/Cerezyme	No control group
Zaizov, 1995,[117] Israel	Retrospective Case series Before–after	18	1–3.5 years on ERT	Hb; Plt; Liv; Spl; Skel; Ceredase/Cerezyme	No control group
Zimran, 1993,[118] USA, Israel, Netherlands	Retrospective Case series Before–after	33	NR	Hb; Plt; Liv; Spl; Ceredase	No control group; combines three separate studies. Data from refs. 96 and 119
Zimran, 1994,[120] Israel	Retrospective Case series Before–after	29	6–28 months	Hb; Plt; Liv; Spl; Ceredase	No control group
Zimran, 1995,[121] Israel	Prospective Case series Matched pair trial	10	12 months	Hb; Plt; Liv; Spl; Cerezyme	No control group (both groups received ERT)

ab, antibody levels to Ceredase; Coag, blood coagulation factors; GD, Gaucher's disease; Hb, haemoglobin; HCG, human chorionic gonadotrophin; HD, high-dose, LD, low-dose; Liv, liver (volume); MRI, magnetic resonance imaging; NR, not reported; QoL, quality of life; Plt, platelets; REE, resting energy expenditure; SF-36, Short Form 36; Skel, skeletal involvement (outcomes various); Spl, spleen (volume); ^{99m}Tc, technetium-99m.

analogue (calcitriol), or ERT, or ERT plus calcitriol for the first 6 months of the trial.[28]

The studies by Kaplan[69] and Brautbar[63] resembled, and are tentatively classified as retrospective cohort studies, with exposure and non-exposure being represented by +ERT and –ERT, respectively. Vlieger[64] had a case–control-like design with age-matched non-Gaucher's disease patients who had received the same imaging procedures as the treatment group representing the control; this study also included non-ERT Gaucher's disease patients. Dayan[65] used healthy volunteers as controls and was described as a 'prospective' case–control study, but here is listed as a case series. Cohen[66] studied plasma human chorionic gonadotrophin (HCG) levels comparing Ceredase-treated patients with age-matched untreated controls. Richards[67] used healthy volunteers as control in measuring antibody responses to ERT. A further 13 studies examined, and sometimes compared, ERT-treated patients and patients who did not receive ERT, with outcome measures in most made before and after ERT; these were classified as before and after studies and or case series. The remaining 42 studies were uncontrolled.

There were indications that 13 of 61 non-RCT studies may have been prospective. Patient numbers were usually low (typically ten to 30), follow-up was short and patient mix was often ill defined or of unexplained provenance, or both. Only one study[68] examined UK patients. In general there was considerable within-study and between-study heterogeneity.

Quality of included studies

Although the two RCTs[28,61] were of reasonable quality, the Grabowski study[61] failed to mention methods for allocation concealment and blinding and was underpowered for its purpose of demonstrating equivalency. The Schiffmann study[28] was well designed but lack of success in recruitment meant that it also lacked power.

Of the 61 non-randomised studies, 58 case series were assessed using generic criteria described in the section 'Quality assessment' (p. 12). The reporting of these studies generally lacked detail and clarity, so quality assessment depended considerably on marginal interpretation of reports that were not explicit. Their quality is summarised in *Table 6*. The quality of the other three studies[63,64,69] according to design-specific criteria, was moderate and is summarised in *Table 7*. Full details of studies are available in an electronic document upon request to the authors.

General considerations

Few published studies measured what would be considered primary outcomes for the review question, such as quality of life or mortality. Most measured symptom-related surrogate markers that might reasonably be expected to reflect patient well-being; the most frequently encountered outcomes concerned changes in organ volume and haematological changes, particularly haemoglobin

TABLE 6 *Quality summary of case series studies*

	Categorisation of 58 case series according to quality criteria			
Quality criterion	**Yes**	**No**	**Can't tell**	**ND or NA**
Were eligibility criteria explicit?	35	19	–	4
Was sample source/selection described?	28	29	–	4
Were patients assembled at same time?	8	38	9	3
Was a method of diagnosis stated?	34	18	1[a]	5
Were clinical details described?	37	18	–	3
Were individual patient data reported?	27	28	–	3
Was outcome assessment blinded?	6	4	44	4
Was blinding method adequately described?	0	6	–	52
Was follow-up time stated?	43	10	–	5
Were withdrawals stated?[b]	22	30	1	5[c]
Were reasons for withdrawals stated?[d]	22	0	32	4

[a] "With documented GD".
[b] When number analysed = number recruited the withdrawals were assumed to be none and stated implicitly.
[c] Single time-point measure in Ida (1999).[76]
[d] Where withdrawals were zero, reasons are judged implicit and present.
NA, not applicable (e.g. paper refers to alternative publication for details); ND, not determined: study not extracted (Zimran 1993,[118] translation difficulty).

TABLE 7 *Quality summary of studies with cohort and case–control-like design*

Cohort-like design			**Case–control-like design**	
Quality criterion	**Brautbar, 2004[63]**	**Kaplan, 1996[69]**	**Quality criterion**	**Vlieger, 2002[64]**
Were groups and their prognostic factors described?	Yes	No	Was case definition explicit?	No
Were groups assembled at similar stage in disease progression?	Can't tell	Can't tell	Were cases reliably diagnosed?	Probably, but can't tell
Was treatment reliably ascertained?	Can't tell	Can't tell	Were controls randomly selected?	Can't tell
Were groups comparable for confounders?	No	Can't tell	Were cases and controls comparable?	No
Was outcome assessment blinded?	Can't tell	Can't tell	Was assessment equitable for two groups?	Yes
Were dropout rates disproportionate?	NR	Can't tell	Were case and control response rates the same?	Yes
Were reasons for dropouts provided?	NR	NR	Were reasons for lack of response specified?	No
Were dropout rates high?	NR	NA		
Was follow-up sufficient for outcomes?	Yes	Yes		

and platelet levels. A variety of other outcomes was reported that might reflect disease-related skeletal or lung involvement.

The outstanding feature of the published studies was their extreme within-study and between-study heterogeneity, which extended to populations investigated (age range, disease severity, symptoms experienced, proportion splenectomised), treatment regimens administered (dose level, frequency of administration and permittance of raising/lowering of dose during the treatment period), length of follow-up, outcomes measured and their modes of measurement, and the methods selected for representing the results of ERT treatment. The available evidence is therefore very disparate and the heterogeneity precludes any meaningful combination of outcome measures to generate overall effect sizes. The results are therefore summarised below by outcome in a way that reflects the broad range of results reported.

RCT studies: main findings

The RCT by Schiffmann[28] randomised 29 splenectomised adults to three arms: receiving vitamin D analogue, or ERT or ERT plus analogue for the first 6 months of the trial. After 6 months all patients received ERT at doses such that cumulative dose at 24 months was the same in each arm. The ERT-only arm never received analogue, while the other two arms received analogue for the whole 24 months. Outcomes measured included bone density, bone-marrow fat fraction, liver volume, and haemoglobin (g dl^{-1}) and platelet levels ($\times 10^3$ mm^{-3}).

Results for ERT-treated arms from baseline to 24 months are presented with the other before and after studies in the later sections. This section mainly considers the results for the first 6 months, which represent the randomised part of the trial in which a no-ERT control can be compared with ERT. The results for the first 6 months are summarised in *Table 8*. The authors presented graphs showing group means at baseline and at 6 months, but not means for individual patient change at 6 months relative to baseline. There were no significant differences between group means at baseline. The no-ERT group exhibited slight deterioration from baseline in haemoglobin and platelet levels, whereas in both ERT arms increases were observed so that group means for haemoglobin at 6 months were significantly different in the no-ERT versus ERT plus analogue groups ($p < 0.01$) and platelets at 6 months were significantly different in the no-ERT versus ERT-only groups ($p < 0.05$).

The ERT-only group experienced a decrease in liver volume of approximately 25%, while the ERT plus analogue and no-ERT groups experienced small decreases ($p > 0.05$ for all group comparisons).

Large increases in bone-marrow fat fraction relative to baseline were observed in the ERT arms but a decrease in the no-ERT group ($p > 0.05$ for all group comparisons at baseline, $p < 0.001$ for no-ERT group versus ERT-only and ERT plus analogue groups at 6 months); when the no-ERT group subsequently received ERT after 6 months

TABLE 8 *Changes in haemoglobin, platelets, liver volume, bone density and marrow during 6 months of RCT*

	Haemoglobin (g dl^{-1})			Platelets ($\times 10^3$ mm^{-3})			Liver volume (l)			Bone-marrow fat fraction			Bone density by SECT (mg cm^{-3})			Bone density by DECT (mg cm^{-3})		
	No ERT + D *n* = 9	ERT *n* = 10	ERT + D *n* = 10	No ERT + D *n* = 9	ERT *n* = 10	ERT + D *n* = 10	No ERT + D *n* = 9	ERT *n* = 10	ERT + D *n* = 10	No ERT + D *n* = 9	ERT *n* = 10	ERT + D *n* = 10	No ERT + D *n* = 9	ERT *n* = 10	ERT + D *n* = 10	No ERT + D *n* = 9	ERT *n* = 10	ERT + D *n* = 10
Baseline[a]	12.38 (0.37)	11.69 (0.63)	12.81 (2.31)	249 (33)	252 (26.5)	199 (19.9)	3.5 (0.28)	3.41 (0.31)	3.16 (0.43)	6.1 (0.74)	7.2 (1.6)	7.2 (1.6)	151.1 (23.4)	150.1 (19.0)	151.8 (18.4)	144.4 (28)	159 (32.5)	155.6 (34.3)
6 months[a]	11.94 (0.5)	12.0 (0.56)	13.87 (0.31)	239 (26)	339 (36)	272 (23)	3.3 (0.26)	2.73 (0.28)	3.0 (0.49)	3.6 (0.83)	14.3 (1.3)	12.0 (1.8)	148.1 (29.8)	141.8 (17.1)	144 (18.5)	144.7 (28.8)	150 (52.1)	144 (30.4)
Group % change from baseline	–3.5%	2.76%	8.3%	–4%	34%	37%	–5.6%	–24.9%	–6.2%	–41%	99%	67%	–2%	–6.2%	–5.2%	0%	–6%	–7.8%

Data are mean (SE). Data were read from graphs and then group percentage change from baseline was calculated; SE could not be read reliably from graphs in all cases.
[a] Graphs depict SE but are labelled SD.
D, vitamin D analogue calcitriol; SECT and DECT, single-energy and dual-energy computed tomography.

TABLE 9 *Results of studies that reported change in global scores of disease severity after ERT*

Study	Outcome output	Result and time					*p*
		Diagnosis	Baseline	6 months ERT	12 months ERT	18 months ERT	
Alfonso, 2003[70]	Mean (SD) SSI		11.0 (3.7)			9.0 (3.0)	<0.001 vs baseline
Caubel, 2003[89a]	SSI	8.8	14.2	11.4	8.1		
	Clinical score[b]	2.7	5.7	2.84	1.1		NR
Hollak, 1995[100]	*Overall response*[b]						
	No response			7/25	8/19	1/7	NR
	Moderate response			17/2	8/19	4/7	
	Good response			1/25	0/19	0/7	
	Complete response			0/25	0/19	0/7	

[a] Data read from graph (no SD provided), study of paediatric patients.
[b] Outcome measured as proportion of patients with each type of response using author's own clinical scoring system for disease severity.

the group mean fat fraction increased in a similar way to the ERT groups (see in *Table 11*). Bone density remained unchanged (–2% and 0% change by SECT and DECT, respectively) in the no-ERT group, but decreased in both ERT arms according to both measurement procedures ($p > 0.05$ for all group comparisons). After 6 months bone density continued to deteriorate in both ERT arms (see *Table 11*); it also deteriorated in the no-ERT patients when they received ERT from 6 months onwards. Schiffmann and colleagues interpreted these findings as indicating that absence of ERT for 6 months might have delayed adverse bone density changes and increases in bone-marrow fat fraction.

The results of this RCT support the conclusion that ERT delivers beneficial effects for anaemia, thrombocytopenia and hepatomegaly, but that inducing changes in bone marrow may in fact exacerbate the development of osteopenia at certain sites in splenectomised adults.

The RCT by Grabowski[61] compared Ceredase and Cerezyme with 15 patients in each arm; individual patient data were provided for pre-ERT and after 9 months of ERT. The results did not demonstrate a difference in effectiveness between the two enzyme preparations, but was not powered to show equivalence. Nonetheless, in this review, based on laboratory studies, both ERTs will be considered to be equivalent and to exert a class effect. In essence, for the purpose of assessing the effectiveness of ERT, this study does not differ in design from other before and after studies that report results for populations treated with either one or other or both of the enzymes; therefore, the results were combined for all 30 patients and these are presented together with the other before and after studies in the following sections.

Effects of ERT on health-related quality of life

Five studies[55,91,97,98,106,115] made reference to health-related quality of life (HRQoL) changes subsequent to ERT, but none included utility values. One study[115] was uninterpretable owing to incomplete reporting. These studies and other quality of life studies of Gaucher's disease are reviewed in the section 'Review of quality of life data in type 1 Gaucher's disease' (p. 55).

Effects of ERT on global scores of disease severity

The Zimran SSI[16,17] provides an overall or global score of disease severity for patients with different symptomatic features. It encompasses patient scores for cytopenia, organomegaly of spleen and liver, liver disease and liver function tests, skeletal involvement, CNS and other organ (lungs, kidneys) involvement. Lower scores imply less severity (see *Table 2* for further details). Many studies[55,71,72,74,77,93,94,96,100,101,120,121] report the SSI for patients at baseline, but only Alfonso[70] and Caubel[89] report on SSI before and after ERT; both studies used the early SSI version,[16] which included age at diagnosis as a scoring factor. Caubel[89] also compared this result with that using their own alternative clinical global score. One further study, by Hollak,[100] reported results in terms of another overall response score. The results of these studies are summarised in *Table 9*.

All three studies indicated improvement in patients' global score after ERT treatment. The two scoring systems used by Caubel[89] delivered essentially parallel changes through time, with 12 months of ERT reducing severity scores below those at diagnosis.

Effects of ERT on organomegaly

Liver and spleen volumes were estimated by a variety of techniques, including:

- palpation or ultrasound to determine the linear extension of the organ below the costal margin, registered in centimetres. Unfortunately, this measure depends on two variables (ribcage morphology and organ size). Normality is defined when extension = 0 cm
- ultrasound to determine the product of the three longest measures along the axes length, width and depth. This is registered in cubic centimetres and termed 'the organ volume index'. It is not equivalent to the actual organ volume. Some authors convert volume index to a more real value using an equation that relates ultrasound to MRI measurement of organ volume
- MRI or computed tomographic (CT) scans; the result is registered in cubic centimetres.
- a measure termed cranial caudal diameter (in centimetres) has also been used for the liver.[111]

MRI and CT are recognised as the most accurate and precise of these procedures.

Volume, and changes in volume subsequent to ERT, were reported in various ways. Some authors quoted organ volumes (cm^3) or volume index, at various time-points. However, if these are not related to body size the values have limited meaning. Some studies report percentage change in organ volume at various time-points relative to

baseline: however, the significance of these changes depends on the initial size of the organ and its degree of enlargement. The most meaningful parameter reported was the degree of enlargement relative to that expected for body weight and how this changed with ERT.

Liver

According to Weinreb's analysis of 496 patients in the ICGG Gaucher Registry,[116] pre-ERT liver enlargement of ERT-treated patients is about 1.93-fold, with splenectomised patients (n = 114) having greater enlargement (2.43-fold, SD 1.34) than patients (n = 382) with an intact spleen (mean 1.78, SD 0.7).

Fourteen data sets were found in the included studies[61,82–84,87,93,95,96,99,107,108,116,120] that reported on ERT changes in liver volume in terms of enlargement above normal or provided sufficient data for this to be calculated. These results are summarised in the scatterplot shown in *Figure 2*.

Investigators considered the volume of the liver to be normal if it was less than 1.2 times that expected, assuming that the liver should be 2.5% of body weight. Baseline enlargement ranged from 1.74-fold to 3.3-fold (the latter in a study of type III patients) with large standard deviation, reflecting the different severities of disease in the study populations and the small number of patients in studies. Mean enlargement approached normalisation on ERT treatment in several studies, with those studies with longest follow-up reaching the lowest mean values. In most studies the follow-up was too short to see the full extent of volume decrease. Weinreb[116] reported data indicating that the proportion of patients with enlarged liver (>1.25-fold normal) reduced from 80% to 45% after 2 years of ERT, and this agrees approximately with the mean and lower SD values for the studies shown in the scatterplot.

Four studies[55,70,110,117] reported liver changes in terms of centimetres of extension of the organ beyond the costal margin (*Figure 3*). The full results are summarised in Appendix 4.

Liver size approximates to normal when extension beyond the costal margin is zero. The pattern of

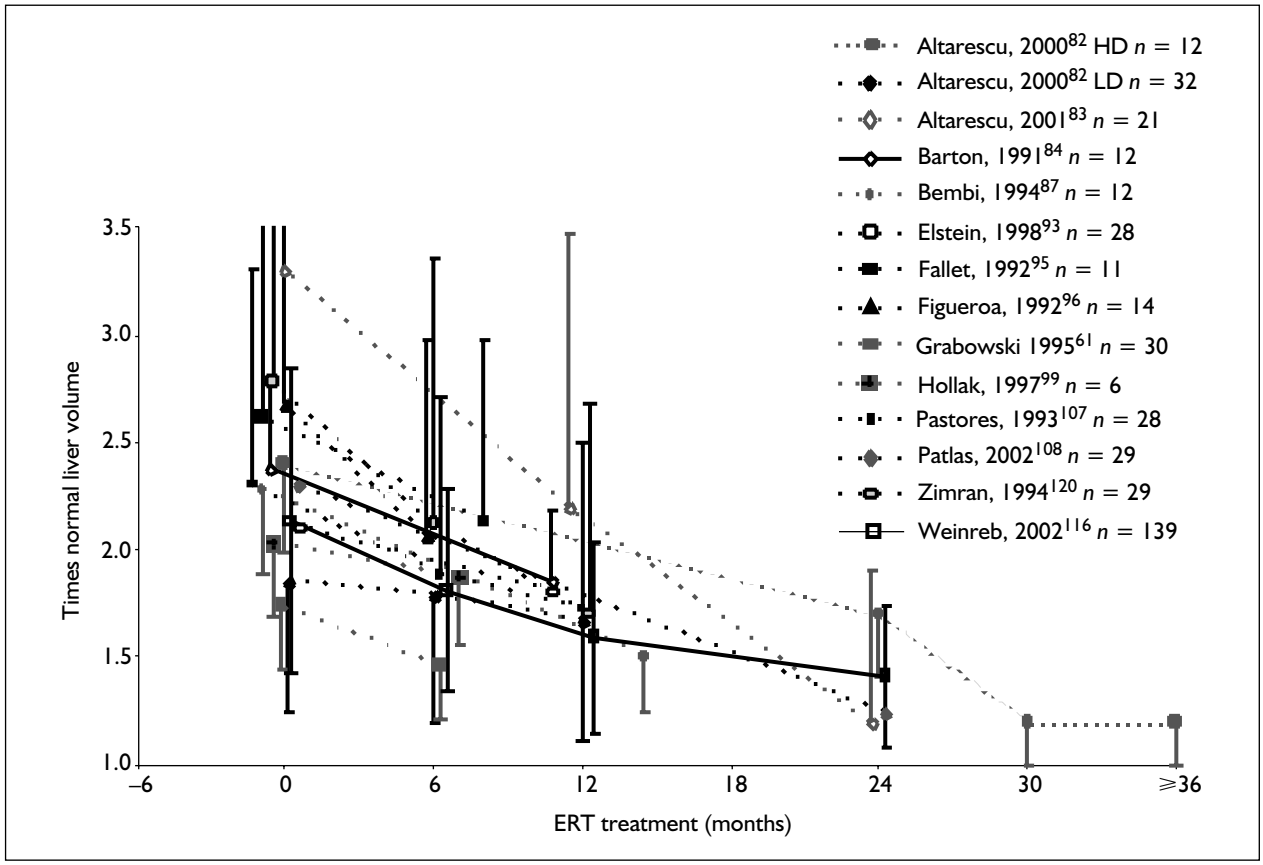

FIGURE 2 *Change in degree of liver enlargement above normal with duration of ERT treatment. Error bars (where calculable) are standard deviation;* n *refers to numbers of patients at baseline. Altarescu (2000)[82] contained high-dose (HD) and low-dose (LD) responses and these are shown separately.*

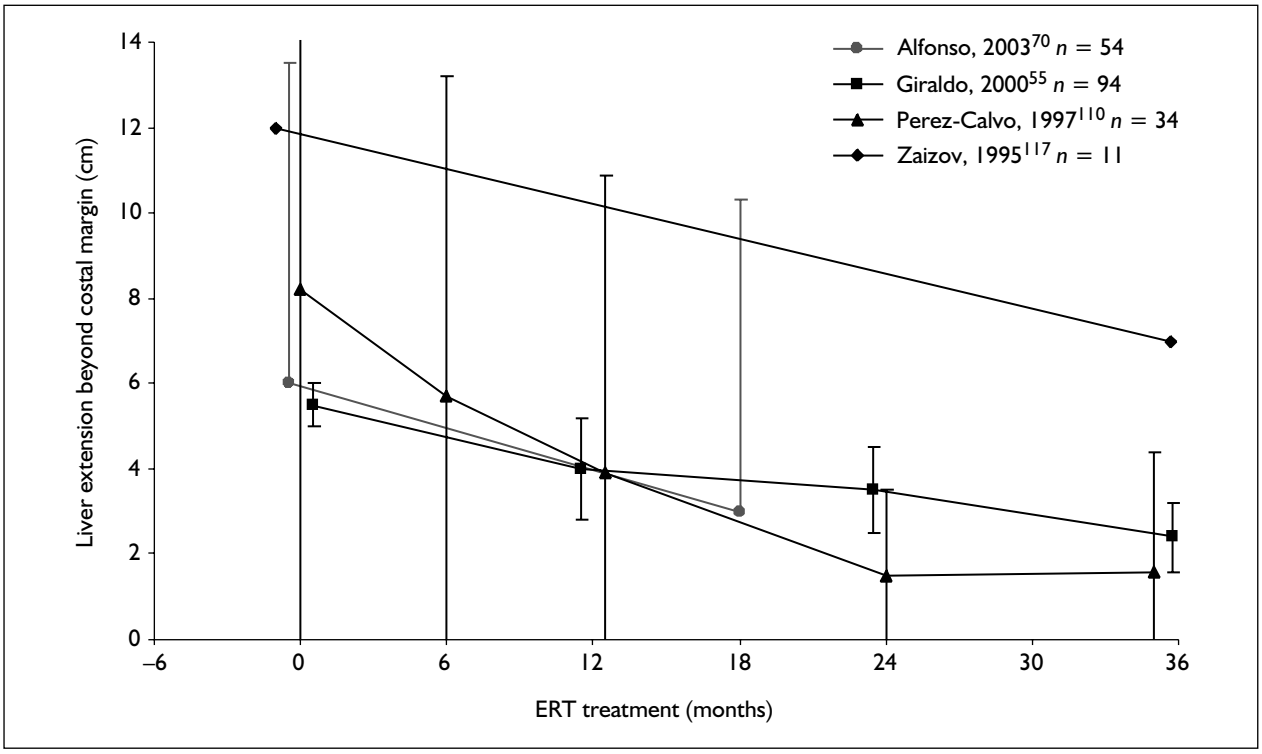

FIGURE 3 *Change in extension of liver beyond costal margin with duration of ERT treatment. Error bars (where calculable) are standard deviation;* n *refers to numbers of patients at baseline.*

results in these studies corresponds approximately with those for the factor of enlargement over normal (*Figure 2*).

Several studies reported other measures of liver volume at baseline and time-points after ERT. These included liver volume, volume index, percentage change in individual or group liver volume, or volume index relative to baseline. In some cases these could be calculated from data provided. These results are summarised in *Table 33* (Appendix 4). These measures give an indication of change during ERT and show reduction in size but, without information on body size, or starting volume in the case of percentage change, they have little precise meaning.

Spleen

According to Weinreb's analysis of 400 patients in the ICGG Gaucher Registry,[116] pre-ERT mean enlargement of the spleen of ERT-treated patients is about 19-fold (SD 16).

Twelve data sets (in 11 included studies[61,82–84,87,93,95,96,99,107,116]) reported change in spleen volume during ERT in terms of degree of enlargement or provided sufficient data for the appropriate calculation to be made. The results are summarised in the scatterplot shown in *Figure 4*. Mean baseline enlargement in these studies ranged from 15-fold to 50-fold, with large standard deviations indicating patient heterogeneity within studies and small numbers analysed. Nearly all patients had spleens enlarged over five-fold before ERT. In all studies considerable reduction in mean enlargement was observed, with means and lower SD values approaching approximately five-fold in most studies by 6–12 months of ERT and an approximate 50% reduction in degree of enlargement. Follow-up appeared rarely sufficient for total achievable reduction to have been monitored. Weinreb[116] reported data indicating that ERT reduced the proportion with spleen enlarged over five-fold from approximately 88% to approximately 66% after 2 years. Caubel[89] reported a 58% reduction in degree of enlargement after 12 of months ERT. These values correspond approximately with the data shown in *Figure 4*.

Four publications[55,70,110,117] reported change in spleen volume measured in linear extension beyond the costal margin. These results are summarised in *Figure 5* and *Table 34* (Appendix 4).

These results correspond approximately with those shown in *Figure 4*, which describe changes in spleen enlargement during ERT.

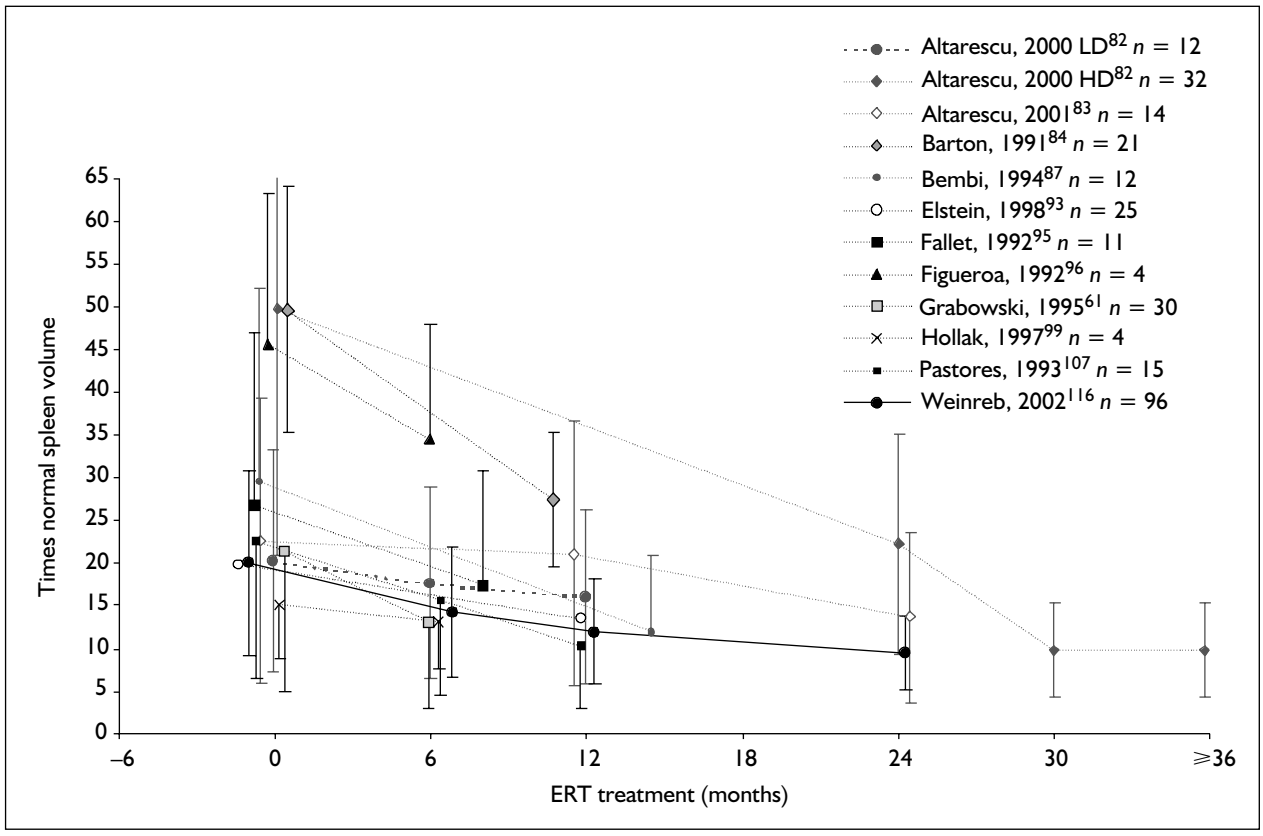

FIGURE 4 *Change in degree of spleen enlargement with duration of ERT treatment. Error bars (where calculable) are standard deviation;* n *refers to numbers of patients at baseline. Altarescu (2000)[82] contained high-dose (HD) and low-dose (LD) responses and these are shown separately.*

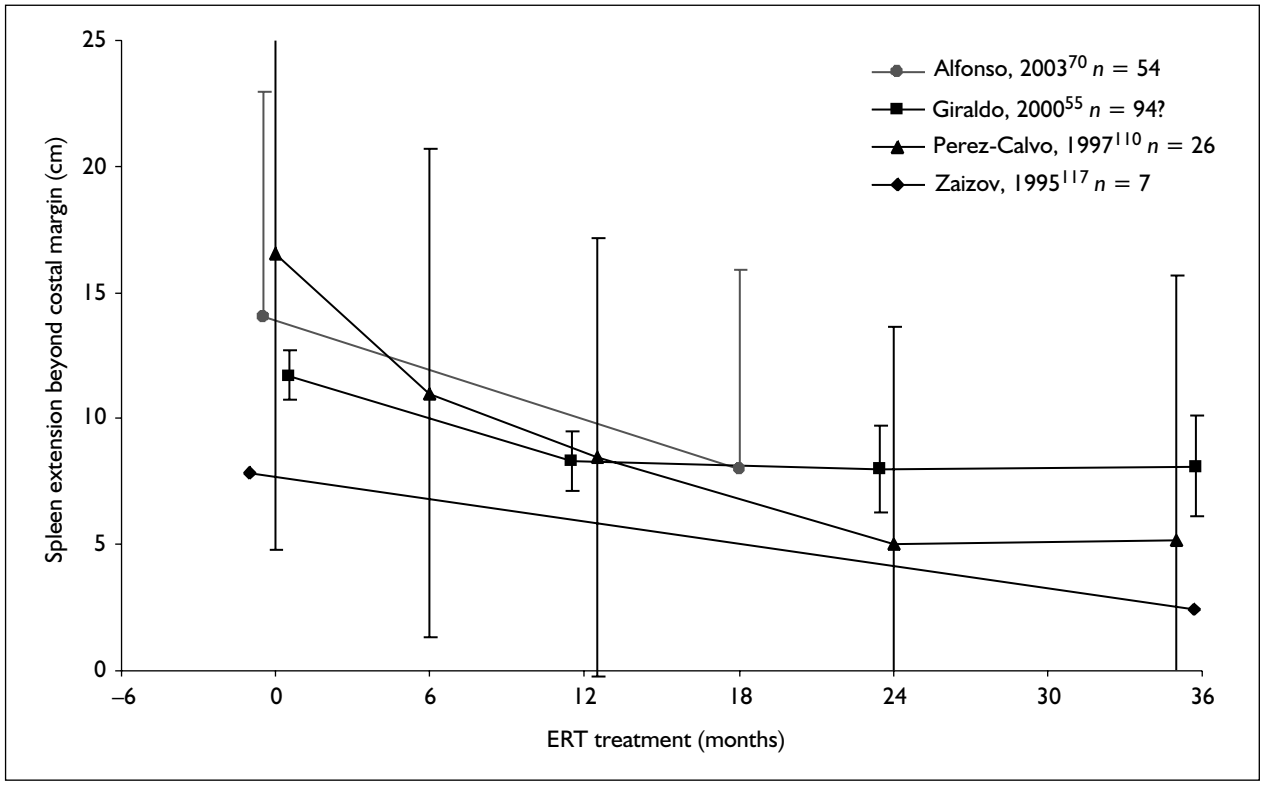

FIGURE 5 *Change in extension of spleen beyond costal margin with duration of ERT treatment. Error bars (where calculable) are standard deviation;* n *refers to presumed numbers of patients at baseline.*

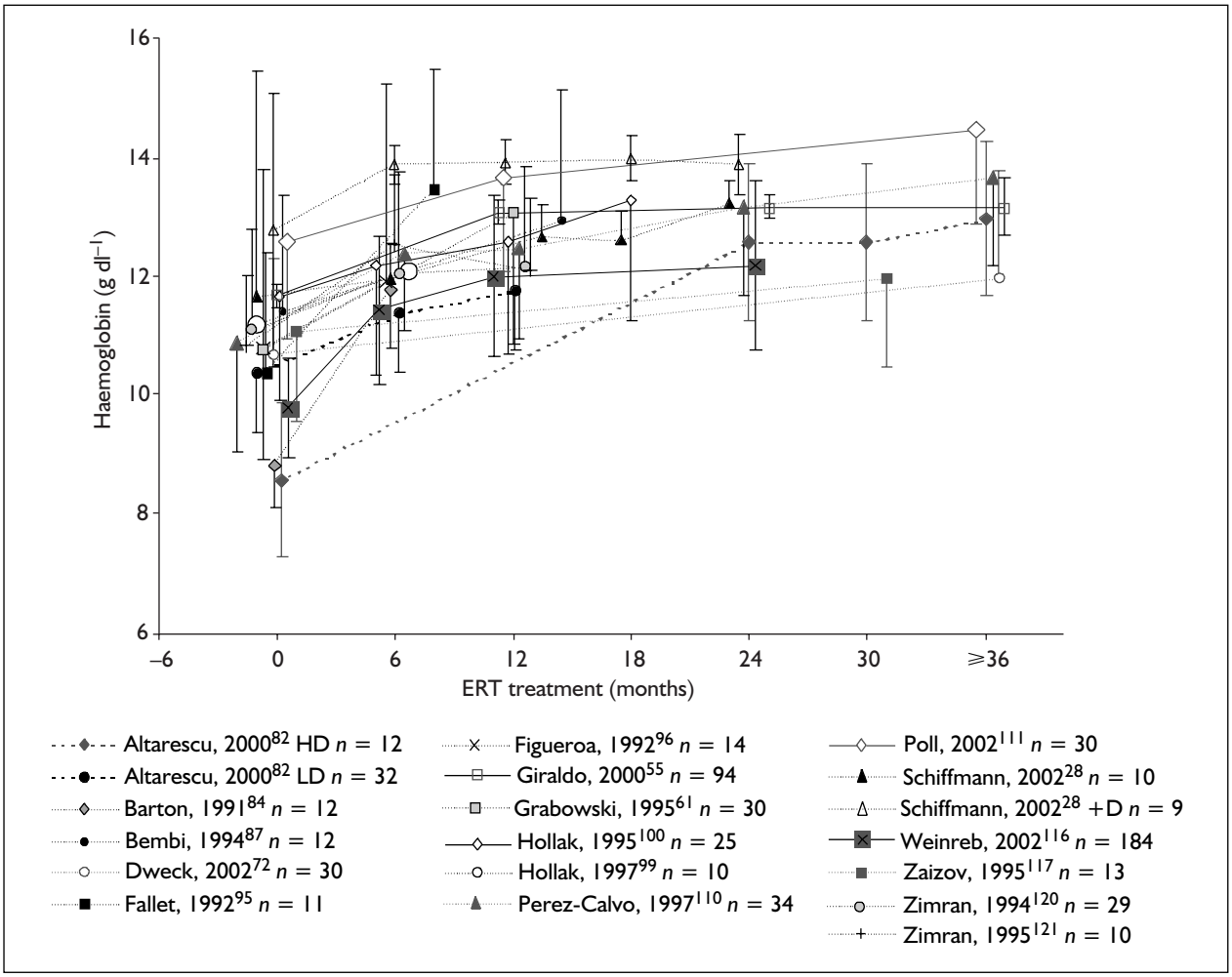

FIGURE 6 *Change in haemoglobin levels with duration of ERT treatment. Error bars (where calculable) are standard deviation;* n *refers to presumed numbers of patients at baseline. Altarescu (2000) contained high-dose (HD) and low-dose (LD) responses and these are shown separately.*

Effect of ERT on haemoglobin levels

The normal haemoglobin range is usually acknowledged to be around 12–16 g dl^{-1}. According to Weinreb's analysis of 911 patients in the ICGG Gaucher Registry,[116] the pre-ERT haemoglobin level of ERT-treated patients averaged 11.31 g dl^{-1}, with splenectomised patients (n = 269) having higher levels (mean 11.8, SD 1.7) than patients (n = 642) with intact spleens (mean 11.1, SD 1.8). Nineteen data sets (16 studies[28,55,61,72,82,84,87,95,96,99,100,110,111,116,117,120,121]) reported haemoglobin levels in terms of grams per decilitre during ERT. *Figure 6* summarises the results.

The mean pretreatment haemoglobin level ranged from 8.6 to 12.8 g dl^{-1}; therefore on average, the study patients were anaemic. According to ICGG Gaucher Registry analysis 63% of splenectomised and 94% of non-splenectomised patients have haemoglobin levels below 12 g dl^{-1} pre-ERT and 11% and 24% have levels below 10 g dl^{-1}, respectively. The data in *Figure 6* show that after about 1 year of ERT haemoglobin levels, on average, approach the lower end of the normal range. Treatment beyond 1 year appears to bring about a relatively small further increase in haemoglobin level. Caubel[89] reported that after 6 and 12 months of ERT mean gains in haemoglobin were 1.5 and 1.9 g dl^{-1}, respectively. The data shown in *Figure 6* correspond reasonably with these values, as does the mean increase of 10.5% at 6 months and 11.2% at 12 months reported by Elstein[93] for a group with baseline mean haemoglobin of 11.3 g dl^{-1} (n = 28).

Effect of ERT on platelet levels

According to Weinreb's analysis of 910 patients in the ICGG Gaucher Registry,[116] pre-ERT platelet numbers of ERT-treated patients averaged 140.8×10^3 mm^{-3}, with splenectomised patients (n = 267) having strikingly higher numbers (mean

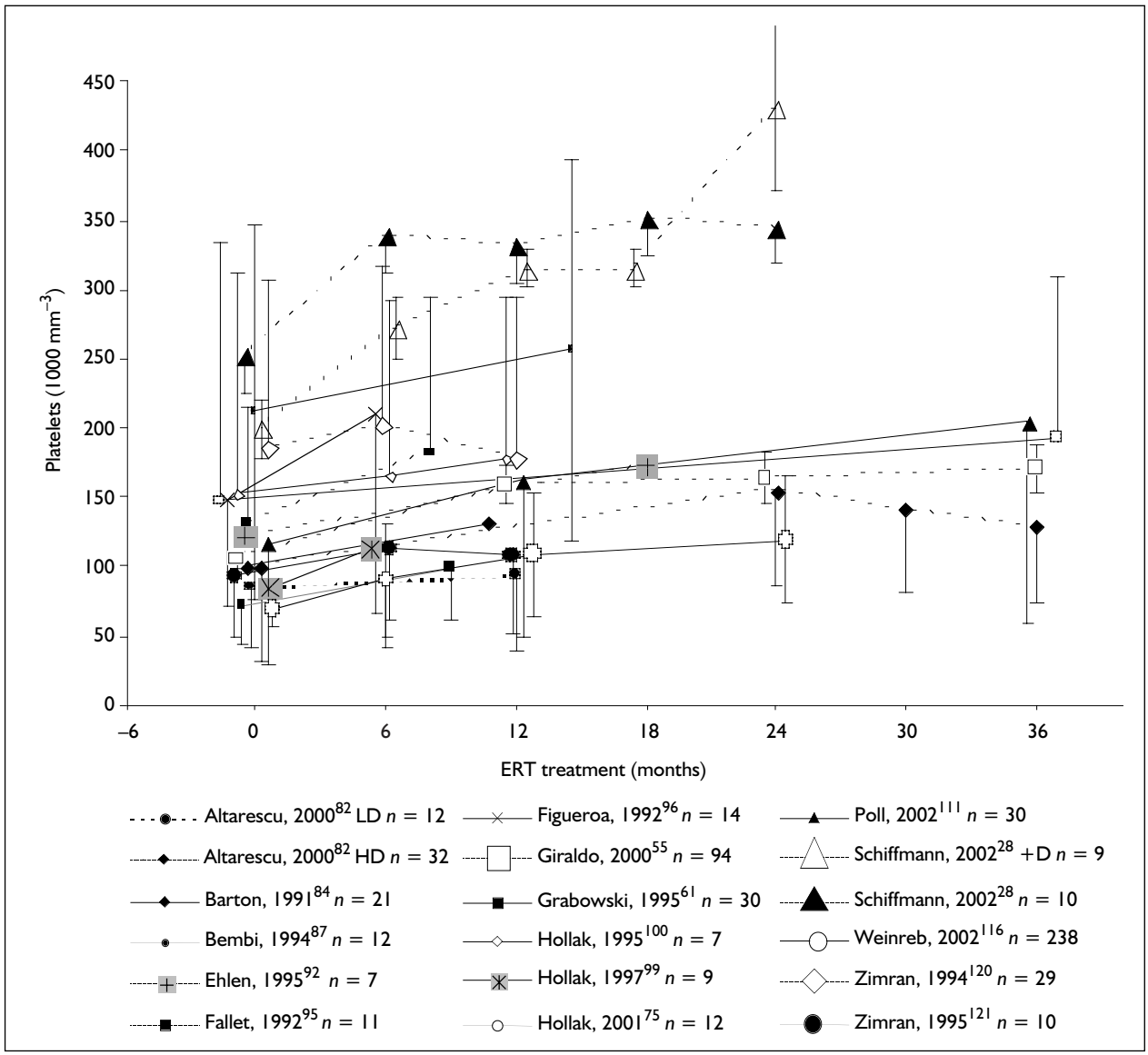

FIGURE 7 *Change in platelet numbers with duration of ERT treatment. Error bars (where calculable) are standard deviation;* n *refers to presumed numbers of patients at baseline.*

240, SD 125) than patients (n = 643) with intact spleens (mean 92, SD 57). The lower end of the normal range is approximately 150×10^3 mm^{-3}. Eighteen data sets (16 studies[28,55,61,75,82,84,87,92,95,96,99,100,111,116,120,121]) reported change in platelet numbers during ERT. The results are summarised in *Figure 7*.

Baseline levels in these studies ranged from 71.4 to 252×10^3 mm^{-3}, although in most studies mean baseline levels were below the lower normal range, indicating that patients may have a tendency towards bleeding. ERT increased mean platelet levels in all studies. The response was apparently slower than that observed for haemoglobin and appeared poorer for studies where the patients started at a lower pre-ERT level.

Effect of ERT on skeletal involvement

Investigators reported several outcomes that are thought to relate to skeletal manifestations of Gaucher's disease. These included bone-marrow status, bone or joint pain or bone crises, bone density or thickness and fracture rates. A measure of bone-marrow status was the most commonly reported outcome. Measurements were made using a variety of methods and outcomes reported in a variety of ways. *Table 10* summarises these results.

These studies demonstrate changes in bone marrow during ERT that presumably depend on or reflect the replacement of Gaucher cells in the marrow by the more normally resident cell types. The relationship of these marrow changes to

TABLE 10 *Bone-marrow changes during ERT*

Study	Measurement method and output unit	Baseline/ follow-up	Outcome results Mean (SD)	*p*
Altarescu, 2001[83a]	MRI signal intensity at 11 anatomical sites. Units on an 11-point scale	Baseline 2–6 years ERT	3.7 (1.9), $n = 9$ 2.4 (1.3) $n = 9$	
Rosenthal, 1995[113b]	MRI signal intensity at 11 anatomical sites (lower extremities). MRI score on an 11-point scale	Baseline 6 months ERT 42 months ERT	6.42 (2.54) $n = 11$ 6.17 (2.48) $n = 12$ 4.64 (2.58) $n = 11$	p vs baseline ns $= 0.006$
Vlieger, 2002[64]	MRI vertebral bone-marrow signal intensity ratio to nearby bone signal intensity; 'vertebral disc ratio'		Mean change vs baseline	p vs baseline
		1 years ERT 2 years ERT 3 years ERT 4 years ERT	0.14, $n = 11$ 0.10, $n = 12$ 0.12, $n = 11$ 0.14, $n = 13$	<0.05 <0.05 <0.05 <0.05
Rosenthal, 1995[113]	MRI Dixon quantitative chemical shift. Lumbar fat fraction, % of total proton signal (normal values stated as 15–20%)	Baseline 6 months ERT 42 months ERT	7.27 (6.73), $n = 12$ 8.96 (6.01), $n = 12$ 22.92 (6.58), $n = 11$	p vs baseline ns <0.001
Hollak, 2001[75]	MRI Dixon quantitative chemical shift at ROI, three lumbar vertebrae. Fat fraction, % units	Baseline 4 years ERT	20.5 (10), $n = 12$; 3/12 normal 37.7 (10), $n = 12$; 11/12 normal	NR
Schiffmann, 2002[28c]	MRI Dixon quantitative chemical shift. Lumbar fat fraction, % of total proton signal	Baseline 6 months ERT 12 months ERT 18 months ERT 24 months ERT	7.2 (1.6), $n = 20$ 13.2 (1.4), $n = 20$ 14.1 (0.7), $n = 20$ 14.7 (1.0), $n = 20$ 14.5 (1.7), $n = 20$	Significance tests in this study were between ERT and no ERT
Rosenthal, 1995[113b]	^{133}Xe (breathed) uptake by bone marrow. Gamma camera counts/unit time at distal femoral and proximal tibial metaphyses	Baseline 6 months ERT 42 months ERT	0.152 (0.067), $n = 11$ 0.134 (0.051), $n = 12$ 0.099 (0.030), $n = 9$	p vs baseline ns $= 0.018$
Poll, 2001[58,59]	Bone marrow MRI signal intensity (femur and tibia), subjective interpretation of images (blinded assessors) to determine whether increased signal after ERT, patients classified as responders	Median follow-up 36 months ERT	19/30 were responders	NR
Beutler, 1995[71]	Bone-marrow MRI signal intensity (vertebral); subjective interpretation of images. Proportion of patients with increased signal intensity after ERT	Median follow-up 26 months ERT (range 20–37)	4/4 improved marrow signal	NR
Terk, 2000[81]	Bone-marrow MRI signal intensity (femur); subjective interpretation of images. Proportion of patients with increased signal intensity after ERT	Median follow-up 36 months ERT	14/32 with increased intensity	NR
Lorberboym, 1997[103]	^{99m}Tc (i.v.) scintigraphy; subjective interpretation of gamma camera images at femora/tibia (peripheral) and sternum/pelvis/lumbar (central). Proportion of patients with improved or changed marrow distribution after ERT	Mean (SD) follow-up 31.6 (11.5) months	Central: 14/19 improved Peripheral: 20/24 detectable changes	<0.001 NR

[a] Type III patients; [b] seven of 12 patients aged less than 17 years; [c] Data from two ERT arms combined; data read from graph; all patients splenectomised.
ns, not significant; ROI, region of interest.

skeletal manifestations of the disease or to patient well-being is uncertain.

Six included studies reported bone mineral density or bone thickness changes during ERT. The results are summarised in *Table 11*.

The results from several studies that included children[83,88,113] indicated that during ERT bone thickness and bone density tended to move towards more normal values expected for the age and gender of the child. Rosenthal and colleagues[113] remarked that children in their

TABLE 11 *Bone density and thickness changes during ERT*

Study	Measurement method and output unit	Baseline/ follow-up	Outcome results Mean (SD)	*p*
Bembi, 2002[88a]	X-ray absorptiometry to measure bone mineral density (lumbar spine); *Z* score away from normal	1st read[b] 2 years later 5.5 years later	–2.17 (1.25), *n* = 10 –1.58 (0.31), *n* = 10 –0.99 (0.86), *n* = 10	NR
Rosenthal, 1995[113c]	Dual-energy quantitative CT measure of trabecular bone density (lumbar spine); mg cm^{-3} converted to % of normal for age	Baseline 6 months ERT 42 months ERT	92.0 (12.6), *n* = 12 89.8 (13.0), *n* = 12 97.9 (10.7), *n* = 11	*p* vs baseline ns = 0.016
Schiffmann, 2002[28d]	Dual-energy quantitative CT measure of trabecular bone density (lumbar spine); mg cm^{-3}		(ERT) (ERT + D)	
		Baseline	159.0, *n* = 10 155.6, *n* = 10	
		6 months ERT	150.0, *n* = 10 144.4, *n* = 10	
		12 months ERT	142.2, *n* = 10 152.2, *n* = 10	
		18 months ERT	147.8, *n* = 9 144.4, *n* = 9	
		24 months ERT	138.9, *n* = 8 142.2, *n* = 8	
Schiffmann, 2002[28d]	Single-energy quantitative CT measure of trabecular bone density (lumbar spine); mg cm^{-3}		(ERT) (ERT + D)	
		Baseline	151.1, *n* = 10 151.8, *n* = 10	
		6 months ERT	141.8, *n* = 10 144.0, *n* = 10	
		12 months ERT	140.0, *n* = 10 148.1, *n* = 10	
		18 months ERT	140.7, *n* = 9 142.0, *n* = 9	
		24 months ERT	133.7, *n* = 8 133.7, *n* = 8	
Altarescu, 2001[83e]	Plain X-ray determination of mid femur cortical thickness; % of normal thickness for age	Baseline 1–6 years ERT	72.3% (24.2), *n* = 9 85.5% (10.2), *n* = 9	*p* vs baseline = 0.04
Elstein, 1996[73f]	Plain X-ray determination of mid femur cortical thickness (calculated as a % of bone width[g]). Also proportion of patients with increase, decrease or no change	Baseline 2.5 years (median) ERT	33, *n* = 14 40, *n* = 14 13/14 increase, 1/14 no change	NR
Rosenthal, 1995[113c]	Plain X-ray determination of mid femur and tibial cortical thickness. mm converted to % of normal for age	Baseline 6 months ERT 42 months ERT	64.1 (14.9), *n* = 12 67.2 (12.1), *n* = 12 85.5 (17.7), *n* = 11	*p* vs baseline ns = 0.01[h]

[a] Italian data only; patients all children.
[b] First read during year 1 of ERT.
[c] Age range 7–42 years.
[d] All patients adult and splenectomised.
[e] Type III patients mostly children (18/21 <10 years old).
[f] All adult patients.
[g] Calculation method not clearly explained.
[h] All increases occurred in children (6/12 patients <16 years old).

sample accounted for all of the increase in bone thickness observed. The numbers of children in these studies were small and the results strongly dependent on the estimate of normal values.

The study by Schiffmann[28] on splenectomised adults indicated a diminution of bone density with ERT that extended over 2 years of treatment. Without a control group one cannot necessarily attribute this to ERT rather than disease progression. However, the first 6 months of this study had an RCT design and included an untreated control group that, in contrast to the ERT-treated groups, failed to show loss of bone density or increase in marrow fat fraction during the first 6 months of the study. Subsequently, this group also received ERT and then displayed the reduction in bone density with time that was observed in the other two groups. The balance of the small amount of evidence available indicates that ERT may be accompanied by reduced bone density, but that in children this may be masked by growth changes that make comparisons through time difficult to interpret.

A few studies reported quantitative or semi-quantitative information on bone pain, joint pain or bone crises before and during ERT. It was not always clear how the outcome had been measured

TABLE 12 *Bone pain changes during ERT*

Study	Baseline pre-ERT/follow-up time on ERT	Results
Weinreb, 2002[116a]	Baseline	59% with chronic bone pain; 41% no chronic bone pain; $n = 668$
	During 1 year of follow-up on ERT	35% with chronic bone pain; 65% without chronic bone pain
	During second year of follow-up on ERT	30% with chronic bone pain; 70% without chronic bone pain
Weinreb, 2002[116b]	Baseline	29% with bone crises; 71% without bone crises; $n = 668$
	During 1 year follow-up on ERT	18% with bone crises; 82% without bone crises
	During second year of follow-up on ERT	5% with bone crises; 70% without bone crises
Bembi, 2002[88cd]	Pre-ERT	2/10 experienced bone pain
	Follow-up 3–9 years	0/10 experienced bone pain
Caubel, 2003[89c]	Pre-ERT	12/17 experienced joint pain
	1 year follow-up	6/17 experienced joint pain, 4 of the 6 with reduced pain
Cohen, 1998[90c]	Median follow-up 30 months	Relative frequency of bone crises over equal pre-ERT and post-ERT durations: 4/10 unchanged during ERT; 2/10 increased during ERT; 4/10 decreased during ERT
Fallet, 1992[95]	Median follow-up 8 months	6 patients reported reduced pain intensity and frequency; $n = 11$
Schaison, 2002[114]	Pre-ERT	14% with bone pain
	6 months ERT	Bone pain diminishes
	1 year ERT	Further reduction in bone pain; $n = 108$
Belmatoug, 1995[86]	Follow-up 6 to 24 months	Most reported a subjective reduction in bone pain; $n = 26$
Beutler, 1995[71]	Median follow-up 26 months ERT (20–37)	4/4 improved

[a] Data calculated allowing for low follow-up rates after ERT initiation.
[b] Data calculated to allow for low follow-up rates after ERT initiation, no follow-up information for those free of crises at baseline.
[c] Patients in these studies were predominantly or exclusively children.
[d] Italian data only.

and again investigators reported results in various ways. *Table 12* summarises these results.

Bone pain and bone crises appear to diminish in frequency and intensity in many patients given ERT. However, apart from the ICGG Gaucher Registry study of Weinreb,[116] quantitative data are meagre and the pre-ERT duration over which pain or crises were monitored was only clear in the study by Cohen.[90] Several individual descriptions of considerable improvements with regard to pain and mobility in severely disabled patients were reported. Undoubtedly, other examples of this sort could be found among the numerous case studies of individual patients in the literature.

Several studies[71,89,90] provided information on bone fractures during ERT; except for the study by Cohen[90] the fracture rate pre-ERT was not reported. Of ten patients studied by Cohen, four suffered pre-ERT fractures but none subsequent to implementation of ERT; although study duration before and after-ERT was equal for the other outcome monitored (bone crises), it was not clear that this was also the case for fractures. Caubel and colleagues[89] reported absence of fractures in 17 children followed for 1 year on ERT. Beutler 1995[71] reported four patients who experienced fractures during ERT, three during the first year but only one after the first year.

Three studies report data on skeletal involvement that could not be extracted in a convenient form. Ida and colleagues[76] presented associations between severe skeletal involvement and several patient characteristics, including treatment (ERT or BMT) and Mariani[78] and Magnaldi[105] investigated bone marrow with scintigraphy (^{99m}Tc uptake) and MRI, respectively, but data pre-ERT and post-ERT were not extractable.

Adverse events and withdrawals

Most studies did not report adverse events or reported that no serious events occurred. Adverse events appeared not to have been monitored systematically in any of the included studies. Lack of a systematic approach, short follow-up and small patient numbers mean that adverse events, if they occurred, may not have been detected or reported.

Immunological reactions to intravenously infused protein can be anticipated. Three studies specifically investigated seroconversion during ERT with placental enzyme (Ceredase). Murray and colleagues[80] observed no conversion in the 12 patients (ERT for 8.5–19 months). Richards[67] and Rosenberg[112] studied 262 and 1122 patients followed for 3 months to 3 years and 18 months, respectively. Seroconversion with immunoglobulin G (IgG) antibodies occurred in approximately 13% of patients (median time to conversion 6 months), was transient, lasting for few months, and was followed by tolerance. No corresponding studies were found that were specific for recombinant enzyme. In the RCT by Grabowski and colleagues[61] six out of 15 and three out of 15 seroconverted with Ceredase and Cerezyme treatment, respectively, during 9 months of ERT, suggesting that the recombinant enzyme may be no worse immunologically than the placental preparation.

Richards and colleagues[67] report that 14 patients out of 262 (~5%) experienced episodic immediate hypersensitivity-like reactions associated with pruritus, urticaria, upper airway involvement, and chest and abdominal discomfort. Lack of evidence of immunoglobulin E (IgE) antibodies and the demonstration of increased complement degradation products (>50% C3 conversion) indicated that these reactions were probably IgG mediated. Rosenberg and colleagues[112] reported that 74 out of 1430 patients (~5%) had similar reactions again attributable to IgG. Schaison and colleagues[114] studied 108 patients on ERT for a mean of 3 years and reported two severe anaphylactic shock reactions.

Other adverse events that were reported apparently occurred infrequently and were categorised as follows: precocious puberty (high-dose Ceredase containing HCG) 1/21;[83] mild diarrhoea 'few';[86] transient hypocalcaemia 4/12;[87] abdominal discomfort at infusion 1/29[120] or abdominal pain 1/45;[71] and catheter-associated infection or event 'few'.[100] In 500 patient-months of therapy Beutler and colleagues[71] reported that two patients developed catheter infections; pruritus 3/30,[61] and 2/32;[107] nausea or dizziness 1/29,[120] and 'few';[114] and pruritus, nausea or dizziness 3/30.[61]

In many studies the number of patients recruited was greater than the number analysed; reasons for discrepancy were unclear, but probably mainly due to losses to follow-up and records missing in retrospective studies. Although withdrawals from treatment were mentioned in a few studies (see *Table 6*; full details are available in electronic format from the authors), no studies estimated rates of withdrawal formally. Elstein and colleagues[94] studied the effect of withdrawal on outcome measures in 15 patients apparently from a pool of an unspecified number (>100) of treated patients; the reasons for withdrawal were listed as: financial constraints $n = 5$, personal concerns $n = 4$, pulmonary hypertension $n = 3$, personal concerns about pulmonary hypertension $n = 1$, reactive arthritis $n = 1$ and desire to serve in the army $n = 1$. Schaison and colleagues[114] studied 108 patients in receipt of ERT for a mean of 3 years and reported ten withdrawals from treatment for reasons of pregnancy or a clear impression of improvement or cure. Withdrawals for pregnancy were recorded in other studies,[74] as were withdrawals for financial reasons.[117]

Other outcomes reported

Other outcomes and parameters reported in patients treated with ERT included: blood lipoprotein particle concentrations and blood lipids,[70] resting energy expenditure,[99] blood coagulation factors,[101] saliva output,[65] pregnancy outcomes,[74] growth trajectory in children,[69,77] and right ventricular systolic pressure (RVSP).[79] Full details are available in electronic format from the authors.

Mistry and colleagues[79] examined 134 consecutive patients referred for comprehensive clinical examination, 94 in receipt of ERT and 40 not. Before and after ERT measures for several outcomes were provided, but for PHT, rather than reporting data for ERT-induced changes the authors compared the prevalence of asymptomatic PHT (>35 < 50 mmHg) and symptomatic PHT (>50 mmHg RVSP) amongst treated and untreated patients. Symptomatic disease was rare (1/134). Asymptomatic PHT was more common in non-ERT than in ERT-treated patients (12/40 versus 7/94, $p < 0.001$) and mean RVSP was higher (30 versus 23 mmHg, $p < 0.001$). Regression analysis indicated that among ERT-treated patients asymptomatic PHT was associated

with increased age but not with treatment duration. Mistry also reported a reduction in RVSP observed in eight patients referred for severe PHT and treated with ERT, supplemented with vasodilators in most cases. The authors concluded that many Gaucher's disease patients are predisposed to develop PHT and that ERT, with or without vasodilators, should be initiated for those at high risk.

In some studies, notably that of Beutler and colleagues,[71] individual patient data were reported in graphical form with variable scalings for the axes. Extracting these data was too labour intensive to be undertaken within the constraints of this review; the relatively small numbers involved mean that this would not be expected to influence overall trend of results reported here.

Intervention type and dose

Despite methodological limitations, small patient numbers and short follow-up, the Grabowski RCT that compared Ceredase with Cerezyme[61] appears to demonstrate equivalent efficacy of the two preparations. In all subsequent publications little or no distinction has been made by the investigators between results obtained with patients treated with either enzyme or both enzymes.

Among and within the included studies a great variety of dosage regimens was used (e.g. Bembi[87] delivered five different dose regimes among 11 patients, and Ida[76] and Figueroa[96] delivered three between 12 and 14 patients respectively). Variation occurred in terms of cumulative monthly dose, frequency of infusions and dose level of a single infusion. In addition, initial dose regimens were often modified, by either escalation or diminution of dose or its frequency, during an individual patient's course of treatment. The initial monthly cumulative dose ranged from 20 to 480 IU kg^{-1},[83] the dose/infusion from 1 IU kg^{-1} [96] to 120 IU kg^{-1} and frequency of infusion from daily[96] to once every 2 weeks. Regimens termed high dose generally accumulated 60–120 IU kg^{-1} per month, while low dose corresponded to <30 IU kg^{-1} per month (e.g. ~15 IU kg^{-1} per month[99]). Often dose regimens were described as "individualised".[75,92,95] Adoption of an initial dose programme for a given patient was generally based on clinical judgement relating to disease severity and prognosis, whereas changes in regimen were usually dependent on clinical judgement regarding the speed and extent of response to therapy and the remaining scope for further improvement. The criteria exercised in these clinical judgements were rarely reported other than in descriptive terms (e.g. "particularly fast progression"), but discussion with experts reveals that changes in surrogate markers are often used as indicators of progression.

No study compared the efficacy of different dose regimens in groups of patients that were reliably comparable at baseline. Rather, allocation of different doses within studies was on the basis of differences between patients. This makes valid comparisons difficult and inferences about relative effects of different dose regimens from these studies are likely to be confounded. Some investigators[120] compared different regimens across studies; however, population heterogeneity, small patient numbers and changing dosage during treatment mean that inferences based on these comparisons are highly speculative.

Patient subgroups

Subgroups of patients exist within the included studies.

The most common distinction made was between splenectomised patients and those with an intact spleen. In a few instances baseline characteristics of splenectomised and non-splenectomised patients were provided separately, together with change at time-points during ERT. Except for the report by Weinreb and colleagues[116] the number of patients in each category was small. The heterogeneity at several levels precludes combination of results from different studies.

Comparison of the effect of ERT on surrogate markers in splenectomised and non-splenectomised patients has not been undertaken in groups equivalent to each other at baseline or administered equivalent treatment. Therefore, any observed differences in outcomes may be attributable to a number of factors including disease severity or different dose regimes or spleen status. The largest study was that of Weinreb.[116] Haemoglobin and platelet levels and degree of liver enlargement were compared in splenectomised and non-splenectomised patients at various time-points during ERT. The results were further stratified according to disease severity at baseline using essentially arbitrarily cut-offs to give four subgroups. The only statistically significant difference in ERT response between splenectomised and non-splenectomised patients remarked on by the authors concerned percentage decrease in liver volume; however, since volume decrease is only meaningful in terms of baseline enlargement this result is difficult to interpret. In this study the number of patients with available

baseline data greatly exceeded the number with data at each time-point during ERT [for haemoglobin there were data for 911 patients at baseline (70% non-splenectomised) of whom 589 were anaemic, but data for only 184 (73% non-splenectomised) were analysed at time-points up to 2 years]. Only results for patients who were anaemic at baseline were included. This means that there may be selection bias as patients included for data at ERT time-points may not be representative of the ERT population. To compare baseline values for patients used for determining the effect of ERT with those of the whole baseline patient population, it was necessary to reaggregate data for the subgroups. When this was done some imbalance was found (for haemoglobin, initial degree of liver enlargement, and most noticeably for initial platelet levels) between the whole baseline population and the populations used for determining the effects of ERT on these parameters (see *Table 35*, Appendix 5).

Any differential effects of ERT on splenectomised and non-splenectomised patients may be of marginal future relevance since it may be anticipated that there will be few presentations of splenectomised patients.

Some studies reported outcomes only for subgroups of ERT-treated patients exhibiting given levels of severity of particular symptoms at baseline (e.g. thrombocytopenia, anaemia). Again, considerable heterogeneity between studies in terms of treatment, follow-up and patient characteristics makes combination of study results unprofitable. Such subgroup results add little to an understanding of the effects of ERT.

Some studies concerned paediatric populations,[72,88,89] but most included patients across a broad age range. (Full details are available in electronic format from the authors.) Information is too sparse and study details are too various for any conclusions regarding the differential efficacy of ERT in children and adults.

Altarescu and colleagues[83] studied type III patients, and some other studies included type III patients, but only as a small proportion. Again, data are sparse and currently, setting aside neuropathic manifestations of the disease, there is no convincing evidence that type III patients respond differently than type I patients to ERT. One small study of eight type III patients[122] that did not meet inclusion criteria reported stabilisation of neuropathic symptoms after ERT. Formal assessment of the impact on quality of life of ERT for type III patients has not been addressed.

Patient subgroups can be defined by genotype. Genotyping of patients was reported in a number of studies, but was incomplete within studies because of the considerable variety in Gaucher's disease mutations. Other than an abstract,[123] no primary studies were found concerning genotype-related differences in response to ERT.

Conclusions from published data on clinical effectiveness of ERT

Several thousand patients with Gaucher's disease have been treated with ERT, so that accumulated experience probably exceeds 10,000 patient-years. However, the only study of ERT versus non-ERT in which an attempt was made to compare similar groups of patients is represented by the first 6 months of the underpowered RCT of Schiffmann and colleagues,[28] in which 29 patients in three groups were analysed; even here, baseline balance was not guaranteed because of small numbers. In this study a potentially beneficial effect was observed in two haematological surrogates (haemoglobin and platelet levels) and also, less obviously, on hepatomegaly. The rest of the studies are of designs susceptible to many biases and most report little about efforts made to guard against the influence of potential biases. Consequently, although it seems clear that ERT is beneficial, the degree and time-course of benefit have remaining uncertainties.

A considerable number of clinically heterogeneous before and after studies, both uncontrolled and inappropriately controlled (i.e. non-equivalence in compared patients), has been performed. These demonstrate improvements both in haematological parameters and in hepatomegaly and splenomegaly. In general, these parameters on average appear to approach normality in the majority of patients after about 1 year or more of treatment. For organomegaly and haemoglobin the rates and extents of response on average appear greater the more abnormal the pre-ERT condition. Platelet levels appear to improve more slowly and to a lesser degree the more severe the initial thrombopenia. Liver size in most cases approaches 1.2 times that expected for body weight. Spleen enlargement appears to reduce to between five and ten times normal in most patients who had splenomegaly at start of treatment. How these effects on surrogates translate into patient well-being and survival or the need for services and resources has not been reliably estimated.

Quality of life improvements with ERT have been reported. Nonetheless, studies based on the SF-36 indicate that patients on ERT continue to have reduced HRQoL compared with the general population. No studies attached utility values to quality of life measures.

The effect of ERT on skeletal involvement also appears to be positive in terms of pain, crises and fracture rate, but the quantitative evidence for these benefits is extremely weak. The possibility that ERT may exacerbate depletion in bone density argues for caution in interpretation of results and points to the necessity for careful monitoring and supplementary measures that may offset the process.

The high price of ERT, as well as a desire not to expose patients to unnecessarily high doses of a therapeutic agent, has led clinicians to explore lower dose regimens. To make robust inferences about the relative effectiveness of different regimens it is desirable that compared groups of patients should on average be as similar as possible, especially for prognostic factors, so that outcome differences truly depend upon dosage differences. No study was found that performed such a comparison. Individualised dose regimens, varying in infusion frequency and accumulated dose per month, were allocated on the basis of differences between patients, making comparison about the relative effectiveness of various regimens almost impossible. Although some authors believe that the evidence appears to indicate that low doses may achieve similar end-points in surrogate outcomes to high doses (but possibly after a longer period), this conclusion has to be considered tentative as the evidence is muddied by the use of individually tailored regimens.

The evidence about the clinical effectiveness of ERT is, with the notable exception of the first 6 months of the underpowered Schiffmann RCT,[28] entirely based on studies describing the clinical course of patients given ERT with no reliable comparator population. Improvements in most non-neurological outcomes are demonstrated after starting ERT. However, the degree of health gain is likely to exceed that demonstrated by improvement in health state as patients may have deteriorated further had they not received the treatment. Thus, in order to estimate the degree of health gain achieved by the 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 Gaucher's disease so that health gain from treatment can be reliably modelled.

Natural history of type I Gaucher's disease

This section focuses on Gaucher's disease type I and reviews the evidence about the expected progression of the disease in untreated patients. Although this section refers to the natural history of the disease, its focus is the clinical pathway of patients in the absence of disease-modifying ERT and assumes the use of the supportive interventions that constituted standard treatment until the early 1990s when ERT became available.

Quantity and quality of research available

Sixteen papers reporting multiple clinical characteristics of a cohort of patients with type I Gaucher's disease were identified by the literature search.[17,54,71,89,124–135]

In addition, 15 papers that focused on one clinical domain or the relationship between two clinical domains were identified. Five of these concerned skeletal complications, four considered the relationship between skeletal and visceral symptoms, including the impact of splenectomy, and the remainder considered skeletal symptoms in isolation, pulmonary symptoms, growth retardation or pregnancy in Gaucher's disease.[10,74,77,136–147]

The review concentrates on the papers that report multiple clinical characteristics. The other papers are used to inform our understanding of the relationship between the different clinical characteristics; such as splenectomy and bone disease.

Natural history: studies of multiple clinical aspects

The first paper to report a natural history cohort was Fried, in 1973.[54] This retrospective case note review included 105 patients with Gaucher's disease, diagnosed before 1967 in Israel. The overwhelming majority of the cases (98/105) were Ashkenazi Jews. Unfortunately, the paper did not report individual clinical data. Fried reported the extreme heterogeneity of the age at diagnosis, which has subsequently been confirmed by all other natural history papers. In Fried's cohort, 20% were diagnosed before 5 years of age and 38% by 15 years of age. Slightly over 12% of

patients were diagnosed after the age of 45. Thus, 50% of patients were diagnosed between the ages of 15 and 45 years. Fried argued that this extended age distribution indicated an "'incomplete penetrance' of the gene. Thus it should be expected that some individuals identified as homozygotes on a biochemical basis will be essentially healthy", an expectation that has since been shown to be true.

The first paper to provide clinical data on a cohort of patients specifically with type I Gaucher's disease was published by Beighton and Sacks in 1974.[134] This was a prospective study of 17 patients undertaken in southern Africa. The patients were identified by a survey of South African Medical Centres and doctors likely to encounter patients with Gaucher's disease. Among the 17 patients, the mean age at diagnosis was 16 years (SE 3.12) and the mean age at evaluation was 33.8 years (SE 3.33). Forty-one per cent of patients had some degree of splenomegaly and 53% of patients to have some degree of hepatomegaly. Fifty-three per cent of patients had undergone a splenectomy at the time of the evaluation. The mean age at splenectomy was not reported. Eighty-two per cent of patients had some evidence of bone disease on X-ray or scan; 53% of patients had bone pain and 70% of patients had avascular necrosis and/or pathological fracture. Eighteen per cent of patients reported some pulmonary problems. One patient died at the age of 42. The patient had first presented at 2 years of age, with a firm diagnosis being established at the age of 20. No cases of malignancy or liver disease were reported. Thirty-five per cent of the cases were reported to be asymptomatic and a further 29% were reported to be in good or fair health. Ten out of the 13 adult survivors were reported to be either employed or self-employed at follow-up; and 11 were reported to be married, ten of whom had children.

The completeness of the case ascertainment cannot be established. Thirteen of the cases were Ashkenazi Jews. There was one case each of Sephardic Jew, Afrikaans, English and Zulu. Given the partial nature of healthcare provision for the majority non-white population of South Africa at this time, it is likely that many more cases existed than were identified by this survey.

The data reported were cross-sectional and thus give only a limited indication as to the likely clinical pathway of the disease. They do, however, demonstrate that heterogeneity within Gaucher's disease is not confined to the age at diagnosis, but is also found in the clinical manifestations of the disease after diagnosis.

In the same year, Matoth and colleagues reported the clinical characteristics of 17 patients from Israel.[133] In this prospective study, the mean age at diagnosis was 9.2 years (SE 2.76) and the mean age at evaluation was 17.77 years (SE 2.68). The much earlier age of diagnosis seen in this study may reflect the greater exposure to Gaucher's disease in Israel, where the underlying prevalence is high. The proportion of patients with splenomegaly was the same as in Beighton and Sacks,[134] but 10% fewer had undergone a splenectomy. This probably reflects the much lower age of patients in this study. The mean age at splenectomy was 7.94 years (SE 1.52). The proportion of patients with severe bone involvement (pathological fracture and/or avascular necrosis) was only 11% compared with 70% in Beighton and Sacks. A further important finding reported by Matoth was that the level of enzyme activity was not correlated with the severity of disease.[133]

In 1979 Hodson and colleagues[131] reported the clinical characteristics of 12 patients with type I Gaucher's disease who had presented in infancy, in southern Africa. This was a retrospective study of medical records. The mean age at presentation was 3.29 years (SE 0.59). Only one-third of patients had cytopenia, but 83% of patients had splenomegaly. One-third of patients had undergone a splenectomy; however, age at splenectomy was not reported. Forty-one per cent of patients had hepatomegaly. Only one patient had bone pain, and two patients had avascular necrosis or pathological fracture. One-third of patients had pulmonary problems and all patients reported delayed growth. One patient died at the age of 16 years. Unfortunately, the paper did not report the age at follow-up, making it difficult to assess the severity of the disease progression in this cohort.

The largest single natural history study in the literature was reported by Lee in 1982.[135] Lee obtained data from medical records on 275 patients with Gaucher's disease in the USA. Of these, 239 had type I, 23 had type II and 13 had type III disease. Neither the mean age at diagnosis nor the mean age at evaluation was reported. Forty-eight per cent of patients had undergone a splenectomy; however, age at splenectomy was not reported. Ninety-seven out of the 239 (41%) type I patients had bone disease, but no details of the nature of the bone disease are

provided. At one extreme, all these patients may have had Erlenmeyer flask deformity, at the other they may all have had avascular necrosis. Eleven per cent of patients had a malignancy. Thirty-five type I patients died, of whom 19 had malignancies. The average age at death was 52 years. However, no information on the age at diagnosis of these patients or the age of the surviving members of the cohort is reported. As a result, it is not possible to establish the average life expectancy of people with type I Gaucher's disease from this data set. Lee compared the incidence of bone disease in patients with and without splenectomy and reported no support for the hypothesis that splenectomy increased the likelihood of bone disease. In patients with type I disease and bone disease, the number of patients with bone disease developing postsplenectomy (41) was approximately equal to the number of patients with bone disease but no splenectomy (39). In addition, 17 patients had bone disease that had preceded splenectomy. However, without data on duration of disease before and since splenectomy, this information cannot be used to refute strongly a relationship between splenectomy and bone disease.

In 1989 Zimran and colleagues reported a cohort of 47 patients with type I Gaucher's disease.[16] The primary objective of the study was to explore the correlation between genotype and phenotype. To this end the authors proposed a severity scoring index ranging from 0 to 30 (see the section 'The Zimran Severity Score Index', p. 6). The mean age at diagnosis was 18.3 years; mean age at evaluation was not reported. Fifty-three per cent of patients had undergone a splenectomy. Thirty-eight per cent of patients had hepatomegaly and 25% of patients had abnormal liver function. Forty-six per cent of patients had severe bone disease; that is, chronic pain, fractures and/or a hip replacement.

It is worth noting the criticisms of the scoring system. These are well summarised by Mistry and Abrahamov:[21]

> "A more unifying severity score index (SSI) for Type I disease was proposed by Zimran and associates (1989) and has been invaluable for demonstrating the differing clinical impact of various mutations at the glucocerebrosidase gene locus. The SSI is a composite of a notional score assigned to the age of presentation, presence of splenectomy, degree of splenomegaly, extent of hepatomegaly and hepatic dysfunction, cytopenia in relation to splenectomy and skeletal disease. Whilst SSI can be used in this way, it is important to remember its limitations. For example it can be misleading in those patients who have minimal visceral disease but severe skeletal disease. Also there are no histological correlates in this scoring system and it gives no indication of the extent of fibrosis or infarction in target organs…. It would be important to evaluate a modified version of SSI incorporating these new techniques for assessing skeletal disease in the context of genotype…"

The modified version of the SSI (see *Table 2*) was used in Zimran's subsequent natural history paper, published in 1992.[17] However, one important clinical characteristic of the disease not included in the revised scale was delayed growth and puberty. This may reflect the low incidence of delayed puberty in the 53 patients to whom the revised scale was first applied.

The cohort of 53 patients with type I Gaucher's disease was recruited prospectively between 1984 and 1991 in the USA. The mean age at diagnosis was 20.02 years (SE 2.76) and the mean age at evaluation was 37.56 years (SE 2.75). Thirteen per cent of patients had cytopenia, 45% had splenomegaly and 32% of patients had undergone a splenectomy. The mean age at splenectomy was 15.58 years (SE 2.271). The proportion of patients with hepatomegaly was not reported. Thirty per cent of patients had bone disease on the basis of X-ray or scan results. Eleven per cent had mild or occasional bone pain. Twenty-six per cent had necrosis or pathological fractures. Two per cent of patients had delayed growth and 2% also had pulmonary problems. There was no reported mortality or malignancy among the 53 patients. The mean score on the SSI was 7.79 (SE 0.718). Nineteen patients had the genotype 1226G/1226G, six had 1226G/1448C, 11 had 1226G/84GG and six had 1226G/? (The question mark indicates 'unknown or rare'.) The remaining 11 patients had seven different genotypes.

This paper was the first to suggest that type I Gaucher's disease may be stable in adulthood in many patients, and to draw out the implications that this would have for appropriate use of the newly available ERT. Clearly, if the disease stabilises or becomes indolent as part of its natural history, the value of treatment during the indolent phase will be limited.

The hypothesis was based on a follow-up of a subgroup of the 53 patients (n = 29). In 19 of the 29 patients (65%) no disease progression was reported. The mean length of follow-up for those who had progressed and those who had not progressed was effectively identical (5.52 versus 5.6 years). The mean age at final evaluation was

43.1 years and the mean SSI was 9.55. The increase in mean SSI score was largely attributable to two patients who had increased their SSI by 4 points each. As the first paper to report baseline clinical characteristics and changes in those characteristics over time, this paper represented a substantial contribution to the understanding of the natural history of type I Gaucher's disease.

Comparable data were subsequently reported in studies from the USA, The Netherlands, Japan and Romania.[71,124–126] Further follow-up data on 23 of these patients were reported by Beutler and colleagues.[71] With an average of 3 years' further follow-up, 16 patients had not progressed further, four patients had increased their SSI by 1 point and three patients had progressed by more than 1 point. The Beutler paper is described in more detail below.

In 1993 Amaral and colleagues[130] reported the clinical characteristics of 16 Portuguese patients with type I Gaucher's disease. In this prospective study the mean age at diagnosis was 15.3 years (SE 3.3) and the mean age at evaluation was 33.6 years (SE 5.6). Fifty-six per cent of patients had splenomegaly and 75% of patients had hepatomegaly. Thirty-one per cent of patients had had a splenectomy, but the age at splenectomy was not reported. Sixty-eight per cent of patients had bone disease on X-ray or scan and 25% had chronic bone pain. The proportion of patients with aseptic necrosis or pathological fracture was not reported. One patient died in this cohort, but malignancies were not reported.

This study used the 1989 version of Zimran's SSI,[16] which cannot, unfortunately, be directly compared with the 1992 revised SSI. The genotypes of these patients were very different to the genotypes reported by Zimran. Neither the 1226G nor the 1448C allele was reported in this sample. This said, a similar heterogeneity of disease severity to that reported in Zimran's 1989 paper is presented,[16] in that around half of the cases were classified as mild. The SSI data were graphed, and therefore it is not possible to link the time since diagnosis data to disease severity. As a result, this paper helps neither to support nor to reject the Zimran hypothesis that Gaucher's disease is more stable in adulthood.[17]

In 1995, Beutler and colleagues[71] reported the clinical characteristics and SSI for 45 patients with type I Gaucher's disease, before and after treatment with ERT. As reported above, 23 of these patients were in the follow-up cohort of Zimran's 1992 study.[17] Recruitment for this prospective study began in 1984 and finished in 1991, before the introduction of ERT. Thus, the data can be considered to represent natural history data.

The mean age at diagnosis was 17.47 years (SE 2.42) and the mean age at evaluation was 41.11 years (SE 3.01). Fifty-three per cent of patients had undergone a splenectomy, but the age at splenectomy was not reported. The mean SSI was 8.24 (SE 0.776). The majority of data required to calculate the SSI were not reported. The largest single genotype group was the mild 1226G/1226G (36%); 16% had the 1226G/1448C genotype and 20% had the 1226G/84GG genotype. The remaining 13 patients had 11 different genotypes.

With regard to the natural history of disease, the authors consider that the data on the patients in the untreated period confirm the findings reported in Zimran (1992), "that adult patients with Gaucher's disease show only very slow progression or none at all."[71]

Beutler and colleagues report that in untreated adults, no adult patient developed new lesions in a bone that had previously been normal on X-ray. They go on to argue that: "This observation is of some importance in shaping criteria for treatment of patients with Gaucher's Disease, since skeletal manifestations of the disorder are the only ones that are likely to be irreversible with prophylactic treatment. It is difficult to justify prophylactic treatment in adults."[71]

In 1993 Sibille and colleagues[129] reported a study of 161 patients, examining the correlation between genotype and phenotype. The data were obtained through a combination of retrospective case-note review and prospective examination.

The cases were grouped according to genotype:

1. N370S/N370S
2. N370S/84GG
3. N370S/L444P
4. other (N370S/IVS2+1 or ? or ?/?).

Table 13 summarises the clinical characteristics of the sample by genotype. Thirty-six per cent of patients had splenomegaly and 31% of patients had undergone a splenectomy. Fifty-five per cent of patients had hepatomegaly. The use of the bone

TABLE 13 *Genotype/phenotype data (Sibille* et al.*, 1993[129])*

Genotype	Age at onset (years)	Bone involvement[a]	Liver enlargement[b]	Splenic enlargement[b]	Splenectomy cases	Age at splenectomy (years)
N370S/N370S *n* = 59	34.68 (19.1)	2.03 (0.763)	1.22 (0.354)	8.58 (15.5)	6	56 (15.5)
N370S/84GG *n* = 37	9.09 (7.57)	3.53 (1.14)	2.67 (0.93)	33.7 (13.4)	17	21.18 (13.4)
N370S/L444P *n* = 17	16.9 (11.3)	3.11 (1.23)	2.11 (0.33)	22.3 (12.1)	4	4 (19.1)
Other *n* = 48	14.28 (11.4)	3.03 (1.19)	2.08 (0.68)	23.83 (18.06)	23	26.1 (18.24)

Data are shown as mean (SD).
[a] Bone involvement score Hermann *et al* (1986).[148]
[b] *n*-fold increase over normal.

score made it impossible to identify the proportion of patients with severe bone disease, as distinct from bone disease on X-ray or scan alone. Thirty-six per cent of patients had the N370S/N370S (1226G/1226G) genotype, 10.6% of patients had the N370S/84GG genotype and 23% had the N370S/L444P (1226G/1448C) genotype. The remaining patients were N370S/IVS2^{+1}, N360S/? or ?/?.

On the basis of the data reported in *Table 13*, Sibille and colleagues argue that "by using five clinical parameters of Gaucher's Disease involvement, (age at onset, bony severity, liver and splenic enlargement and age at splenectomy) the degree and severity of involvement of symptomatic patients can be predicted from the genotypes with a high degree of confidence".[129]

However, while the data presented by Sibille may argue strongly for the relative mildness of the N370S/N370S (1226G/1226G) genotype, it is not nearly as clear that the remaining three genotypes are substantially different in phenotype. Even within this Ashkenazi Jewish population this genotype accounts for only 36% of the sample. The data provided by the National Specialist Commissioning Centre directors suggest that this genotype accounts for a considerably smaller proportion of the UK type I Gaucher's disease population (Professor Cox, Addenbrooke's Hospital; Dr Raith, Royal Manchester Children's Hospital; and Dr Vellodi, Great Ormond Street Hospital; personal communications, 2005).

A further difficulty with Sibille's conclusion is that the age of the patients at the time of evaluation is not stated. Thus, the comparison across the genotypes may not be a comparison of like with like. The patients with the more 'severe' genotypes may simply be older, and thus have more severe symptoms assuming that the disease is relentlessly progressive.

In 1997 Boot and colleagues[127] addressed the question of the prognostic value of genotype in predicting the prognosis of patients with Gaucher's disease, using a sample of 73 patients from The Netherlands. The sample included 63 patients with type I disease. The SSI for each patient was calculated and presented in a graph. However, the data required to calculate the SSI were not reported in the paper. No cases of malignancy were reported. One patient died at the age of 21, with severe pulmonary involvement. In the 40 patients for whom genotype was available, the distribution was very different to that reported by Zimran, Beutler or Sibille.[17,71,129] Only 2.5% had the mild 1226G/1226G genotype; 40% had the 1226G/1448C genotype and 35% had the 1226G/? genotype.

Boot and colleagues argue that their data are inconsistent with a useful prognostic role for genotype information, given the large variation of SSI within genotype.[127] Like Sibille,[129] Boot and colleagues do not provide evidence on the age at diagnosis or age at evaluation. Thus, it is not possible to assess the degree to which the comparisons across genotype are comparisons of like with like.

In 1997 Woodfield and colleagues[128] reported the clinical characteristics of 14 patients with type I Gaucher's disease in New Zealand.[128] The mean age at diagnosis was 14.9 years (SE 3.9) and the mean age at evaluation was 25.2 (SE 4.3). Eleven of the 14 patients had type I Gaucher's disease. Thirty per cent of the patients had undergone a splenectomy and the mean age at splenectomy was 9 years (SE 4.08). Sixty-two per cent of patients had hepatomegaly and 23% had abnormal liver

function tests. Thirty-eight per cent of patients reported chronic pain. No deaths or malignancies were reported. The N370S and L444P alleles accounted for two-thirds of the recorded alleles. However, neither the mild N370S/N370S nor the more severe L444P/L444P genotype was present in this cohort. The SSI was not reported.

In 1998 Ida and colleagues[126] reported clinical characteristics of 35 Japanese patients with type I Gaucher's disease. As the study was undertaken by the laboratory that provided diagnostic confirmation for all cases in Japan, it was considered that these patients represented the complete symptomatic population in Japan. Data were obtained either from a retrospective evaluation of medical records or through a prospective clinical evaluation. The mean age at diagnosis was 7.95 years (SE 1.45) and the mean age at evaluation was 12.1 years (SE 1.675). Sixty per cent of patients had undergone a splenectomy, but the age at splenectomy was not reported. The higher rate of splenectomy in this group may be explained in part by use of splenectomy as a diagnostic strategy in five patients. Splenectomy was also undertaken as part of the preparation for bone-marrow transplantation. Excluding these patients brings the level of splenectomy down to 45%, which is in the middle of the range reported in the other natural history studies. Fifty-one per cent of patients had hepatomegaly and 11% of patients had chronic bone pain. There were no cases of malignancy.

Unusually, five out of the 35 patients died; however, the cause of death is not reported. If these deaths were related to splenectomy and/or bone-marrow transplantation, then the disease may be no more aggressive in the Japanese population than in other populations. It may be that the clinical strategies are more aggressive in Japan. This highlights an important limitation of the revised Zimran SSI: more aggressive clinical practice with regard to splenectomy will produce apparently more severe disease.

The genotypes observed in this population were different to those observed in other studies. Neither the 1226G nor the 84GG allele was observed, while the 1448C (L444p) allele accounted for approximately half of all the known alleles.

Ida and colleagues[126] report follow-up SSI scores for 27 of the 35 patients. The mean duration of follow-up was 11.5 years. In contrast to Zimran and Beutler, the mean change in SSI was 3.64, and only five out of the 27 patients had the same SSI at baseline and follow-up. The authors conclude that "Our data demonstrate that Type I Gaucher's Disease tends to be severe and progressive in Japanese patients".

Although the high SSI scores, and the substantial mortality, indicate that Gaucher's disease is a much more aggressive condition in the Japanese population, the data presented by Ida and colleagues do not reject the hypothesis that Gaucher's disease may be stable in adulthood. Only five out of the 35 patients were adults at baseline. Indeed, the mean age excluding the adults was 3.4 years. At follow-up only 12 of the 35 patients were adults. The mean age of the paediatric group at follow-up was 7.4 years. Of the four adults for whom Ida and colleagues report an SSI at baseline and follow-up, the SSI for two remained unchanged and the SSI for the remaining two had increased by 1 point.

A fourth study reporting baseline and follow-up disease severity was presented by Maaswinkel-Mooij and colleagues in 2000.[125] They report a retrospective study of 20 untreated type I Gaucher's disease patients from The Netherlands. The data were on patients before 1991, when ERT became available. The patients were members of the Dutch Gaucher's Association who gave permission for their data to be extracted from their medical records, so it is a self-selected sample of the Dutch Gaucher's disease population. The mean age at diagnosis was 22.95 years (SE 2.64) and the mean age at initial evaluation was 34.38 years (SE 2.8). The mean SSI at initial evaluation was 5.05. Unusually, the majority of patients (60%) were diagnosed in adulthood.

The 1226G (N370S) allele accounted for nearly 70% of the alleles observed in this population. The 20 patients were drawn from 16 families. One group of three cases was related and two groups of two patients were related. Eleven out of the 20 patients had at least one unknown allele. The 1226G/? genotype accounted for 40% of this sample. For the purposes of comparison, Boot and colleagues reported that in 40 unrelated Dutch patients, this genotype accounted for 35% of patients. They also reported that the 1226G/1448C genotype accounted for 40% of genotypes.[127] This genotype accounted for 15% of patients in this sample.

At the final evaluation, 45% of patients had cytopenia, 15% had splenomegaly and 10% had hepatomegaly. Fifteen per cent of patients had abnormal liver function tests. Twenty per cent of patients had bone disease present on scan or

X-ray, 30% had chronic pain and 25% had avascular necrosis or pathological fractures. No malignancies or deaths were reported.

The mean age at follow-up was 40.75 years and the mean duration of follow-up was 12.65 years. The change in mean SSI was 4.95. Five patients accounted for over 55% of the change in SSI. However, it is clear that the degree of progression among adults in this sample was very different from that observed in Zimran, Beutler or Ida.[17,71,126] These data are not consistent with a stable disease course in adulthood; some patients, at least, continue to have an aggressive disease experience in adulthood.

Drugan and colleagues report the clinical characteristics of 20 type I Gaucher's disease patients.[124] The patients were drawn from all over Romania; however, no information is given to indicate how representative the sample is of the Romanian population. The mean age at diagnosis was not reported; the mean age at evaluation was 24.2 years (SE 3.18). Ninety per cent of patients had cytopenia, 40% had splenomegaly and 45% of patients had undergone splenectomy. The mean age at splenectomy was 12.1 years (SE 2.35). Eighty-five per cent of patients had hepatomegaly. Ninety-five per cent of patients had bone disease on X-ray or scan, 65% had chronic pain and 15% had avascular necrosis or pathological fractures. No malignancies, pulmonary problems or mortalities were reported. However, 20% of the patients had delayed growth. The mean SSI was 14.6. Six distinct genotypes were reported in this study: 1226G/1226G (15%), 1448C/1448C (5%), 1226G/1448C (25%), 1226G/recnil (15%), 1226G/? (35%) and 1448C/? (5%). Only two patients did not have the 1226G allele.

The mean disease severity in this sample was higher than all the other studies except for Caubel.[89] Only one patient had an SSI below 10, but it is not obvious why this should be. The genotypes seen in this sample were present in the Zimran and Beutler cohorts, but the disease severity in these studies was much lower. It may be that the supportive management strategies identified in the NIH consensus conference[149] were not as readily available in Romania, leading to more severe symptomatic disease.

The most recent study to describe the clinical characteristics of a sample of paediatric patients with Gaucher's disease is from Caubel and colleagues.[89] The sample included three patients with type III Gaucher's disease. They undertook a retrospective search of patient case notes. The data obtained were used to describe disease progression between baseline and the start of treatment, and then after treatment had started.

The average age at diagnosis for type I patients was 5.3 years. The mean age at the start of treatment was 19.67 years. The most common genotype was 1226G/? (7/17) and the next most common genotype was 1226G/RecNcil (3/17). The genotype was unknown for one patient and the remaining patients each had different genotypes.

Unfortunately, the data on clinical characteristics are not reported separately for the type I and type III patients, making it difficult to report comparable data. As there were only two cases with type III Gaucher's disease, the summary clinical characteristics data are reported here.

The mean time from disease onset to the start of treatment was 11.9 years. At this point, five patients had undergone a splenectomy and 12 patients had splenomegaly. Twelve patients also had hepatomegaly. Ten patients had delayed growth and five patients had avascular necrosis or pathological fractures. Two patients reported pulmonary involvement.

Summary of studies of multiple clinical aspects

The literature reviewed above is consistent with widely stated descriptions of type I Gaucher's disease as a genetically and clinically highly heterogeneous disease, which is potentially fatal. Perhaps unsurprisingly in such a rare disease, the individual data sets are small and thus in isolation can provide little if any definitive information on the long-term clinical pathway of Gaucher's disease, or whether it can be predicted on the basis of clinical information available at or close to the time of diagnosis. Although many of the data reported are consistent with Zimran's hypothesis that Gaucher's disease is stable in adulthood,[17] the study by Maaswinkel-Mooij, notably, is not consistent with this.[125]

Similarly, while Sibille and colleagues show that the N370S/N370S genotype is associated with much milder disease, their argument for differentiating between other genotypes in terms of severity remains unconvincing.[129]

Fortunately, many of the papers reviewed above report patient-level data with regard to genotype, age, splenectomy and disease severity. As a result there is an opportunity to examine some questions

regarding the natural history and the relationship between genotype and phenotype by pooling the published data. Several reanalyses of published natural history data are reported in the section 'Modelling the natural history of Gaucher's disease' (p. 47).

Natural history: skeletal symptoms of Gaucher's disease

Stowens and colleagues[10] report skeletal complications on a sample of 327 patients seen at the NIH in the USA, between 1976 and 1983. The degree of clinical heterogeneity associated with Gaucher's disease generally is seen with regard to skeletal symptoms:

> "The severity of the problems range from asymptomatic persons with neither radiographic, scintigraphic or histological evidence of bone involvement to those whose skeleton is completely devastated by a process of osteopenia, osteonecrosis and osteosclerosis."

Within symptoms the clinical heterogeneity is maintained. Quoting Stowens again:

> "Skeletal pain in our patients developed either acutely or chronically, and was associated with an orthopaedic deformity or occurred without obvious change in bone shape."

Acute bone pain is normally associated with bone crises, sometimes called bone infarctions. The process of a bone infarction is described by Stowens as follows:

> "The initial discomfort is localised and intensifies over a few hours to severe pain focused in or near one of the articular regions of the affected bone…. During the first day of a crisis, pain, fever and leukocytosis usually appears, as do signs of inflammation, such as redness, heat, swelling and tenderness… The pain increases over 1 to 3 days and subsides in 5 to 10 days. With a gradual abatement of all symptoms, the episode usually resolves within 2 to 4 weeks".[10]

Femora, vertebrae and humeri are the most frequently affected bones in Gaucher's disease; however, bone changes have been reported in "ribs, radii, ulnae, mandibles, carpal, metacarpal, pelvic and phalangeal bones".[10]

In addition to acute bone pain, people with type I Gaucher's disease report arthritis-like pain, osteopenia and osteoporosis.

Several papers report data on proxy outcomes for bone disease such as *T*-scores, *Z*-scores and bone remodelling. However, three papers (other than those considered above) reported the prevalence of different bone symptoms in a defined sample; the first study was by Goldblatt and colleagues in 1978,[146] the second by Katz and colleagues in 1993,[141] and third by Ida and colleagues in 1999.[150]

Goldblatt and colleagues[146] report on the orthopaedic involvement of 35 patients from southern Africa,146 identified following a national survey of Gaucher's disease. (It is unclear what proportion of these patients were also reported in the Beighton and Sacks natural history paper.[134]) Twenty-eight of the subjects were Ashkenazi Jews, three were Afrikaner, two were British and two were described as 'Negro'. Eighteen were female. The average age was 36.17 years (SE 2.40).

They report the prevalence of non-specific bone (19/35), pseudo-osteomyelitis (13/35), acute arthritis (21/35) and collapse of femoral head (21/35), pathological fractures (3/35), kyphoscoliosis (4/35) and hip replacement (9/35). The authors report that the hip replacements were successful and led to substantially regained mobility. Three patients had spinal deformity, which did not lead to spinal cord compression, but one had compromised lung function as a result.

Seventeen of the 35 patients had a splenectomy without, according to the authors, any exacerbation of their skeletal problems. The authors explicitly reject the hypothesis that splenectomy worsens orthopaedic complications of Gaucher's disease. The authors observe that orthopaedic problems were 'age related and usually appeared in the second or third decade of life'.

Katz and colleagues[141] report spinal involvement in 18 children with Gaucher's disease. Eleven were female and eight were male. The mean age at first presentation with spinal problems was 13 years. Eight patients reported non-specific pain, the mean age of onset for which was 12.38 years (SE 1.05). Three patients reported bone crisis, at a mean age of 15.3 years (SE 3.8), and 11 patients had a vertebral collapse, at a mean age of 13.8 years (SE 0.7). Cord compression was seen in two cases, kyphosis in six cases and scoliosis in three patients. These 19 patients represent 38% of all the Gaucher's disease patients seen between 1960 and 1990 at the Beilinson Medical Centre in Tel Aviv, Israel.

Ida and colleagues[150] report the skeletal complications observed in 35 Japanese patients with type I Gaucher's disease. (The subjects in this

paper are largely the same patients as those reported in the natural history paper from the same authors[126] reported above.) Seventeen of the 35 patients were female. The average age was 18.88 years (SE 2.38). Twenty-three of the subjects were children at the time of evaluation.

Fourteen patients had avascular necrosis, eight had pathological fractures and three had a compression fracture. Only one patient was recorded as having had a bone crisis. Four patients had required surgery for their bone problems. Two patients received osteotomies, one patient had an amputation and one patient had a total joint replacement. The mean time from presentation/diagnosis of Gaucher's disease to presentation of severe bone involvement was 3.5 years (SE 4.08).

Ida and colleagues[150] report that severe bone disease was highly correlated with splenectomy; however, they stop short of attributing causality to this relationship. In considering the clinical manifestation of the disease in their sample, Ida and colleagues conclude that type I Gaucher's disease appears to be more aggressive, with earlier skeletal involvement, in Japanese patients than in other reported populations. They propose that this may be due to the absence of the potentially protective 1226G genetic mutation and the high prevalence of the potentially aggressive 1448C mutation.

Natural history: pulmonary function in Gaucher's disease

Pulmonary complications, notably primary PHT, are recognised as complications of Gaucher's disease; however, there is very little published research on pulmonary function in Gaucher's disease. Three studies were identified reporting the pulmonary manifestations of type I Gaucher's disease.[137,139,151]

Kerem and colleagues[139] report the prospective evaluation of 95 patients who attended the Gaucher clinic at the Shaare Zedek Medical Centre in Jerusalem. The mean age of patients was 29 years (SD 15). Sixty-two per cent were female. A full battery of pulmonary function tests was completed (forced vital capacity, forced expiratory volume, forced expiratory flow, peak expiratory flow rate, functional residual capacity, residual volume, total lung capacity and carbon monoxide transfer factor). Sixty-eight per cent of subjects had some form of pulmonary function abnormality. However, only 17% had abnormalities on chest X-ray and only 4% of these were classified as severe. The authors recommend the inclusion of pulmonary assessment in the routine evaluation of Gaucher's patients.

In 1998 Santamaria and colleagues[137] reported a prospective study of 13 patients with Gaucher's disease. The mean age was 17.4 years (SE 4.08). They report the results of chest X-rays, CT scans and genotype. All patients except for one with L444P/L444P genotype had pulmonary abnormalities. None of the patients with other genotypes developed pulmonary disease detectable on CT scan or chest X-ray. The authors conclude that the L444P/L444P genotype is a major risk factor for severe pulmonary disease in type I Gaucher's disease.

Harats and colleagues[151] report that patients on ERT have been known to develop primary PHT, suggesting that it does not have a protective effect. Pastores and colleagues[11] report that it does not interfere with the function of therapies for primary PHT.

Natural history: Gaucher's disease and pregnancy

Elstein and colleagues[74] report a literature survey of the outcomes of women with Gaucher's disease who have not received ERT. They report on a total of 345 pregnancies. There were 290 live births and 56 abortions, of which 49 were spontaneous. Postpartum bleeding and blood transfusions were seen in 38 of the pregnancies. The authors conclude that most untreated women with mild disease enjoy an uncomplicated course of pregnancy.

Modelling the natural history of Gaucher's disease

The objective of the following analyses is to examine the hypothesis put forward by Zimran and colleagues in 1992[17] and subsequently supported by Beutler and colleagues in 1995[71] that the natural history of Gaucher's disease may include a stabilisation of the disease in adulthood, and to examine the degree to which genotype is predictive of Zimran score.

Data input

The literature review reported in the previous section identified five papers that reported the Zimran's 1992 SSI for each patient, along with patient-level data on age, age at diagnosis and genotype.[17,71,124–126] This information can be used to construct a natural history data set. Those studies that reported the SSI and age at two time-points provided two observations for the

natural history data set. Although there are limitations with the Zimran SSI as a measure of disease severity, it is recognised as a useful measure at the population level.[21] This section provides descriptive statistics on age at diagnosis, age at evaluation, gender, genotype, SSI and splenectomy status, and scatterplots of the data.

Model

If the disease does stabilise in adulthood, disease severity should increase with age, but at a decreasing rate. A simple functional form that is consistent with this proposed relationship is the natural log (sometime called the power function). Regression models were explored for their potential explanatory power.

The following linear regression model was estimated:

$$SSI = \alpha \ln(age) + \beta(splenectomy) + \gamma(genotype)$$

Two alternative specifications of genotype were tested. In the first model, the following genotypes were entered as dummy variables:

1. 1226G/1226G
2. 1226G/1448C
3. 1226G/84GG
4. 1448C/754A
5. 1448C/1448C
6. 1226G/?
7. other (rare and unknown).

Genotype 1226G/1226G (N370S/N370S) was used as the reference genotype.

Based on the results of the first model with individual genotype dummies (see the section 'Results', next column), four group genotypes dummy variables were specified:

1. 1226G/1226G
2. 1226G/other (including 1448C, 84GG and ?)
3. 1448C/plus (including 1448C and 754A)
4. other (rare and unknown).

The genotype 1226G/1226G was also used as the reference for the second model.

For each model the following are reported:

- coefficients, standard errors and significance
- *F*-statistic
- root mean square error (RMSE)
- mean absolute errors (MAEs)
- *T*-test, with the null hypothesis that the mean prediction error is not significantly different from zero.

The last two are complementary tests of the predictive performance of the models compared with the observed data.

Alternative model formulations designed to explore the robustness of the natural log function are also reported.

Results

There were complete data for observations drawn from the five published studies.

The descriptive statistics are reported in *Tables 14–16*. *Table 17* reports the number of observations provided by each study.

These studies report data on patients from the USA,[17,71] The Netherlands,[125] Romania[124] and Japan.[126] Approximately 50% of the observations were provided from the US studies. The mean SSI score was similar in the US and Netherlands patients (7 and 8, respectively), higher in the Japanese patients (10) and highest in the Romanian patients. The mean time since diagnosis was 14.55 years (SE = 0.97). The Romanian study did not report an age at diagnosis. The Japanese study had the shortest time since diagnosis (mean 4.2 years, SE 0.89) and the second American study had the longest time since diagnosis (mean 23.65 years, SE 2.45).

TABLE 14 *Natural history model: descriptive statistics 1 – gender and splenic status*

Gender			Splenectomy		
	n	%		*n*	%
Female	109	44	Yes	100	40
Male	95	38	No	149	60
NR	45	18	NR	0	

TABLE 15 *Natural history model: descriptive statistics 2 – genotype frequency*

		Frequency	%
Valid	1226G/1226G	49	19.7
	1226G/1448C	22	8.8
	1226G/84GG	27	10.8
	1448C/754A	20	8.0
	1448C/1448C	21	8.4
	1226G/?	16	6.4
	Other	94	37.8
	Total	249	100.0

TABLE 16 *Natural history model: descriptive statistics 3 – age and SSI*

		Age at diagnosis	Age at evaluation	SSI
n	Valid	227	249	238
	Missing	22	0	11
Mean		16.45	30.67	9.15
SEM		1.177	1.354	0.342

SEM, standard error of mean.

TABLE 17 *Natural history model: number of observations*

		Country	Frequency	%
Valid	Zimran, 1992[17]	USA	82	32.9
	Beutler, 1995[71]	USA	45	18.1
	Drugan, 2002[124]	Romania	20	8.0
	Ida, 1998[126]	Japan	62	24.9
	Maaswinkel-Mooij, 2000[125]	Netherlands	40	16.1
	Total		249	100.0

Graphical analysis of the data

Figures 8 and *9* show the plot of SSI against age at evaluation for people who have had splenectomy and for those who have not had a splenectomy, respectively. For each genotype (based on the four categories described above) and splenectomy subpopulation, a linear regression of SSI against age is shown.

In general, there appears to be an inverse relationship between age at the time of evaluation and SSI. In those who have been splenectomised,

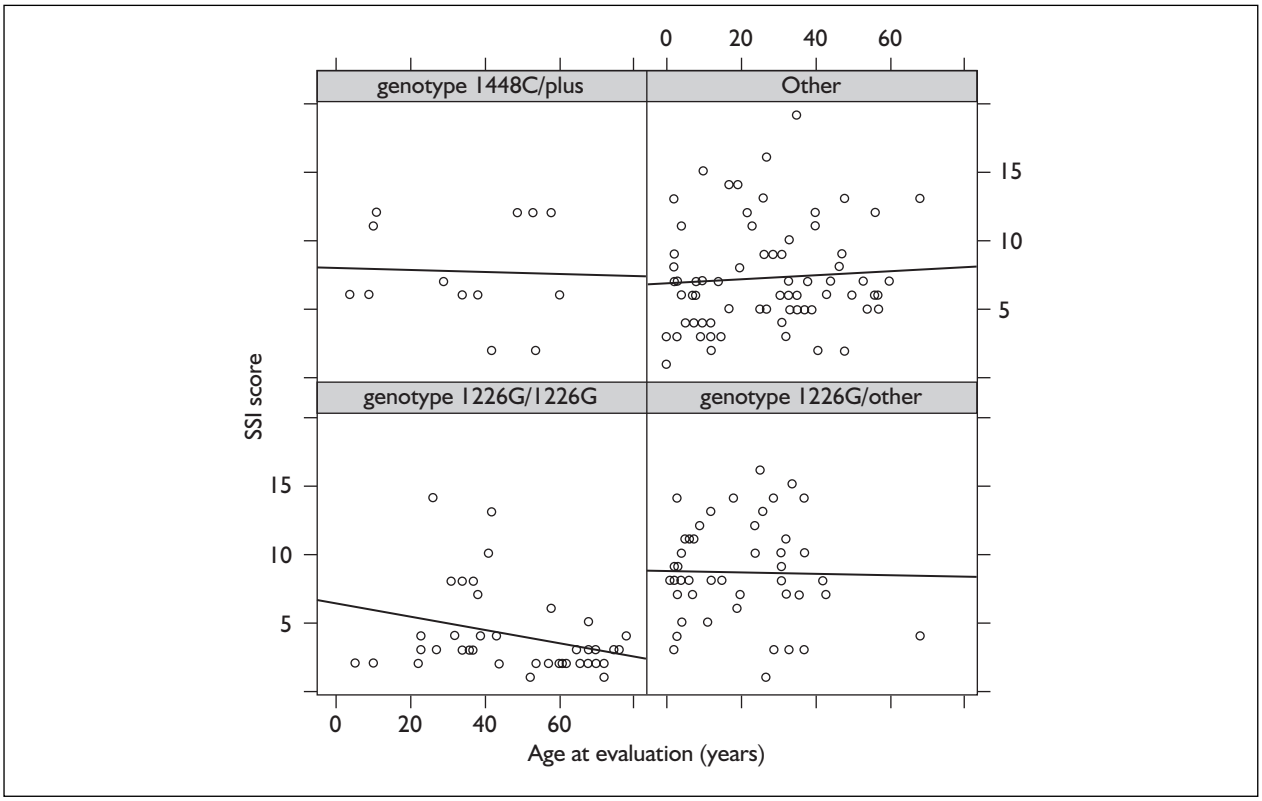

FIGURE 8 *Natural history model: scatterplot for SSI versus age (non-splenectomised patients)*

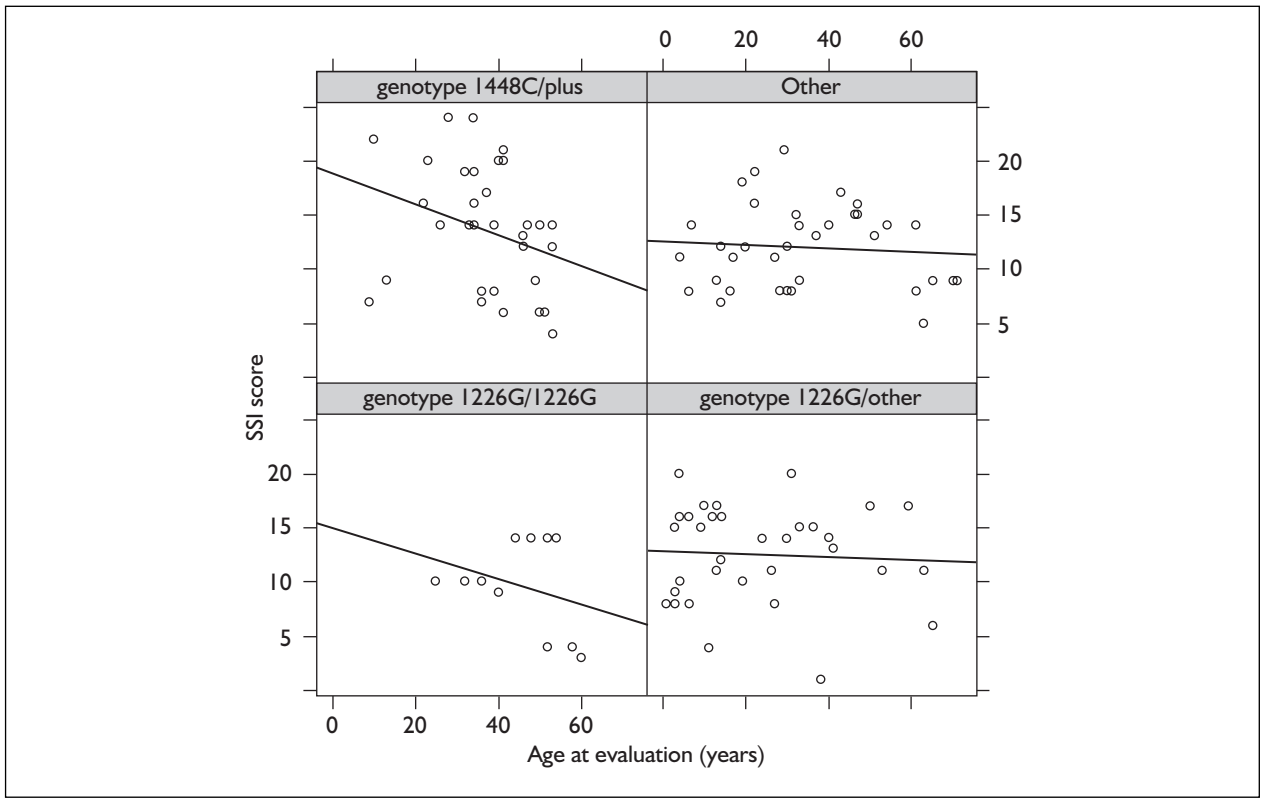

FIGURE 9 *Natural history model: scatterplot for SSI versus age (splenectomised patients)*

the impact of age has a greater negative relationship with SSI than in those that have not been splenectomised.

Tables 18 and *19* report the two log models and their diagnostic statistics.

Both models appear to have acceptable statistical and predictive characteristics.

Testing alternative models

Alternative functional forms were examined to test the robustness of the findings. In model 3

TABLE 18 *Model 1: SSI = f(genotype, splenectomy and natural log age)*

Model 1		Unstandardised coefficients		Standardised coefficients	t	Significance
		B	SE	*β*		
	Natural log of age at evaluation	0.933	0.148	0.286	6.312	0.000
	Splenectomy	4.912	0.616	0.292	7.978	0.000
(geno2)	1226G/1448C	6.455	1.044	0.184	6.181	0.000
(geno3)	1226G/84GG	5.088	1.025	0.160	4.965	0.000
(geno4)	1448C/754A	7.119	0.995	0.193	7.153	0.000
(geno5)	1448C/1448C	6.809	1.068	0.175	6.375	0.000
(geno6)	1226G/?	5.818	1.193	0.141	4.878	0.000
(geno7)	Other	4.397	0.643	0.244	6.834	0.000
	Adj. R^2	0.836		RMSE	4.23	
	F	154.679	0.000	MAE	3.22	
	t-Test	0.154	0.878			

Dependent variable: Zimran SSI 1992; linear regression through the origin.
The reference genotype is N370S/370S (1226G/1226G).
Adj, adjusted.

TABLE 19 *Model 2: SSI = f(grouped-genotype, splenectomy and natural log of age)*

Model 2	Unstandardised coefficients		Standardised coefficients	t	Significance
	B	**SE**	β		
Natural log of age at evaluation	0.921	0.144	0.282	6.388	0.000
Splenectomy	4.872	0.608	0.289	8.017	0.000
1448C other	6.827	0.657	0.321	10.391	0.000
1226G other	5.428	0.858	0.216	6.329	0.000
Other	4.447	0.634	0.247	7.015	0.000
Adj. R^2	0.837		RMSE	4.23	
F	249.99	0.000	MAE	3.23	
t-Test	1.827	0.07			

Dependent variable: Zimran SSI 1992; linear regression through the origin.

TABLE 20 *Model 3: SSI = α(age) + δ(age^2) + β(splenectomy) + γ(genotype)*

Model 3	Unstandardised coefficients		Standardised coefficients	t	Significance
	B	**SE**	β		
Age	0.116	0.039		2.964	0.003
Age^2	–0.002	0.0005		–3.652	0.000
Splenectomy	4.716	0.495		9.511	0.000
1226G/1226G	3.928	0.871		4.510	0.000
1226G/other	7.399	0.615		12.026	0.000
1448C/plus	7.467	0.917		8.139	0.000
Other	6.325	0.667		9.480	0.000
Adj. R^2	0.859		RMSE	4.051	
F	258.3	0.000			
t-Test					

(*Table 20*), a model is fitted adding as a covariate the value of age squared (quadratic) and using dummy variables for the four 'grouped' genotypes and splenectomy.

The following linear regression model was estimated:

$$\text{SSI} = \alpha(\text{age}) + \delta(\text{age}^2) + \beta(\text{splenectomy}) + \gamma(\text{genotype})$$

All coefficients are significant. The *p*-values are significant at the 5% level and the model has a high R^2 value (0.86). The curve is parabolic, consistent with the hypothesis that SSI increases with age up to some maximum, after which there is a tendency for severity to decrease. In this situation, the maximum is reached at an age of approximately 55 years.

One reason for the apparent slowing of disease observed in the data could be due to its cross-sectional nature. It is possible that observations of patients in late middle age or old age represent only patients with relatively slowly progressing disease. Those with more aggressive forms of disease may be underrepresented in older age owing to premature mortality. It has been suggested that age of diagnosis may be a predictor of expected speed of disease progression. To examine this issue, the following model (model 4) divides the data set according to those who were diagnosed below the age of 10 years and those diagnosed from 10 years and older.

A linear regression of SSI as a function of age, splenectomy status and genotype was estimated for those diagnosed after childhood (*Table 21*) and those diagnosed in childhood (*Table 22*). The quadratic form of these models is reported in *Tables 23* and *24*.

Constant terms are not significant at conventional levels in either patient category in *Tables 21* and

TABLE 21 *Model 4: Linear regression of SSI as a function of age, splenectomy status and genotype for those diagnosed after childhood*

Model 4 (not aggressive onset of the disease)	Unstandardised coefficients		Standardised coefficients	t	Significance
	B	**SE**	β		
Constant	2.343	1.459		1.606	0.109
Age	0.013	0.024		0.565	0.572
Splenectomy	6.107	0.904		6.751	0.000
1226G/other	3.231	1.351		2.390	0.017
1448C/plus	4.512	1.349		3.345	0.000
Other	2.508	0.914		2.742	0.006
Adj. R^2	0.864		RMSE	3.704	
F	115.5	0.000			

TABLE 22 *Model 4: Linear regression of SSI as a function of age, splenectomy status and genotype for those diagnosed in childhood*

Model 4 (aggressive onset of the disease)	Unstandardised coefficients		Standardised coefficients	t	Significance
	B	**SE**	β		
Constant	2.809	1.610		1.744	0.082
Age	0.068	0.026		2.537	0.011
Splenectomy	4.022	0.788		5.104	0.000
1226G/other	5.665	1.598		3.545	0.000
1448C/plus	3.497	1.589		2.2	0.028
Other	4.072	1.545		2.636	0.009
Adj. R^2	0.864		RMSE	3.704	
F	115.5	0.000			

TABLE 23 *Model 4: Regression of SSI as a function of age squared, splenectomy status and genotype for those diagnosed after childhood*

Model 5 (not aggressive onset of the disease)	Unstandardised coefficients		Standardised coefficients	t	Significance
	B	**SE**	β		
Constant	–0.655	2.103		–0.312	0.755
Age	0.187	0.094		1.980	0.049
Age^2	–0.001	0.001		–1.891	0.060
Splenectomy	5.834	0.868		6.721	0.000
1226G/other	3.017	1.284		2.350	0.019
1448C/plus	3.975	1.515		4.013	0.000
Other	2.339	0.870		2.688	0.007
Adj. R^2	0.878		RMSE	3.505	
F	112.4				

22. The speed of progression is greater in the aggressive disease model, although age is not a statistically significant predictor of SSI in the less aggressive disease model.

In *Tables 23* and *24*, the constant term is not statistically significant. All the other parameters are statistically significant at conventional levels.

Discussion

The analyses presented above suggest that the natural log model is an appropriate functional form; that is, type I Gaucher's disease may be well described as a disease that is aggressive in childhood, but with a substantial reduction in the rate of progression in adulthood. This said, the

TABLE 24 *Model 4: regression of SSI as a function of age squared, splenectomy status and genotype for those diagnosed in childhood*

Model 5 (aggressive onset of the disease)	Unstandardised coefficients		Standardised coefficients	t	Significance
	B	**SE**	β		
Constant	0.740	1.586		0.467	0.641
Age	0.394	0.073		5.350	0.000
Age^2	–0.006	0.001		–4.714	0.000
Splenectomy	3.294	0.761		4.326	0.000
1226G/other	6.079	1.515		4.013	0.000
1448C/plus	3.843	1.506		2.551	0.011
Other	4.014	1.463		2.745	0.006
Adj. R^2	0.878		RMSE	3.505	
F	112.4				

results should be treated with caution as the data on which the models are estimated is cross-sectional rather than longitudinal.

This reanalysis of the patient-level data in the published literature generally supports the hypothesis of Zimran and colleagues that Gaucher's disease is more stable in adulthood, although it appears that the rate of progression slows markedly, rather than stabilises.

A simple observation of the distribution of disease severity index in the data set supports this. Nearly 80% of the patients have mild disease (SSI ≤10). If the disease were relentlessly aggressive, we would expect to see many more patients in the moderate and severe categories, given the duration of follow-up.

Further, the analysis indicates that genotype is a strong predictor of disease severity. A substantial degree of the variation in disease severity score appears to be explained by a combination of genotype, splenectomy and age. Unsurprisingly, given the small numbers in the data set, the standard errors on the predictions are relatively large. Consistent with the natural history literature, there are particular cases where disease severity is markedly worse than the model predicts, notably the six (11%) observations with genotype N370S/N370S, who have an SSI in the moderate category. However, at the population level there is a significant degree of predictability in disease progression. This predictability may justify trials of therapy attenuation or even cessation in adulthood.

This said, there is a number of caveats to be borne in mind. Notably, the data set is small. Although this is to a degree unavoidable in such a rare disease; it is clear from the review of the natural history literature that many more data exist. Many of the studies considered in the previous section clearly had comparable data, but it was not reported in a manner that made it possible to incorporate into the analysis. In addition, the ICGG Gaucher Registry could, in principle, have been a source of comparable data for many patients with Gaucher's disease who are not currently on therapy.

Further, the ideal data set for assessing the natural history of Gaucher's disease would consist of repeated observations on a substantial number of observations. The present data set, for the most part, contains single disease severity–age data pairs. While the duration of disease of the patients in the data set is such that one would expect to see more patients with the severe disease severity index score (SSI ≤20), if Gaucher's disease were truly a relentlessly aggressive disease, there would be a risk that the data set is flawed by informative censoring; the very severe patients may simply not be included in the published literature, possibly because of premature mortality. This said, the reporting of mortality in the natural history literature is so poor that it is difficult to assess the degree to which life expectancy is significantly reduced in the Gaucher's disease population.

The largest single genotype group in the data set is 'unknown' or rare. The model coefficient on this group suggests these are at the milder end of this disease. However, there are over 20 different genotypes in this group. The small number of representatives of each genotype may represent the severe end of the disease distribution in particularly mild genotypes or the mild end of particularly severe genotypes, or the coefficient may reflect a genuine similarity in the severity of

disease across all genotypes. There is no way of establishing which of these it is. Again, in principle the data to inform this question should be available after the therapy has been in use for over 13 years; unfortunately, however, this is not the case.

There are limited data on patients in childhood. Ninety-two of the observations in the data set were on people aged less than 18 years, 58% of which came from one study.[151] Nearly 45% of the children had the L444P allele in their genotype. It would be very useful to have more observations in the younger age range and across the range of genotypes.

Summary

Type I Gaucher's disease is a highly heterogeneous disease in both its clinical presentation and its underlying genotype. Many people with the milder form are asymptomatic for much if not all of their lives. Many more have mild symptoms. The symptoms are primarily visceral (blood, spleen, liver) and skeletal (bone marrow, osteopenia, osteoporosis, bone pain, bone crises and avascular necrosis).

There is a number of rarer manifestations associated with the condition. While respiratory involvement is common, it is rarely sufficiently severe to produce substantial morbidity. Several case studies have identified patients with type I Gaucher's disease developing Parkinson-like symptoms. It has also been observed that the incidence of malignancies in Gaucher's disease is much higher than in the general population. In addition, it is well established that physical development (growth and puberty) can be substantially retarded as a result of type I Gaucher's disease. However, the modes of action for these rarer symptoms are not well understood.

The majority of studies identified examined one or two clinical dimensions of the disease. Only 16 papers were identified that attempted to describe the multifactorial development of the condition and its relation to underlying characteristics such as age and genotype. The partial level of information reported in many of the papers made it difficult to deduce the natural history of the disease (e.g. reporting the age at death of the observed deaths, but nothing about the age distribution of the surviving members of the cohort).

Five papers were identified that reported patient-level data using the only Gaucher's disease severity framework available: the Zimran SSI. In these papers there was a clear dichotomy over two important issues: whether the progression in type I Gaucher's disease stabilises in adulthood, and whether the clinical disease course is predictable from a patient's genotype.

The pooled patient-level data from these five papers were reanalysed in an attempt to obtain additional understanding of type I Gaucher's disease in regard to these two questions. The findings support the hypothesis that the genotype is strongly predictive of the clinical expression of the disease (as measured by the SSI) at the population level. Although the findings do not support the hypothesis of stabilisation, they indicate a substantial slowing in the rate of progression in the disease with age.

These findings must be viewed in the light of the caveats described above. However, in the absence of any alternative model of untreated disease progression, model 2 (above) is used to inform the estimation of the cost-effectiveness of ERT in type I Gaucher's disease (Chapter 5).

Chapter 5
Economic analysis

Review of quality of life data in type I Gaucher's disease

Introduction

Quality of life information is critical for the construction of a model of cost-effectiveness and therefore this section reviews any published study of quality of life in type I Gaucher's disease, irrespective of whether ERT was a consideration in the study. The methods used to identify the literature reviewed below are described in the section 'Methods for economic analysis' (p. 13). In addition to the published literature, the study team was given some access to two patient-level data sets containing health-related quality of life data for patients with type I Gaucher's disease. The first of these is referred to as the Spanish Registry, held by Dr Pilar Giraldo and colleagues at the University Hospital in Zaragoza, Spain. The second is the International Gaucher Registry which is overseen by the ICGG and sponsored by Genzyme Corporation of Cambridge, Massachusetts, USA (henceforth referred to as the ICGG Gaucher Registry).

The first section reviews the published literature. Then, results of the analysis of the Spanish Registry data are presented. The third section presents the results of some analyses of the ICGG Registry undertaken by Genzyme-supported biostatisticians in response to the authors' data requests. At the end of this section summary observations are made on the state of knowledge regarding HRQoL in Gaucher's disease and the impact of therapy upon it.

HRQoL in the published literature

Clarke and colleagues (1997)[153]

Clarke and colleagues[153] measured preferences for three Gaucher's disease states for healthy adults (n = 39), people with chronic illness (n = 38) and people with Gaucher's disease (n = 32). Participants were selected from a convenience sample from San Francisco (USA) and Montreal (Canada). People with chronic diseases suffered from symptoms considered similar to those of Gaucher's disease.

The assessments were undertaken on three vignettes that were used to describe patients with Gaucher's disease. The vignettes were developed by Gaucher's specialist physicians, nurses and patients. These were presented using multimedia tools including pictures, voice-over narrations and animation. The presentation first provided a physician's description of Gaucher's disease and then introduced the three patients.

Case 1: child with low blood counts
This is a 10-year-old boy with slight, painless hepatomegaly and splenomegaly, and thrombocytopenia (bruising and bleeding very easily). He has to be careful with what physical activity he does, tires easily but leads a relatively normal life. (Mapping this to the Zimran SSI yields a score of 3, not done in the paper.)

Case 2: middle-aged parent with bone disease
This is a 40-year-old woman who has bone problems. Her legs and arms often ache; the pain is described as mild but she requires painkillers. She can do most things during this period. This pain is very bad for about a week every 6 months, when she cannot do normal activities. She seems to suffer from anaemia and avoids vigorous activities. (Zimran SSI score 3 or 4.)

Case 3: teenage girl with enlarged abdomen
This is an 18-year-old girl with a very large liver and spleen. This restricts her activities and she also suffers from anaemia. (Zimran SSI score 7.)

Utilities were measured using three methods: standard gamble (SG), time trade-off (TTO) and a previously untested approach, the risk–risk trade-off. The computer presentation provided training in each of the methods using practice examples. Participants rated each health state and their own current health state using each of the three methods.

The results show that the Gaucher's disease patients had a mean TTO own health utility of 0.86, with the lowest value being 0.8.

The mean valuations for the three vignettes were similar when all respondents (healthy, chronically ill, Gaucher's disease) were pooled. Using TTO produced values of 0.87, 0.82 and 0.8 for cases 1, 2 and 3, respectively. SG valuations were slightly

higher at 0.93, 0.91 and 0.9, respectively. Risk–risk trade-off scores were substantially lower at 0.38, 0.32 and 0.31, respectively. This is an unvalidated method, however.

Healthy adults rated their own health at 0.93, only slightly higher than how they rated the three Gaucher descriptions, valued at 0.87, 0.86 and 0.82, respectively, using TTO.

None of the three cases was seen as particularly serious when ranked using TTO or SG, the two commonly favoured techniques. The lowest of the 95% confidence intervals around mean valuations was 0.71 for cases 2 and 3 when respondents with pre-existing chronic disease were rated using TTO. People with Gaucher's disease did not rate the conditions differently to the healthy adults.

Masek and colleagues (1999)[106] (study funded by Genzyme)

Using the SF-36 instrument, HRQoL in 25 adults with Gaucher's disease was investigated over a 2-year period. This is a prospective study in which SF-36 was administered before the start of ERT and at 6-monthly intervals thereafter for 2 years.

The study therefore assesses changes in quality of life from initiation of therapy to 2 years after the start of therapy. There is no comparator to indicate the quality of life that these patients would have experienced had they been left untreated.

All patients were aged over 18 years of age, had type I Gaucher's disease and had not yet commenced ERT. Patients were drawn from US hospital clinics. Thirty-seven patients were recruited of whom 25 went on to receive ERT and complete the study.

SF-36, Symptom Checklist-90R, Health Survey and an adult activities checklist were administered at entry to the study, and again at 6-monthly periods after the commencement of ERT. Where the gap between baseline and start of ERT was greater than 3 months, participants completed another assessment at the start of therapy.

SF-36 results are presented for each of eight separate health dimensions over time on a scale of 0–100, and in comparison to mean US population norms.

At baseline, SF-36 scores ranged from 70.6 (social function) to 42 (vitality). Vitality showed a statistically significant improvement within 6 months of starting treatment but dropped back with continued treatment. However, the rise in vitality to 56 after 2 years of treatment remained a statistically significant improvement. Other significant improvements were observed in role–physical (52 to 80), physical function (67 to 77), general health (51 to 59), social function (71 to 87) and mental health (65 to 74).

The two patients aged over 70 years did not exhibit such improvements with treatment. It is feasible that other illness or ageing offset any gains from ERT.

The results also indicate that scores for every dimension of SF-36 were substantially worse than for the US population before the commencement of ERT and that after 2 years of ERT only general health remained significantly lower than the population mean.

Hayes and colleagues (1998)[98]

This is a study that is essentially qualitative in nature. It gives detailed information on a range of quality of life issues, but this is limited to just 16 patients with type I Gaucher's disease.

Seven patients had received ERT without splenectomy, six had ERT and splenectomy, and three had not received ERT. Patients were drawn from a single clinic in the USA. The study interviewed patients face to face (with the exception of three patients who were interviewed by telephone). Thirteen caregivers were also interviewed.

Details recorded were age, gender, genotype, ERT dosage history and duration. Questions were asked about symptoms and their perceptions of how those symptoms had changed as a result of ERT, splenectomy or other factors. The impact of disease on quality of life was asked about in relation to physical activity, social life and emotional health.

Pastores and colleagues (2002)[154]

This was an epidemiological survey designed to identify the incidence of neurological symptoms in type I Gaucher's disease. The survey included modified SSI and SF-36 Health Survey. Participants were drawn from type I patients attending New York Lysosomal Disease Unit and represented those who attended for routine ERT. Fifty-six patients were approached and one declined.

Few details are given of the study results in terms of quality of life, since this was not the primary aim of the study.

The mean SSI was 6.3 (range 3–12). It is stated that scores below 10 are considered mild and 11–20 is moderate, consistent with other uses of the SSI. Patients were therefore considered to be well controlled on ERT. Mean subscale scores for SF-36 were similar to those of the US population. The exceptions to this were bodily pain and mental health.

The authors conclude that this demonstrates the effectiveness of ERT, since previous reports[91] cite decreased physical and functional well-being among untreated type I patients.

Damiano and colleagues (1998)[91]

This study is described as a standardised assessment of the HRQoL of patients with Gaucher's disease who are receiving ERT. It was a retrospective assessment, so patients were asked to evaluate the changes in their HRQoL from the onset of ERT (periods ranging from 1 month to 4 years earlier). The analyses were restricted to patients over the age of 14 years who had been receiving ERT for at least 1 month (n = 212, mean age 45 years, SD 17). A questionnaire was constructed that included the SF-36 instrument. Mean SF-36 scores from the sample of Gaucher's disease patients were then compared with age- and gender-adjusted US norms and found to be significantly worse for physical function, role limitations due to physical problems, bodily pain, general health and vitality. Since initiation of ERT, patients reported improvements in their physical, general and emotional well-being. Improvements in general health were greater for patients who had been on ERT longer. This study provides aggregate SF-36 scores within each dimension for patients with varying levels of severity of Gaucher's disease.

Patients were asked to recall their HRQoL before the commencement of therapy which may be confounded by a number of factors.

Comparisons of treated Gaucher's disease patients with the general US population are not entirely useful for the purpose of establishing the impact of ERT, since no information is given regarding untreated disease progression.

Giraldo and colleagues (2005)[155]

This paper went to press at the time of writing. It considers data analysed in the following section.

HRQoL obtained from the Spanish Registry

Dr Giraldo provided access to the Spanish Gaucher's Disease Registry and a full summary of analyses is reported in Appendix 6. In brief, the SF-36 was recorded for a subgroup of patients on the Spanish Gaucher's Disease Registry at baseline (n = 60) and 2 years after the initiation of therapy (n = 51). However, there were uncertainties concerning the exact date of administration of the survey both at baseline and at follow-up, in relation to the data collection of clinical variables. It should be noted that commencement of ERT does not necessarily coincide with the time of baseline observation. Some patients were already on ERT, whereas others started at a later time. Two years after commencement of therapy is therefore an indeterminate time from baseline observation. It has been assumed that baseline SF-36 would have been administered at the same time as baseline clinical data checked at initial assessment and analyses presented on these data only (*Table 25*).

A statistically significant (at the 5% level) positive relationship was observed between SF-6D score and the presence of anaemia, that is those classified as having anaemia had an SF-6D score 0.1 higher than those without.

A relationship of a similar magnitude was observed with treatment on ERT. There was a statistically significant negative relationship with age at diagnosis, and duration between diagnosis and initial assessment. A decrease in SF-6D was also observed for genotype 'other' (i.e. not N370S/N370S or N370S/other), which included the mutation L444P/L444P, compared with N370S/N370S. Although not statistically significant, the data indicated a positive relationship between SSI and SF-6D. This finding may be influenced by the difference in times between assessment of SF-36 and clinical data. In addition, it can be seen in *Figure 10* that only one patient falls into the 'severe' SSI disease category.

HRQoL from the ICGG Gaucher Registry

At a minimum, the assessment of quality of life using the SF-36 is recommended on an annual basis by the ICGG Gaucher Registry and more frequently where patients experience significant clinical events or ERT dose changes. On this basis, and given the recommendations for the collection of clinical data at similar or more frequent intervals, the ICGG Gaucher Registry has the potential to identify the relationship between individual clinical parameters, or groups of clinical parameters (as in the Zimran SSI), and quality of life with great accuracy. These relationships were

TABLE 25 *Univariate analysis: Short Form 6D (SF-6D) score regressed against individual variables*

	Coefficient	95% CI	*p*	R^2
Age at diagnosis	–0.006	–0.008 to –0.003	<0.001*	0.25
Duration between diagnosis and initial assessment (years)	–0.007	0.002 to 0.012	0.008*	0.12
Chitotriosidase	0.000	0.000 to 0.000	0.273	0.03
Zimran score	0.007	–0.006 to 0.021	0.278	0.03
Genotype ('N370S/N370S' base category)				0.13
N370S/Other	–0.051	–0.184 to 0.082	0.445	
Other	–0.236	–0.420 to –0.051	0.013*	
Anaemia	0.112	0.007 to 0.218	0.038*	0.08
Thrombocytopenia ('no' base category)				0.02
Mild	–0.042	–0.158 to 0.075	0.473	
Moderate	–0.024	–0.162 to 0.114	0.731	
Severe	–0.082	–0.278 to 0.114	0.403	
Hepatomegaly ('no' base category)				0.011
Mild	0.008	–0.133 to 0.150	0.909	
Moderate	0.044	–0.093 to 0.182	0.521	
Severe	0.009	–0.150 to 0.168	0.911	
Splenomegaly ('no' base category)				0.19
Mild	0.300	–0.156 to 0.756	0.173	
Moderate	0.117	–0.187 to 0.420	0.412	
Severe	0.156	–0.156 to 0.467	0.290	
Bone crisis	0.048	–0.054 to 0.151	0.348	0.02
Bone necrosis	0.042	–0.081 to 0.165	0.494	0.01
On ERT	0.122	0.027 to 0.217	0.013*	0.13

CI, confidence interval.
* Significant at the 5% level.

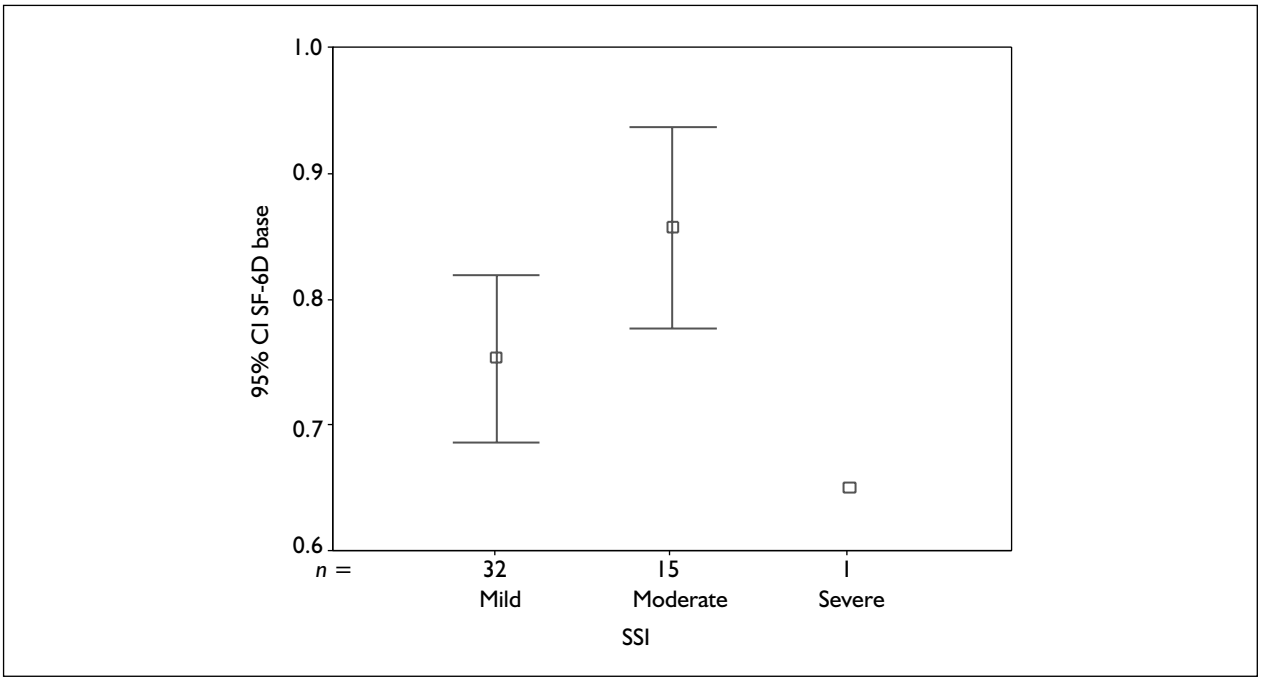

FIGURE 10 *Representation of SF-6D versus Zimran SSI based on Spanish Registry data*

examined using registry data to inform the appropriate structure of a cost-effectiveness model.

In 2004 the authors requested relevant data from the ICGG Gaucher Registry (see Appendix 7). Conflicting accounts were received about the data that were available on the registry, especially regarding quality of life. In 2005, Genzyme provided simple analyses that show the relationships between SF-36 and individual disease parameters: spleen volume (n = 348), platelet count (n = 769), liver volume (n = 457), haemoglobin (n = 812), bone pain (n = 699), bone crisis (n = 964) and bone disease (n = 513), and a multiple regression of SF-6D as a function of all seven disease characteristics (n = 75) conducted only on those patients who had full data. The relationship between SF-6D and disease symptoms was statistically significant (at the 5% level) for bone pain only. However, it is perhaps unsurprising that bone crises are not significant in this analysis since only one person experienced a bone crisis in this group.

Simple linear regression analyses were also performed using normalised haemoglobin (n = 812), platelet count (n = 796), liver volume (n = 457) and spleen volume (n = 348) as explanatory variables. *t*-Tests compared mean SF-6D in groups by bone pain (n = 699), bone crisis (n = 694) and bone disease (n = 513). These analyses indicated that there was no statistically significant relationship between spleen volume or liver volume and SF-6D. The slope between both haemoglobin level and platelet count on SF-6D, while statistically significant, showed a negligible impact on SF-6D.

The presence of bone pain has a significant impact on SF-6D. The mean SF-6D for those with bone pain is 0.68 (95% CI 0.66 to 0.70) compared with 0.82 (95% CI 0.81 to 0.84) for those without. Similarly, those with bone crises have a lower mean SF-6D of 0.59 (95% CI 0.53 to 0.65) compared with 0.77 (95% CI 0.76 to 0.78) for those without. No difference in mean SF-6D was detected between those patients with bone disease compared with those without.

HRQoL: conclusions

Evidence suggests that many of the symptoms of Gaucher's disease, in isolation, do not cause a substantial decrement in HRQoL.

Valuations of Gaucher's disease that correspond to mild Zimran SSI states show decrements no larger than 0.1 of a QALY compared with own health in otherwise healthy adults.[153] Valuations are similar from patients with Gaucher's disease. These valuations are of health states that entail multiple disease symptoms (organomegaly, blood disorders and bone pain). The finding in this study that the patient with bone pain is not considered to be in a worse health state than other patients with Gaucher's disease is surprising and contradicts findings from the ICGG Gaucher Registry. It is possible that the wording of the vignette is the reason for this apparently high valuation (the vignette stresses the mild degree of bone pain experienced, with infrequent instances of severe bone pain).

Bone involvement appears to cause a significant decrement in HRQoL, according to the ICGG Gaucher Registry. The definition of bone disease used is particularly wide and does not distinguish those elements of skeletal involvement that cause considerable pain and/or disability (e.g. avascular necrosis, infarction) from asymptomatic involvement (e.g. lytic lesions, Erlenmeyer flask deformity). Bone involvement is one of the most severe symptoms of Gaucher's disease and these limited data support anecdotal evidence that the value of ERT is predominantly in reducing the extent of this symptom.

It was not possible to use the ICGG Gaucher Registry either to validate or to modify the Zimran SSI. Availability of, and access to, suitable data would also have allowed development of a scoring system relevant to children. Importantly, the impact of growth retardation and delayed puberty on HRQoL, which are not included in the Zimran SSI, could be determined. Uncertainty surrounding estimates of the effectiveness of ERT could be substantially reduced by such analyses.

Existing economic analyses of ERT for Gaucher's disease

Of ten retrieved papers judged of potential relevance based on the abstract, four met the inclusion criteria[38,41,156,157] and six[96,104,117,158–160] were excluded (one contained no formal economic evaluation and five did not report any cost analysis). General study characteristics of the included papers are summarised in *Table 26*.

All economic evaluations produced very high ICERs (further details are provided in Appendix 8). The most recent published study was published in 1996.

TABLE 26 *Characteristics of economic evaluation studies*

Author	Hallam and Bryant, 1996,[41] section 1	Hallam and Bryant, 1996,[41] section 2	Beutler and Garber, 1994[156]	WMHTAC, 2004[38] (unpublished)	Whittington and Goa, 1995[157]
Country of origin	UK	UK	USA	UK	
Currency/base-year prices	£sterling/?	£sterling/?	$US/?	£sterling, 2004	Review paper
Intervention/comparator	ERT (Ceredase)/ no ERT	ERT (Ceredase)/ no ERT	No formal comparison. Analysis of dose regimens	ERT (Ceredase and Cerezyme)/ no ERT	
Study type	CUA	CUA	CUA	CUA	
Study group	Not specified	Type I disease; adults and children	Type not specified; assume 70-kg adult	Type I disease; adults and children	
Perspective	NR	NR	NR	Health service	

CUA, cost–utility analysis.

De novo model of cost-effectiveness of ERT: introduction

The objective of the following economic analysis is to estimate the difference in costs and QALYs of ERT in the management of type I Gaucher's disease compared with standard supportive care in the UK, based on currently available evidence. This evidence is almost exclusively published data. Other data sources, most crucially the ICGG Gaucher Registry, were only able to supply limited relevant information to inform any cost-effectiveness model. Constraints of time and the relative lack of information precluded a separate analysis specific to type III Gaucher's disease.

Structure of decision model

The model is outlined in *Figure 11* and considers a birth cohort of patients with type I Gaucher's disease distributed across four main genotype categories: N370S/N370S, L444P/other, N370S/other and other. These are the four categories shown to be important predictors of disease severity, as described in the section 'Model' (p. 48). Negatively correlated beta distributions were assigned to these proportions to satisfy the condition that they sum to one.

The Zimran SSI provides a framework in which type I Gaucher's disease progression can be described. Its usefulness is currently limited by the fact that the measure is not validated. In addition, the relationship between HRQoL and SSI has not been studied and therefore assumptions have to be made to express changes in SSI in terms of QALYs. Nevertheless, estimates of health state utilities can be attributed to certain components of the index. SSI was therefore considered a useful means of linking information on disease progression in the absence of ERT treatment with alternative scenarios regarding the effectiveness of ERT, and expressing these differences in terms of the costs and QALYs of different health states as defined by SSI. Given the paucity of data, the structure of the decision model is crude. However, were additional data to be made available they could be incorporated with relatively simple modifications.

Several assumptions have been made in constructing the decision model. These are outlined in detail below. Uncertainty in parameters is incorporated in the model by probabilistic sensitivity analysis. Cost-effectiveness acceptability curves (CEACs) are used to convey uncertainty in the outputs of the model. A number of one-way sensitivity analyses is also presented to reflect alternative structural assumptions. Parameter values and probability distributions used in the base-case analysis are presented in Appendix 9.

Benefits are expressed in terms of QALYs, which are derived from existing published literature and estimates from the ICGG Gaucher Registry. Costs are expressed in 2003/04 prices. Discount rates of 3.5% are applied to costs and benefits.

Untreated cohort

All patients are unsplenectomised at the start of the model, which operates on an annual cycle basis. SSI progression is predicted by *Table 19*, with

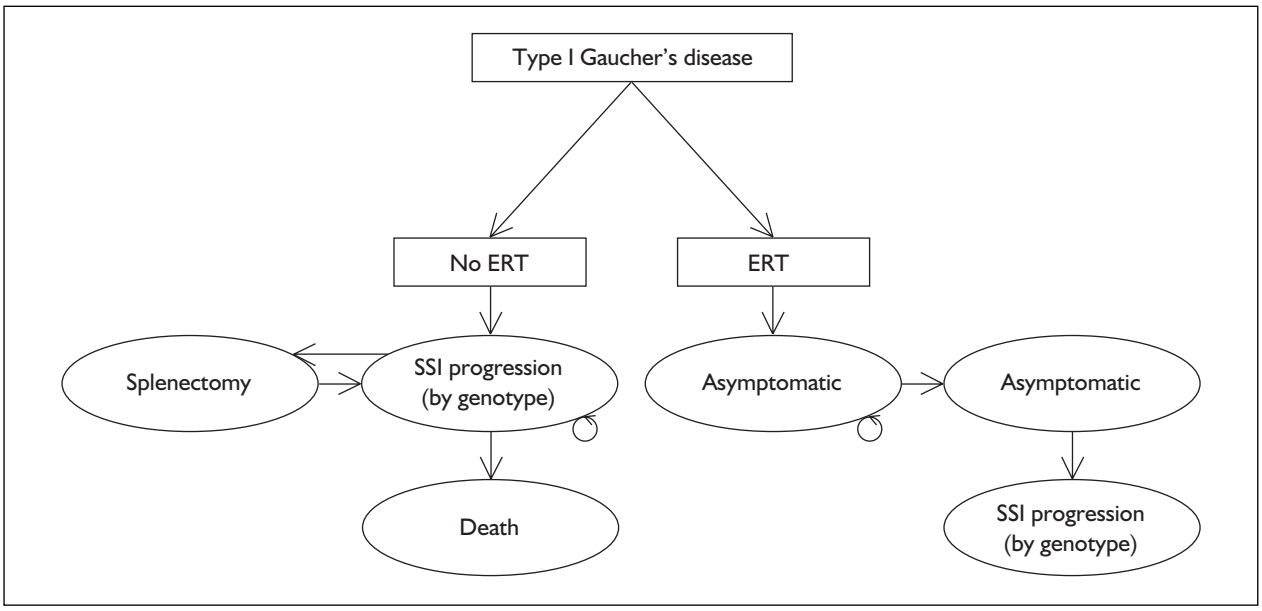

FIGURE 11 *Model schematic*

multivariate normal probability distributions assigned to reflect the uncertainty in coefficient estimates and the correlations between these parameters. It is assumed that the risk of splenectomy is zero until the SSI reaches a minimum of 3. After that point, the risk of splenectomy is based on the rates observed in the natural history sample, adjusted for genotype. Relatively few cases reported age at splenectomy (14%). In those studies where age at splenectomy was reported no individual was splenectomised over the age of 38 years. In the cost-effectiveness model, the risk of splenectomy returns to zero at the age of 40 years. Splenectomy has an immediate impact on SSI. In addition, the cost-effectiveness model assumes that Gaucher's disease causes premature death. The model reflects this, despite the concerns raised about the paucity of data demonstrating such an effect (see the section 'Discussion', p. 52). The life expectancy was set at 65 years. This was based on Cox's observation that life expectancy in type I Gaucher's disease is over 60 years.[5]

Treated cohort

Patients treated with ERT are assumed to remain in an asymptomatic state in most cases; that is, ERT is a complete cure for type I Gaucher's disease. No progression on the Zimran SSI score is assumed for most patients. However, there is a small underlying annual risk of the development of skeletal complications. This is assumed to be 0.2% per annum, based on the observation of one clinical expert that they believed there was better than a 1 in 3 chance that 20% of patients would develop skeletal complications while on therapy. This risk is then spread over 30 years and a beta distribution applied to reflect an assumed 95% confidence interval of 5 to 60% lifetime risk. This may be a conservative estimate. The ICGG Gaucher Registry indicates that 23% of patients experienced severe skeletal manifestations at the start of ERT, and after 5 years of treatment 21% of those registered had the same condition, although these comparisons should be treated with caution.

Those patients who do develop skeletal complications are assumed to have the HRQoL of patients in the moderate SSI category. They face the same costs as the untreated group. They also face the same risk of progression to the severe disease state as the unsplenectomised, untreated patients of the same genotype. This assumption is made on the basis that skeletal complications drive the transition from moderate to severe in the SSI, and the development of skeletal complications indicates that the disease process is not controlled.

ERT is assumed to eliminate entirely Gaucher's disease-specific mortality. The probability of death is equivalent to that of the general population for treated patients. In addition, it is assumed that splenectomy does not occur in patients who are treated with ERT.

Quality of life

Asymptomatic persons are assigned utilities corresponding to the mean, age-adjusted, own health weights derived from the Measurement and Valuation of Health Study.[161]

For those in 'mild' SSI states (defined as SSI ≤10) a value of 0.82 was applied. This value corresponds to the healthy population value derived by the TTO method for scenario 3 (patient with organomegaly and blood disorders) in Clarke.[153] This scenario was considered the worst of the three states that respondents were asked to value and the estimated SSI is 7. This valuation was used as a multiplier in the model. Mean general population values fall below 0.82 where age exceeds 55 years. Therefore, patients in the mild SSI category were assigned age-adjusted QALY scores multiplied by 0.82. For example, for a patient aged less than 25 years, the QALY for being in the mild SSI state is 0.77 (0.94 × 0.82).

For those in 'moderate' SSI states (defined as 10 < SSI ≤ 20) it was assumed that typical patients would experience organomegaly, blood disorders and bone pain. The model therefore used the value of 0.86, based on scenario 2 (patient with bone pain and anaemia) in Clarke (1997),[153] from healthy adults using the TTO method. This value was multiplied by the mild multiplier and the age-adjusted normal health value. In addition, it was assumed that some patients would experience bone crises. Using data from the National Gaucher's Registry (Appendix 10) of patients, it was estimated that approximately 25% of patients would experience bone crises. The additional decrement in HRQoL for these patients was based on data supplied from the ICGG Gaucher Registry. The mean reduction in SF-6D utility score for patients with bone crises, compared with those without, is 0.18. This score was applied as a further multiplier. The mean QALY score for the moderate SSI is 0.66 for an individual aged below 25 years.

For those considered to be in 'severe' SSI states (defined as SSI >20) it was assumed that all would experience bone crises, organomegaly and blood disorders. The mean QALY score for this health state is therefore 0.54 for a person aged less than 25 years. This estimate is slightly lower than 0.59, the mean SF-6D score, for patients with bone crises enrolled on the ICGG Gaucher Registry. Those without bone crises have a mean score of 0.77, similar to the estimate applied to those in mild SSI states.

All QALY multipliers were assigned beta probability distributions.

Costs

Monitoring costs are assumed to be the same for treated and untreated patients, as it was understood that the monitoring arrangements are mandated by the NSCAG arrangement with the four treatment centres. The model therefore excludes these costs.

Mild SSI patients are assumed to receive monthly blood transfusions. The total cost per cycle is estimated as £912.

'Moderate' SSI patients are assumed to receive the same blood transfusions and 2 weeks of nursing home care per annum. The 25% of patients in this group who experience bone crises also incur costs that consist of bisphosphonates and bone surgery each year. The total cost per cycle is estimated as £3144.

'Severe' patients are assumed to incur costs of 4 weeks of nursing home care per annum, plus blood transfusions, bisphosphonates and bone surgery. The total cost is estimated as £7857.

The cost of splenectomy was drawn from NHS reference costs for major abdominal surgery (£2751) and bone surgery from the same source (hip replacement £4660). Nursing care costs were estimated as £496 per week.[162] The annual cost of bisphosphonates was as used by Stevenson and colleagues (2004).[163] Costs drawn from NHS reference costs were assigned normal probability distributions.

The unit cost of ERT is £2.975[37] The mean number of units per month for patients on the National Gaucher's Registry is 2395. Therefore, the annual cost used in the model is £85,501.

Results

Base-case analysis

Base-case results are shown in *Table 27*. Irrespective of genotype, costs and QALYs generated on treatment are identical since it was assumed that ERT is completely effective for the treatment of type I disease, with the exception of a small remaining risk of skeletal disease.

For the hypothetical cohort as a whole, the incremental cost per QALY is £391,000. This varies by genotype and is highest for the N370S/N370S group (£476,000). The treatment of other more severe genotypes is more cost-effective and in the region of £350,000 to £400,000 per additional QALY generated.

The CEAC in *Figure 12* shows that the probability that ERT is cost-effective is zero where the

TABLE 27 *Base-case analysis: cost-effectiveness of ERT*

	Mean cost untreated	Mean cost treated	Mean QALY untreated	Mean QALY treated	Incremental cost	Incremental QALY	ICER	*n*
All patients	£53,692	£2,312,342	18.659	24.432	£2,258,650	5.77	£391,275	200
N370S/N370S	£21,722	£2,312,342	19.615	24.432	£2,290,620	4.82	£475,566	39.4
L444P/other	£62,972	£2,312,342	18.220	24.432	£2,249,370	6.21	£362,120	50.4
N370S/other	£62,972	£2,312,342	18.515	24.432	£2,249,370	5.92	£380,185	34.6
Other	£59,921	£2,312,342	18.520	24.432	£2,252,422	5.91	£380,988	75.6

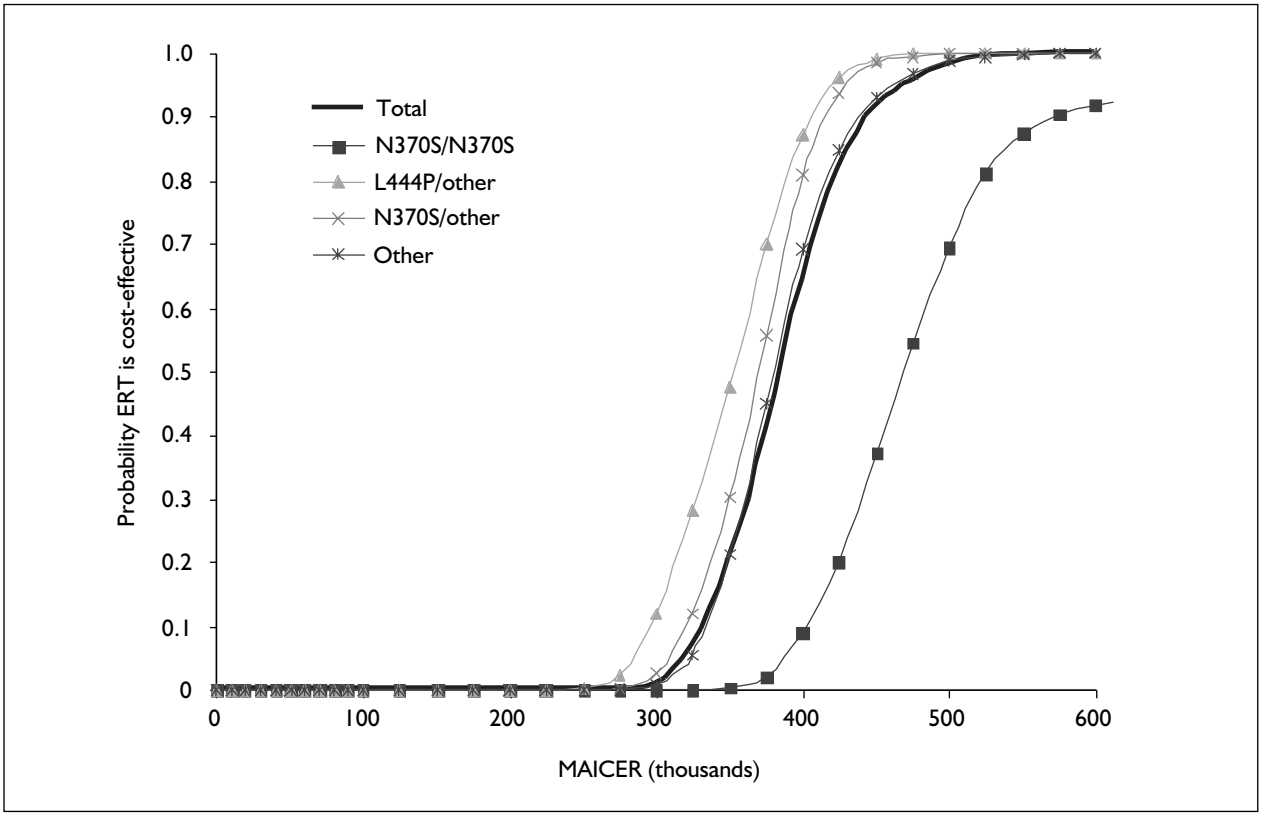

FIGURE 12 *CEAC: base-case analysis*

maximum acceptable incremental cost-effectiveness ratio (MAICER) is £250,000, and at £380,000 the probability is 0.5.

Sensitivity analyses

Analysis 1: ERT does not restore full health

In the base-case analysis, all treated patients are assumed to experience normal health unless they experience skeletal involvement. However, it is likely that ERT does not resolve all disease symptoms and that patients remain at least in a mild disease state. For example, data supplied by the ICGG Gaucher Registry indicate that 5 years after the initiation of ERT, 36% of patients have bone pain, 31% have moderate or severe hepatomegaly and 11% have anaemia. Sensitivity analysis 1 therefore relaxed this assumption by allowing treated patients to progress to mild SSI states and thereby incur the appropriate decrement in quality of life. The additional costs of mild SSI disease were not factored in. The results are shown in *Table 28*.

In this scenario the cost-effectiveness of ERT is substantially worsened. For the overall patient cohort the ICER is in excess of £1.3 million and for the mild genotype cohort £2.6 million.

Analysis 2: disease is more aggressive

Disease progression in the untreated cohort is based on estimates from the literature, as described in the section 'Modelling the natural

TABLE 28 *Cost-effectiveness of ERT: sensitivity analysis 1*

	Mean cost untreated	Mean cost treated	Mean QALY untreated	Mean QALY treated	ICER
All patients	£53,692	£2,322,322	18.659	20.331	£1,356,924
N370S/N370S	£21,722	£2,322,322	19.615	20.502	£2,593,103
L444P/other	£62,972	£2,322,322	18.220	20.177	£1,154,479
N370S/other	£62,972	£2,322,322	18.515	20.340	£1,237,932
Other	£59,921	£2,322,322	18.520	20.340	£1,242,645

TABLE 29 *Cost-effectiveness of ERT: sensitivity analysis 2*

	Mean cost untreated	Mean cost treated	Mean QALY untreated	Mean QALY treated	ICER
All patients	£87,766	£2,313,094	16.918	24.432	£296,178
N370S/N370S	£65,006	£2,313,132	18.576	24.432	£383,904
L444P/other	£102,298	£2,313,085	16.395	24.432	£275,075
N370S/other	£92,496	£2,313,085	16.399	24.432	£276,456
Other	£82,068	£2,313,085	16.931	24.432	£297,430

history of Gaucher's disease' (p. 47). The uncertainty in estimates of disease progression have been incorporated in probabilistic sensitivity analysis. In addition, the base-case model does not entirely reflect the hypothesis that type I Gaucher's disease progresses more slowly in adulthood, since Gaucher-specific mortality has also been factored into the analysis. The untreated cohort in the base-case analysis demonstrates a diminishing speed of disease progression only in those who remain alive. Nevertheless, in sensitivity analysis 2, the impact of modelling disease as more progressive than previously described is explored. The coefficient on log age is 0.921 in the base-case analysis. In this analysis the impact of age on disease severity was trebled. By increasing the magnitude of disease progression in this way, patients of genotype N370S/N370S who are splenectomised are classified as moderate in terms of SSI severity before the end of childhood and those who remain unsplenectomised reach the equivalent degree of severity in adulthood. For each of the other genotype groups, untreated patients are classified as moderate severity in childhood and in most cases progress to severe disease severity in adulthood.

Table 29 reports the costs and QALYs generated by this analysis. The ICER of ERT is lowered by approximately £90,000 for each of the genotype subgroups. The mean ICER for the entire cohort is £296,000 in this scenario.

The equivalent CEAC is shown in *Figure 13*. The probability that ERT is cost-effective in the entire patient cohort is 0.5 at a MAICER of £325,000. In the milder N370S/N370S genotype group this same probability is not reached until the MAICER exceeds £375,000.

Analysis 3a and 3b: treating patients with higher SSIs

The base-case model assumed that ERT is a lifetime treatment and that this commences in relatively mild patients. To assess the impact of waiting to begin treatment only in patients with a relatively severe SSI score, sensitivity analysis 3 considers a cohort with SSI scores at the start of the model of: (a) 5 in unsplenectomised and 8 in splenectomised patients; and (b) 10 in unsplenectomised and 13 in splenectomised patients.

The effect of altering disease severity is that the impact of genotype is reduced such that the patient subgroups appear more similar. *Tables 30* and *31* show the cost-effectiveness of ERT where treatment is restricted to more severe patients. It should be recognised that in this version of the model, the favourable assumptions regarding the effectiveness of ERT are particularly relevant since patients with relatively severe disease without treatment are assumed to be asymptomatic with treatment (excluding the risk of bone disease).

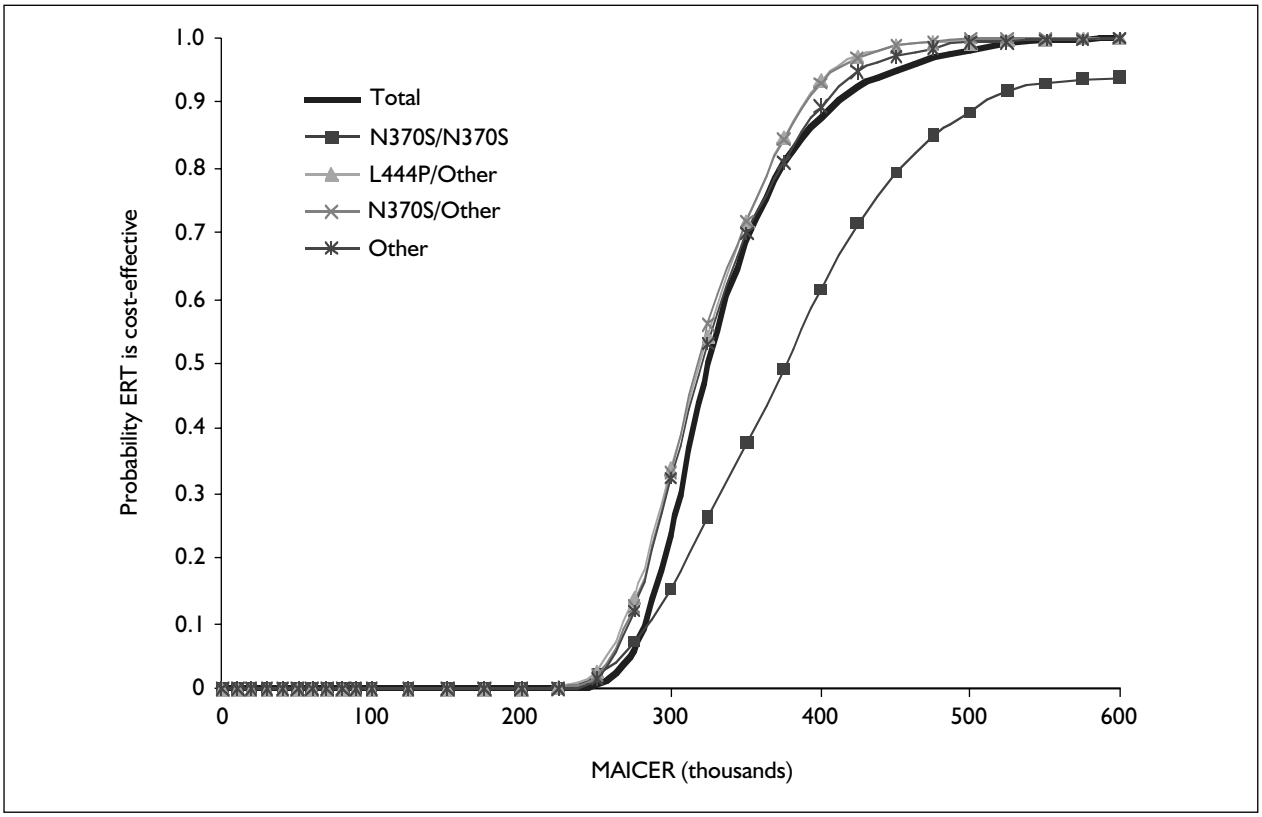

FIGURE 13 *CEAC: sensitivity analysis 2*

TABLE 30 *Cost-effectiveness of ERT: sensitivity analysis 3a*

	Mean cost untreated	Mean cost treated	Mean QALY untreated	Mean QALY treated	ICER
All patients	£67,033	£2,313,094	18.402	24.432	£372,514
N370S/N370S	£24,037	£2,313,132	19.181	24.432	£435,899
L444P/other	£78,463	£2,313,085	18.012	24.432	£348,084
N370S/other	£78,463	£2,313,085	18.301	24.432	£364,475
Other	£74,297	£2,313,085	18.310	24.432	£365,689

TABLE 31 *Cost-effectiveness of ERT: sensitivity analysis 3b*

	Mean cost untreated	Mean cost treated	Mean QALY untreated	Mean QALY treated	ICER
All patients	£80,677	£2,313,094	16.308	24.432	£274,815
N370S/N370S	£80,677	£2,313,132	16.308	24.432	£274,806
L444P/other	£80,677	£2,313,085	16.308	24.432	£274,818
N370S/other	£80,677	£2,313,085	16.308	24.432	£274,818
Other	£80,677	£2,313,085	16.308	24.432	£274,818

Analysis 4: changes in drug cost

ERT is a relatively costly treatment. The base-case analysis estimates an annual patient cost of £85,000. In sensitivity analysis 4, the extent to which the unit cost of ERT drives the cost-effectiveness model is identified. The cost per unit is varied between £0.1 and £5 (base case £2.975) and the resulting ICERs are plotted in *Figure 14*.

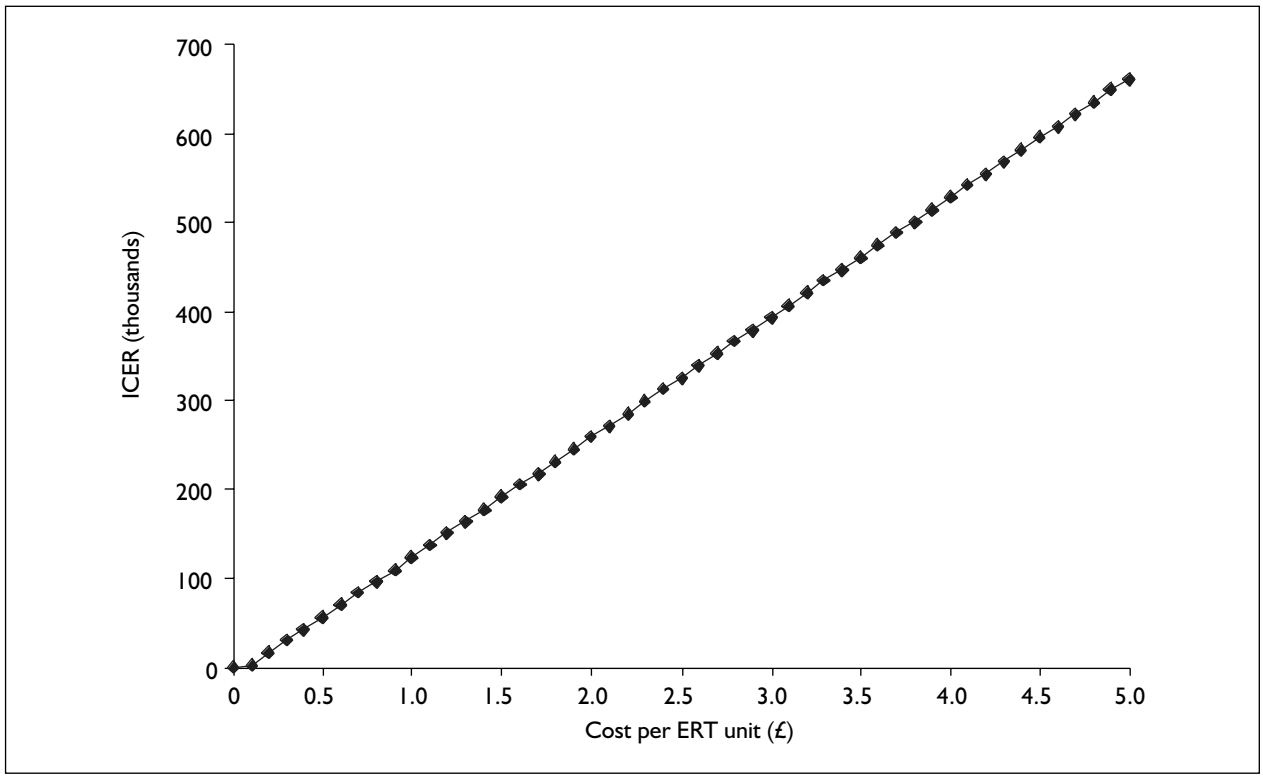

FIGURE 14 *Sensitivity analysis 4: one-way sensitivity analysis of cost of ERT*

An ICER of £30,000 is generated where the price per unit of ERT is £0.3. Where the price of ERT is £1, the ICER rises to £123,000.

Main results

Gaucher's disease is highly heterogeneous, both clinically and genetically. The published literature focuses on this heterogeneity and has not examined in any systematic manner the degree to which clinical expression may be predictable for the majority of patients. This reanalysis of patient-level data from the published literature suggests that there may be more homogeneity, especially within genotype, than is generally assumed. Further work in this area is merited. On the basis of these analyses the cost-effectiveness of therapy was examined under the assumption that the rate of progression slows in adulthood.

The evidence for the effectiveness of ERT in the treatment of visceral symptoms and bone pain is increasingly strong. However, the evidence on the effectiveness of ERT in the prevention of the long-term severe skeletal symptoms of the disease is much weaker. There are no data on the effect of ERT on the mortality rate in Gaucher's disease, although it seems reasonable to assume that there will be at least some reduction.

The evidence on the impact of ERT on HRQoL indicates that visceral symptoms have little impact on HRQoL, but that skeletal symptoms, most notably bone pain, have a significant impact on HRQoL. Only one study explicitly measured the utility value of Gaucher's disease health states. The results were broadly consistent with these findings.

Estimates of the cost per QALY gained range from £360,000 for the more aggressive genotype to £476,000 for the milder genotype, in the base-case analysis. The average across the genotypes is £391,000. However, these figures must be considered in the light of many caveats.

First, the cost-effectiveness model is based on the progression of untreated patients as observed in the published literature and described in the section 'Modelling the natural history of Gaucher's disease' (p. 47). The cost-effectiveness model applies this rate of progression only to those who remain alive in the untreated cohort. Since Gaucher-specific disease mortality is incorporated in the cost-effectiveness model, despite the limited evidence to support this hypothesis, it is possible that the severity of Gaucher's disease, and therefore the cost-effectiveness of ERT, is overestimated.

Second, the use of the SSI measure of disease progression is crude. Within each of the three SSI categories, it is possible for individuals to vary substantially in terms of clinical symptoms and therefore both quality of life and costs. Data availability precludes the use of more sensitive groups.

Third, the effectiveness of ERT is assumed to be complete in terms of visceral symptoms and almost complete in terms of bone disease, and instantaneous in both cases. ERT does not provide such complete relief from symptoms and therefore the base-case analysis may overestimate the cost-effectiveness of treatment.

Alternative scenarios were considered in a one-way sensitivity analysis. Cost-effectiveness ratios are substantially increased if ERT does not return patients to asymptomatic disease. The cost-effectiveness of ERT is improved in patients whose disease progression is worse than that modelled in the base-case scenario or if ERT is given to those experiencing more severe disease.

Chapter 6

Assumptions, limitations and uncertainties

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, they took the unusual step in a systematic review of trying to obtain and analyse primary observational data that had been routinely collected by clinicians. Unfortunately, ICGG Gaucher Registry data, which potentially represented the richest source of observational data for this purpose, were inadequate for the task in hand. (It is of concern to the authors that the decisions about which analyses of ICGG Gaucher Registry data are undertaken and which are not largely depends on people who have a vested interest in the product. This breaches an important methodological principle of scientific research, namely peer review. It is of importance to both the public and patients that analysis of registry data should be undertaken in such a way that analytical, reporting and publication biases are minimised.) A number of substantial assumptions has been required to produce an estimate of the cost-effectiveness of ERT in type I Gaucher's disease, most notably that the SSI categorisation identifies states that are different from each other in relation to HRQoL, and that the states within a broad Zimran category have comparable HRQoL. Where assumptions have been made, the authors have attempted to ensure that these tend to favour rather than detract from the value of ERT.

Of equal importance, because the authors were unable to build a cost-effectiveness model that explicitly took account of the changes in each aspect of Gaucher's disease, and then relate this to change in HRQoL, they have had to make an assumption about how the clinical effectiveness evidence translates into changes in disease status. The effectiveness of ERT is assumed both complete in terms of visceral symptoms and almost complete in terms of bone disease, and instantaneous in both-cases. ERT does not provide such complete relief from symptoms and therefore the base-case analysis may overestimate the cost-effectiveness of treatment.

The cost-effectiveness model is based on the progression of untreated patients as observed in the published literature and described in the section 'Modelling the natural history of Gaucher's disease' (p. 47). The model applies this rate of progression only to those who remain alive in the untreated cohort. Since Gaucher-specific disease mortality is incorporated into the model, despite the limited evidence to support this hypothesis, it is possible that the severity of Gaucher's disease, and therefore the cost-effectiveness of ERT, is overestimated. It was also assumed that people with controlled disease (on treatment) have normal life expectancy. However, it is usual when evaluating chronic diseases to have some data on the effect of treatment on mortality, or on an intermediate outcome that has a known relationship to mortality. Although researchers have been collecting data on people with Gaucher's disease for over 30 years, there is no robust evidence on the mortality rate in Gaucher's disease or on the impact of therapy on mortality rates. Had the authors been able to analyse the data directly, they believe that they would have been able to produce a more satisfactory cost-effectiveness model.

While the natural history model used in the cost-effectiveness analysis is consistent with a hypothesis in the clinical literature, it is still the result of an exploratory analysis. If natural history does not include a substantial slowing of disease progression in adulthood, then the cost per QALY gained from ERT will be correspondingly lower. It is remarkable that even though this clinically important hypothesis was first proposed in 1992 no substantial work has been undertaken to test it more substantially than in the analysis presented in this report.

Chapter 7

Need for further research

Relative to the rarity of the condition, a large number of researchers has compiled data sets on people with Gaucher's disease. It is quite clear that the willingness and ability to collect data on patients with Gaucher's disease exists in 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 robust evidence base. However, while such patient registries have potential in the development of an evidence base 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 authors are very grateful to Dr Pilar Giraldo for access to, and assistance in extracting, information from the Spanish Gaucher's Disease Registry, to Dr Tim Cox for access to National Gauchers Registry data, and to Dr Wraith and Dr Vellodi for providing data from the patients whom they oversee. They were disappointed by the difficulties encountered in accessing information from the largest source of data, the Gaucher Registry, overseen by the ICGG and sponsored by Genzyme, and by the apparent limitations of the data held in the registry.

The authors believe that it is important that, suitably anonymised, data from patient registries are made available to independent researchers for analysis. A necessary condition of access should be a commitment to submit the results of such analyses 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 a model for such an arrangement.

Areas of uncertainty that could be addressed by research include the following:

1. The development and validation of a disease severity index for type I Gaucher's disease.
2. What is the HRQoL in type I Gaucher's disease?
3. How does the rate of disease progression vary by age and genotype?
4. How does the risk of skeletal disease vary by genotype?
5. What is the effectiveness of alternative dose regimens on visceral and skeletal symptoms?
6. What is the effectiveness of ERT on mortality in type I Gaucher's disease?
7. Does the effectiveness of ERT vary by genotype?
8. What is the cost-effectiveness of ERT in type I Gaucher's disease and how does it vary by genotype?
9. Are there treatment strategies that could be developed for a paediatric population (who have the most severe clinical course for type I Gaucher's disease) that could meet current standards of efficiency?

Much of this research could be undertaken through collaborations between the global patient, clinical and academic research communities, and enough patients have been identified to be able to organise RCTs.

Further research could help to clarify the many uncertainties that exist. However, while doing so would be of clinical importance, it is questionable whether, in the current pricing environment, such research would have any substantive impact on policy decisions. From the perspective of informing health policy commissioning 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. (The possible exception to this would be question 9, about investigating efficient alternative treatment strategies for using ERT in paediatric populations.) Moreover, if under EU orphan drug legislation, or on the grounds of equity, the NHS decides that it is important to provide this drug, regardless of its cost-effectiveness, then refining the precision of the ICER estimate also becomes unnecessary as it would not influence any decisions.

It is important to note, however, that the monopoly position of Cerezyme as the only treatment directed against the disease process is

now being threatened. This has the potential to lead to a substantial reduction in the price of Cerezyme. It is important that research into alternative treatments is not stifled.

Moreover, there are also new ERTs for Gaucher's disease in development. The authors believe that it is important that all these new therapies can and should be tested in well-designed trials and that the existence of one treatment should not be used as a barrier to the development of other treatments.

Chapter 8
Discussion

Effectiveness and cost-effectiveness of ERT

Despite the poor quality of the evidence, there is little doubt that ERT is effective in the treatment of visceral symptoms of type I Gaucher's disease. There remains uncertainty regarding its effectiveness in preventing some of the skeletal complications of the condition and it has not been shown to be effective for neurological complications. The precise degree of health gain produced is uncertain because of the lack of adequate comparative studies and information about the natural history of the disease before the introduction of ERT.

Some of the clinicians who treat patients with Gaucher's disease in this country have argued very strongly that the published evidence does not reflect their clinical impressions. However, appropriate analyses to back up these impressions have not been forthcoming and an expert-view elicitation exercise in 2004, attempted with leading clinicians in this field to address this question, was unsuccessful (McCabe C, University of Sheffield; personal communication, 2005).

Although clearly beneficial to patients, Cerezyme treatment is also very expensive. It costs on average approximately £90,000 per annum for each adult patient treated. Treatment is lifelong. Thus, although lifetime treatment with ERT produces health gain it does so at an extremely high cost; the estimated ICER is over £300,000 per QALY, many times above any thresholds that are normally considered acceptable by the NHS. Although the authors have not only undertaken the widest possible review of the published literature, but also sought out as many unpublished data from registries as possible, there remain many uncertainties and assumptions within the effectiveness data and economic model. However, when one considers the high cost of annual treatment for a condition that in most patients is not life-threatening in the short term, one can immediately see 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 that would favour treatment.

The extremely high price of Cerezyme is often put down to the fact that the disease is rare. Sales of the drug have increased year on year. Genzyme revenues from Cerezyme were estimated at over $800 million in 2004.[164] It could be argued that with the increasing number of patients being prescribed the treatment and the likely increase in average dose per patient as young patients progress to adulthood, it seems reasonable to assume that over a decade after the start of production of Cerezyme the operation of economy of scale should and could act to lower per unit production costs compared with time of market entry, and that this would translate to a corresponding drop in purchase price. Production costs of Cerezyme are unpublished. One could argue that orphan drug legislation places companies in a monopoly position in circumstances where there appear to be few external constraints and limited competitive control over the prices charged. This position would be strengthened if purchasers were not to apply the normal standards of cost-effectiveness. With new products for other orphan diseases in the pipeline the sustainability of such a policy is increasingly brought into question.[35]

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Contribution of authors

Keith Abrams (Professor of Medical Statistics) advised on statistical analysis of the ICGG Gaucher Registry data, contributed to the writing of the report and commented on drafts of the report. Amanda Burls (Senior Clinical Lecturer) undertook scoping review at the beginning of the project, contributed to the development of the protocol, provided management advice, liaised with collaborators and stakeholders, wrote the discussion and executive summary, and edited the final report. Martin Connock (Systematic Reviewer) located and extracted clinical effectiveness data, reviewed the clinical effectiveness literature, contributed to writing the background and prevalence sections, and commented on drafts of the report. Nicola Cooper (MRC Research Fellow in Health Services Research) analysed the Spanish Gaucher's Disease Registry and National Gaucher's Registry data, and commented on drafts of the report. Emma Frew (Health Economist) helped to develop the economic model, located and extracted data, wrote sections of the report, and commented on drafts of the report. Anne Fry-Smith (Information Specialist) devised and implemented the bibliographic database searches and wrote the sections on literature searches. Ariadna Juarez-Garcia (Health Economist) contributed to the development of the economic model, reported and analysed the Spanish Gaucher's Disease Registry data, and commented on drafts of the report. Christopher McCabe (Senior Lecturer in Health Economics) reviewed the natural history literature, constructed the natural history model, co-constructed the cost-effectiveness model, contributed to the discussion and conclusion sections, liaised with collaborators and stakeholders, and commented on drafts of the report. David Moore (Research Analyst) coordinated the report, contributed to the scoping review at the beginning of the project and to the development of the protocol, liaised with collaborators and stakeholders, directed the clinical effectiveness review, wrote sections of the report and commented on drafts of the report. Anthony O'Hagan (Director, Centre for Bayesian Statistics in Health Economics) helped to develop the structure of the cost-effectiveness model, aided in the analysis of the natural history data and commented on the interpretation of the results. Alex Sutton (Lecturer in Medical Statistics) analysed the Spanish Gaucher's Disease Registry data and commented on drafts of the report. Allan Wailoo (Lecturer in Health Economics) developed, analysed and reported the cost-effectiveness model, reviewed quality of life literature and commented on drafts of the report.

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Appendix 1

Search strategies

Primary studies

MEDLINE (Ovid)
1966 to July week 5 2004

1 gaucher$.mp. (2867)
2 gaucher disease.mp. (2640)
3 glucosylceramide lipidosis.mp. (12)
4 cerezyme.mp. (15)
5 imiglucerase.mp. (75)
6 beta glucocerebrosidase.mp. (139)
7 b glucocerebrosidase.mp. (2)
8 ceredase.mp. (36)
9 alglucerase.mp. (181)
10 or/1-9 (2919)
11 limit 10 to yr=2003 - 2004 (145)
12 from 11 keep 1-145 (145)

EMBASE (Ovid)
1980 to 2004 week 32

1 gaucher$.mp. (2098)
2 gaucher disease.mp. (1966)
3 glucosylceramide lipidosis.mp. (5)
4 cerezyme.mp. (139)
5 imiglucerase.mp. (211)
6 beta glucocerebrosidase.mp. (145)
7 b glucocerebrosidase.mp. (2)
8 ceredase.mp. (203)
9 alglucerase.mp. (339)
10 or/1-9 (2244)
11 limit 10 to yr=2003 - 2004 (244)
12 from 11 keep 1-244 (244)

CINAHL (Ovid)
1982 to July week 5 2004

1 gaucher$.mp. (45)
2 gaucher disease.mp. (37)
3 glucosylceramide lipidosis.mp. (0)
4 cerezyme.mp. (2)
5 imiglucerase.mp. (3)
6 beta glucocerebrosidase.mp. (0)
7 b glucocerebrosidase.mp. (0)
8 ceredase.mp. (2)
9 alglucerase.mp. (3)
10 or/1-9 (45)
11 limit 10 to yr=2003-2004 (8)
12 from 11 keep 1-8 (8)

Cochrane Library
Issue 3 2004

#1 gaucher*
#2 gaucher disease:Mesh
#3 glucosylceramide lipidosis
#4 cerezyme
#5 imiglucerase
#6 beta glucocerebrosidase
#7 b glucocerebrosidase
#8 ceredase
#9 alglucerase
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

Science Citation Index (Web of Science)
2003 to 2004

#1 TS=gaucher*
#2 TS=glucosylceramide lipidosis
#3 TS=cerezyme
#4 TS=imiglucerase
#5 TS=beta glucocerebrosidase
#6 TS=b glucocerebrosidase
#7 TS=ceredase
#8 TS=alglucerase
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
DocType=All document types; Language=All languages; Database(s)=SCI-EXPANDED;

Appendix 2

List of studies excluded from the ERT effectiveness review

Reference	Reasons
Abrahamov A, Elstein D, Gross-Tsur V, Farber B, Glaser Y, Hadas-Halpern I, *et al*. Gaucher's disease variant characterised by progressive calcification of heart valves and unique genotype [comment]. *Lancet* 1995;**346**:1000–3.	NERT, NOUT
Al Salem AH, Naserullah Z, Qaisaruddin S, Al Dabbous I, Al Abkari H, Al Jam'a A, *et al*. Splenectomy for hematological diseases: the Qatif central hospital experience. *Annals of Saudi Medicine* 1999; **19**:325–30.	NERT, NOUT
Alglucerase: Which patients warrant this expensive treatment? *Drugs and Therapy Perspectives* 1998; **12**(10):5–8.	SEC
Allen MJ, Myer BJ, Khokher AM, Rushton N, Cox TM. Pro-inflammatory cytokines and the pathogenesis of Gaucher's disease: increased release of interleukin-6 and interleukin-10. *QJM* 1997; **90**:19–25.	NOUT
Altarescu G, Phillips M, Foldes AJ, Elstein D, Zimran A, Mates M. The interleukin-6 promoter polymorphism in Gaucher disease: a new modifier gene? *QJM* 2003;**96**:575–8.	NOUT
Amaral O, Lacerda L, Santos R, Pinto RA, Aerts H, Miranda MCS. Type-1 Gaucher disease – molecular, biochemical, and clinical characterization of patients from northern Portugal. *Biochemical Medicine and Metabolic Biology* 1993;**49**:97–107.	NERT, NOUT
Amstutz HC. The hip in Gaucher's disease. *Clin Orthop* 1973;**90**:83–9.	FTEN, NERT, NOUT
Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969–1996. *Pediatrics* 2000;**105**:art-e10.	NERT, NOUT
Ashkenazi A, Zaizov R, Matoth Y. Effect of splenectomy on destructive bone changes in children with chronic (type I) Gaucher disease. *Eur J Pediatr* 1986;**145**:138–41.	NERT, NOUT
Asuman OH, Topcu M. Sphingolipidoses in Turkey. *Brain Dev* 2004;**26**:363–6.	NERT, NOUT
Azuri J, Elstein D, Lahad A, Abrahamov A, Hadas-Halpern I, Zimran A. Asymptomatic Gaucher disease implications for large-scale screening. *Genet Test* 1998;**2**:297–9.	NERT, NOUT
Baer I, Zimmermann HB. [Gaucher's disease in the adult] [in German]. *Deutsche Gesundheitswesen* 1967;**22**:1297–300.	SEC
Baldellou A, Andria G, Campbell PE, Charrow J, Cohen IJ, Grabowski GA, *et al*. Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring [review]. *Eur J Pediatr* 2004;**163**:67–75.	NERT, NOUT
Barton NW, Brady RO, Dambrosia JM. Treatment of Gaucher's disease. *N Engl J Med* 1993;**328**:1564–5.	FTEN, NOUT
Beck M. Variable clinical presentation in lysosomal storage disorders [review]. *J Inherit Metab Dis* 2001; **24**(Suppl 2):47–51.	SEC, NOUT
Becker PS, Dooner G, Valinski H, Kopp D, Novelli E, Swaney W, *et al*. Cell cycle status of primitive colony forming cells infused in patients undergoing gene therapy for Gaucher disease. *Blood* 2000; **96**:3477.	NERT, NOUT

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Reference	Reasons
Beighton P, Goldblatt J, Sacks S. Bone involvement in Gaucher disease. *Prog Clin Biol Res* 1982; **95**:107–29.	NERT, NOUT
Beighton P, Sacks S. Gaucher's disease in Southern Africa. *S Afr Med J* 1974;**48**:1295–9.	NERT, NOUT
Belmatoug N, de Bandt M, Oksenhendler E, Bergmann JF, Dupond JL, Rispal P, *et al*. [Gaucher's disease type 1: apropos of 17 cases] [in French]. *Rev Med Interne* 1993;**14**:995.	NERT, NOUT
Bembi B, Ciana G, Zanatta M, Bottega M, Pelos G, Gornati R, *et al*. Cerebrospinal-fluid infusion of alglucerase in the treatment of acute neuronopathic gauchers-disease. *Pediatr Res* 1995;**38**:425.	Type 2 GD
Bender IB, Bender AL. Dental observations in Gaucher's disease: review of the literature and two case reports with 13- and 60-year follow-ups [review]. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **82**:650–9.	FTEN, NOUT
Bergmann JE, Grabowski GA. Posttranslational processing of human lysosomal acid beta-glucosidase: a continuum of defects in Gaucher disease type 1 and type 2 fibroblasts. *Am J Hum Genet* 1989; **44**:741–50.	NERT, NOUT
Beutler E. Commentary: Dosage–response in the treatment of Gaucher disease by enzyme replacement therapy [comment]. *Blood Cells Mol Dis* 2000;**26**:303–6.	NERT, NOUT
Beutler E. Commentary: the natural history of Gaucher disease. *Blood Cells Mol Dis* 1998;**24**:82.	NERT, NOUT
Beutler E. Economic malpractice in the treatment of Gaucher's disease [comment]. *Am J Med* 1994; **97**:1–2.	SEC
Beutler E. Enzyme replacement therapy for Gaucher's disease [review]. *Baillieres Clinical Haematology* 1997;**10**:751–63.	SEC, NOUT
Beutler E. The cost of treating Gaucher disease [comment]. *Nat Med* 1996;**2**:523–4.	NOUT
Beutler E, Garber AM. Alglucerase for Gaucher's disease: dose, costs and benefits. *Pharmacoeconomics* 1994;**5**:453–9.	SEC, NOUT
Beutler E, Gelbart T, Demina A, Zimran A, leCoutre P. Five new Gaucher-disease mutations. *Blood Cells Mol Dis* 1995;**21**:20–4.	NERT, NOUT
Beutler E, Gelbart T, Kuhl W, Sorge J, West C. Identification of the 2nd common Jewish Gaucher disease mutation makes possible population-based screening for the heterozygous state. *Proc Nat Acad Sci USA* 1991;**88**:10544–7.	NERT, NOUT
Beutler E, Gelbart T, Kuhl W, Zimran A, West C. Mutations in Jewish patients with Gaucher disease. *Blood* 1992;**79**:1662–6.	NERT, NOUT
Beutler E, Kay A, Saven A, Garver P, Thurston D, Dawson A, *et al*. Enzyme replacement therapy for Gaucher disease. *Blood* 1991;**78**:1183–9.	FTEN
Beutler E, Kay AC, Saven A, Garver P, Thurston DW, Rosenbloom BE, *et al*. Enzyme-replacement therapy for Gaucher's disease 3. *N Engl J Med* 1991;**325**:1809–11.	FTEN, NOUT
Beutler E, Nguyen NJ, Henneberger MW, Smolec JM, McPherson RA, West C, *et al*. Gaucher disease: gene frequencies in the Ashkenazi Jewish population. *Am J Hum Genet* 1993;**52**:85–8.	NERT, NOUT
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Reference	Reasons
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Chang-Lo M, Yam LT, Rubenstone AI. Gaucher's disease. Review of the literature and report of twelve new cases. *Am J Med Sci* 1967;**254**:303–15.	NERT, NOUT
Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, *et al*. The Gaucher registry: demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med* 2000; **160**:2835–43.	NERT, NOUT
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Clarke AE, Goldstein MK, Michelson D, Garber AM, Lenert LA. The effect of assessment method and respondent population on utilities elicited for Gaucher disease. *Qual Life Res* 1997;**6**:169–84.	NOUT
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Cox TM, Schofield JP. Gaucher's disease: clinical features and natural history [review]. *Baillieres Clinical Haematology* 1997;**10**:657–89.	SEC

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vom Dahl S, Monnighoff I, Haussinger D, *et al*. Decrease of plasma taurine in Gaucher disease and its sustained correction during enzyme replacement therapy. *Amino Acids* 2000;**19**:585–92.	NOUT (bio only)
Dionisi-Vici C, Rizzo C, Burlina AB, Caruso U, Sabetta G, Uziel G, *et al*. Inborn errors of metabolism in the Italian pediatric population: a national retrospective survey. *J Pediatr* 2002;**140**:321–7.	NERT, NOUT
Di Rocco M, Salemi D, Borrone C. Gaucher's disease. Longitudinal-study in 17 patients in a 10-year period (1970–1980) (authors' transl.)] [in Italian]. *Pediatr Med Chir* 1981;**3**:487–94.	NERT, NOUT
Dreborg S, Erikson A, Hagberg B. Gaucher disease – Norrbottnian type I. General clinical description. *Eur J Pediatr* 1980;**133**:107–18.	NERT, NOUT
Drugan C, Jebeleanu G, Grigorescu-Sido P, Caillaud C, Craciun AM. Biochemical markers of bone turnover as tools in the evaluation of skeletal involvement in patients with type 1 Gaucher disease. *Blood Cells Mol Dis* 2002;**28**:13–20.	NERT
Drugan C, Procopciuc L, Jebeleanu G, Grigorescu-Sido P, Dussau J, Poenaru L, *et al*. Gaucher disease in Romanian patients: incidence of the most common mutations and phenotypic manifestations. *Eur J Hum Genet* 2002;**10**:511–15.	NERT, NOUT
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Elstein D, Abrahamov A, Dweck A, Hadas-Halpern I, Zimran A. Gaucher disease: pediatric concerns [review]. *Paediatr Drugs* 2002;**4**:417–26.	NERT, NOUT
Elstein D, Abrahamov A, Itzchaki M, Zimran A. Commentary: low-dose high-frequency enzyme replacement therapy prevents fractures without complete suppression of painful bone crises in patients with severe juvenile onset type I Gaucher disease [comment]. *Blood Cells Mol Dis* 1998;**24**:303–5.	Type 1
Erikson A. Gaucher disease – Norrbottnian type III. Neuropaediatric and neurobiological aspects of clinical patterns and treatment. *Acta Paediatr Scand Suppl* 1986;**326**:1–42.	
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Esplin JA. Clinical effects of enzyme replacement therapy for Gaucher disease: a review of various dosing regimens. *Semin Hematol* 1995;**32**(3 Suppl 1):28–32.	SEC, NOUT
Evangeliou A, Dafnis E, Perdikoyanni C, Spilioti M, Lionis C, Kalmanti M. Hematological abnormalities in inborn errors of metabolism – how frequent are they? The Cretan experience. *Pediatr Hematol Oncol* 2002;**19**:581–5.	FTEN, NERT, NOUT
Filocamo M, Mazzotti R, Stroppiano M, Seri M, Giona F, Parenti G, *et al*. Analysis of the glucocerebrosidase gene and mutation profile in 144 Italian gaucher patients. *Hum Mutat* 2002; **20**:234–5.	NERT, NOUT
Fink IJ, Pastakia B, Barranger JA. Enlarged phalangeal nutrient foramina in Gaucher disease and beta-thalassemia major. *AJR Am J Roentgenol* 1984;**143**:647–9.	NERT, NOUT
Fleshner PR, Aufses AH Jr, Grabowski GA, Elias R. A 27-year experience with splenectomy for Gaucher's disease. *Am J Surg* 1991;**161**:69–75.	NERT, NOUT
Frenkel EP. Gaucher disease: a heterogeneous clinical complex for which effective enzyme replacement has come of age [review]. *Am J Med Sci* 1993;**305**:331–44.	SEC
Fried K. Population study of chronic Gaucher's disease. *Israel Journal of Medical Sciences* 1973;**9**:1396–8.	NERT
Gagnon DM, Pergament E, Fine BA. Demographic studies from a National Gaucher disease screening program. *Journal of Genetic Counseling* 1998;**7**:385–99.	NERT, NOUT

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Reference	Reasons
Garvey MA, Toro C, Goldstein S, Altarescu G, Wiggs EA, Hallett M, *et al*. Somatosensory evoked potentials as a marker of disease burden in type 3 Gaucher disease. *Neurology* 2001;**56**:391–4.	NERT
Gielchinsky Y, Elstein D, Hadas-Halpern I, Lahad A, Abrahamov A, Zimran A. Is there a correlation between degree of splenomegaly, symptoms and hypersplenism? A study of 218 patients with Gaucher disease. *Br J Haematol* 1999;**106**:812–16.	NERT, NOUT
Gillis S, Hyam E, Abrahamov A, Elstein D, Zimran A. Platelet function abnormalities in Gaucher disease patients. *Am J Hematol* 1999;**61**:103–6.	FTEN
Giraldo P. Incidence of Gaucher's disease in Spain. *Br J Haematol* 1996;**93**:707.	NERT, NOUT
Giraldo P, Montanes MA, Perez-Calvo JI, Pocovi M, Alvarez R, Alonso A, *et al*. Increase of intracellular iron in type 1 Gaucher's disease. Study in 43 patients. *Blood* 2003;**102**:3879.	NOUT
Giraldo P, Perez-Calvo J, Cortes T, Civeira F, Rubio-Felix D. [Type I Gaucher's disease: clinical, evolutive and therapeutic features in eight cases] [comment] [review] [in Spanish]. *Sangre* 1994;**39**:3–7.	FTEN, NOUT
Giraldo P, Perez-Calvo JI, Giralt M, Pocovi M. Clinical characteristics of Gaucher's disease in Spain. Preliminary results of a national inquiry. *Med Clin* 1997;**109**:619–22.	NERT, NOUT
Glenn D, Gelbart T, Beutler E. Tight linkage between Gaucher disease and pyruvate-kinase (pk) deficiency genes. *Blood* 1993;**82**:A33.	NERT, NOUT
Glueck CJ, Freiberg R, Tracy T, Stroop D, Wang P. Thrombophilia and hypofibrinolysis: pathophysiologies of osteonecrosis. *Clin Orthop* 1997;**334**:43–56.	NERT, NOUT
Goldblatt J, Beighton P. Gaucher disease in the Afrikaner population of South Africa. *S Afr Med J* 1979;**55**:209–10.	NERT, NOUT
Goldblatt J, Beighton P. Gaucher's disease in South Africa. *J Med Genet* 1979;**16**:302–5.	NERT, NOUT
Goldblatt J, Sacks S, Beighton P. The orthopedic aspects of Gaucher disease. *Clin Orthop* 1978; **137**:208–14.	NERT, NOUT
Grabowski GA, Hopkin RJ. Enzyme therapy for lysosomal storage disease: principles, practice, and prospects [review]. *Ann Rev Genomics Hum Genet* 2003;**4**:403–36.	NERT, SEC, NOUT
Grabowski GA, Leslie N, Wenstrup R. Enzyme therapy for Gaucher disease: the first 5 years [review]. *Blood Rev* 1998;**12**:115–33.	SEC, NOUT
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continued

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Tournay A, Parker C, Schiffman R, Brady R, Barton N. Enzyme replacement therapy in type 2 Gaucher disease. *Neurology* 1996;**46**:1106.	Type 2 GD
Tsai FJ, Wu JY, Lin SP, Chang JG, Lee CC, Tsai CH. Mutation analysis of type 2 Gaucher disease in Taiwan Chinese and identification of two novel mutations. *Am J Hum Genet* 2000;**67**:1633.	Type 2 GD
Tsuji S, Martin BM, Barranger JA, Stubblefield BK, LaMarca ME, Ginns EI. Genetic heterogeneity in type 1 Gaucher disease: multiple genotypes in Ashkenazic and non-Ashkenazic individuals [published erratum appears in *Proc Nat Acad Sci USA* 1988;**85**:5708]. *Proc Nat Acad Sci USA* 1988;**85**:2349–52.	NERT, NOUT
Tylki-Szymanska A, Czartoryska B. Enzyme replacement therapy in type III Gaucher disease. *J Inherit Metab Dis* 1999;**22**:203–4.	FTEN, NOUT
Tylki-Szymanska A, Czartoryska B, Lugowska A, Gorska D. The prevalence and diagnosis of lysosomal storage diseases in Poland. *Eur J Pediatr* 2001;**160**:261–2.	
Vellodi A, Wraith JE, McHugh K, Young E, Cooper A. Guidelines for the management of pediatric Gaucher disease in the United Kingdom. 2002. London: Institute of Child Health, Great Ormond Street.	SEC
Verma IC, Saxena R, Lall M, Bijarnia S, Sharma R. Genetic counseling and prenatal diagnosis in India – experience at Sir Ganga Ram Hospital. *Indian J Pediatr* 2003;**70**:293–7.	NERT, NOUT
Walley AJ, Barth ML, Ellis I, Fensom AH, Harris A. Gaucher's disease in the United Kingdom: screening non-Jewish patients for the two common mutations. *J Med Genet* 1993;**30**:280–3.	NERT, NOUT
Wasant P, Svasti J, Srisomsap C, Liammongkolkul S, Naylor EW, Matsumoto I. Inherited metabolic disorders in Thailand – Siriraj experience. Southeast Asian *J Trop Med Public Health* 1999;**30**(Suppl 2): 124–37.	NERT, NOUT
Wenger DA, Coppola S, Liu S-L. Insights into the diagnosis and treatment of lysosomal storage diseases. *Arch Neurol* 2003;**60**:322–8.	NERT, NOUT
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Winkelman M, Banker BQ, Victor M. Adult Gaucher disease – a clinico-neuropathologic study. *Neurology* 1982;**32**(4):A159.	NERT, NOUT
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Woodfield MJ, Woodfield DG, Winship IM. Clinical and molecular aspects of Gaucher disease in New Zealand. *N Z Med J* 1997;**110**:316–19.	NERT, NOUT
Young E, Chatterton C, Vellodi A, Winchester B. Plasma chitotriosidase activity in Gaucher disease patients who have been treated either by bone marrow transplantation or by enzyme replacement therapy with alglucerase. *J Inherit Metab Dis* 1997;**20**:595–602.	NOUT, Bio only
Zhao H, Keddache M, Bailey L, Arnold G, Grabowski G. Gaucher's disease: identification of novel mutant alleles and genotype–phenotype relationships. *Clin Genet* 2003;**64**:57–64.	NERT, NOUT
Zharko KP, Mitasova IN, Ermakova RP. [Gaucher's disease in adults] [in Russian]. *Vrachebnoe Delo* 1969; **6**:143–5.	NERT
Zimran A, Bashkin A, Elstein D, Rudensky B, Rotstein R, Rozenblat M, *et al*. Rheological determinants in patients with Gaucher disease and internal inflammation. *Am J Hematol* 2004;**75**:190–4.	NERT, NOUT
Zimran A, Cohen IJ, Zaizov R. Low-dose high-frequency enzyme replacement therapy prevents fractures without complete suppression of painful bone crises in patients with severe juvenile onset type I Gaucher disease: Commentary. *Blood Cells Mol Dis* 1998;**24**:303–8.	SEC
Zimran A, Elstein D. Gaucher disease and the clinical experience with substrate reduction therapy [review]. *Philos Trans R Soc Lond B Biol Sci* 2003;**358**:961–6.	NERT, NOUT

continued

Reference	Reasons
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Zimran A, Gross E, West C, Sorge J, Kubitz M, Beutler E. Prediction of severity of Gaucher's disease by identification of mutations at DNA level. *Lancet* 1989;**334**:349–52.	NERT, NOUT
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Zimran A, Rosenbloom B, Andersson HC, Charrow J, Kaplan P, Kolodny EH, *et al*. Incidence of malignancies among adult patients with type I Gauchisease: Data from a single referral clinic and from the International Gaucher Registry (ICGG). *Blood* 2003;**102**:3874.	NOUT
Zlotogora J, Sagi M, Zeigler M, Bach G. Gaucher disease dase type I and pregnancy. *Am J Med Genet* 1989;**32**:475–7.	NERT, NOUT

FTEN, fewer than patients studied; GD, Gaucher's disease; NERT, ERT not used or, if used, not before and after data for outcome measures; NOUT, no appropriate outcome measure reported; SEC, secondary/review study.

Appendix 3

List of abstracts

The abstracts below report studies not identified in full papers with certainty, which may satisfy the inclusion criteria but with insufficient detail for useful data extraction.

Andersson H, Charrow J, Kaplan P, Kolodny EH, Mistry P, Pastores G, *et al*. The Gauchers Registry: demographics and disease characteristics and response to enzyme replacement therapy (ERT) for 78 pediatric patients (pts). *Blood* 2000;**96**:17.

Barton NW, Doppelt SI, Mankin HJ, Brady RO. Reversal of the clinical manifestations of Gaucher disease by enzyme replacement therapy. *Am J Hum Genet* 1991;**49**:112.

Charrow J, Andersson HC, Kaplan P, Kolodny E, Mistry P, Pastores G, *et al*. Response to enzyme replacement therapy in Gaucher disease patients with N370S/N3. Response to enzyme replacement therapy in Gaucher disease patients with N370S/N370S, N370S compound heterozygotes and L444P/L444P genotypes. *Am J Hum Genet* 2000;**67**:2411.

Fallet S, Grabowski GA. Gaucher disease – efficiacy of enzyme replacement therapy. *Am J Hum Genet* 1991;**49**:113.

Giraldo P. Alglucerase therapy for Gaucher's disease. Preliminary results in Spanish patients. *Br J Haematol* 1996;**93**:708.

Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee MA, *et al*. Enzyme therapy in Gaucher disease type-1 – comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. *Blood* 1994;**84**:A226.

Grabowski GA, Pastores G, Brady RO, Barton N. Gaucher disease type-1 – safety and efficacy of macrophage – targeted recombinant glucocerebrosidase therapy. *Clin Res* 1993;**41**:A390.

Hollak CEM, Aerts JM, Van Weely S, Phoa SS, Goudsmit R, Von Demborne AE, *et al*. Enzyme suppletion therapy for type-1 Gaucher disease – efficacy of very-low dose alglucerase in 12 patients. *Blood* 1993;**82**:A33.

Kaplan P, Andersson HC, Charrow J, Kolodny EH, Mistry P, Pastores GM, *et al*. Growth improvement in response to enzyme replacement therapy (ERT) among children with Gaucher disease: the Gauchers Registry. *Am J Hum Genet* 2001;**69**:2897.

Kim HJ, Ha MJ, Cho JH, Kim BS, Kim MK, Kim SH, *et al*. Clinical assessment of therapeutic response to enzyme replacement therapy in 16 Korean Gaucher pts. *Am J Hum Genet* 1999;**65**:1740.

Patlas M, Halpern IH, Abrahamov A, Elstein D, Zimran A. Repeat abdominal ultrasound evaluation of 103 Gaucher patients treated with enzyme replacement therapy for more than eight years. *Radiology* 1999;**213P**:1285.

Rosenbaum H, Brenner B, Besser M, Rowe JM. Type I Gaucher disease: clinical features in 80 patients and enzyme replacement therapy results in 18 patients. *Blood* 1998;**92**:2203.

Rubio-Felix D, Giraldo P, Perez-Calvo JI, Giralt M. Type-1 Gaucher's disease. Enzymatic replacement therapy and assessment of quality of life. *Blood* 1999;**94**:184–5a.

Rubio-Felix D, Giraldo P, Perez-Calvo JI, Giralt M. Quality of life in type I Gaucher disease: impact of skeletal involvement. *Blood* 2000; **96**:1880.

Weinreb N, Andersson H, Charrow J, Kaplan P, Kolodny E, Mistry P, *et al*. The Gauchers Registry: demographics and disease characteristics of 996 patients (pts) on enzyme replacement therapy (ERT) compared to 438 untreated pts. *Blood* 1999;**94**:929.

Weinreb NJ, Andersson H, Charrow J, Kaplan P, Kolodny EH, Mistry P, *et al*. The Gauchers Registry: Severe bone disease among patients with Gaucher disease in the absence of significant hematologic abnormalities. *Blood* 2000;**96**:18.

Weinreb NJ, Andersson HC, Charrow J, Kaplan P, Kolodny EH, Mistry P, *et al*. Clinical factors influencing the achievement of a complete response (CR) after 24 months of enzyme replacement therapy (ERT) in patients with Gaucher disease: the Gauchers Registry. *Blood* 2001;**98**:70.

Weinreb NJ, Andersson H, Charrow J, Kaplan P, Kolodny EH, Mistry PK, *et al*. Massive and partially refractory splenomegaly significantly influences the platelet (PLT) response to enzyme replacement therapy (ERT) in thrombocytopenic patients with Gaucher disease (GD): report from the Gauchers Registry. *Blood* 2002;**100**:1885.

Zimran A, Kannai R, Cohen Y, Zevin S, Hadashalpern I, Abrahamov A. Low-dose enzyme replacement therapy for patients with Gaucher disease – effects of age, sex, genotype and splenectomy on response to treatment in 29 patients. *Blood* 1993;**82**:A33.

Appendix 4

Organ volume changes

TABLE 32 *Changes during ERT of liver volume measured as extension beyond costal margin*

Study	Distance beyond costal margin (cm)	Months of treatment						
		Baseline	**6**	**12**	**18**	**24**	**30**	**36**
Alfonso, 2003[70]	Mean (SD)	6 (7.5)			3 (7.3)			
	n	*54*			*54*			
	% Change	NA			**–50%**			
	p vs baseline	NA			*p 0.003*			
Giraldo, 2000[55a]	Mean (SD)	5.5 (0.5)		4 (1.2)		3.5 (1)		2.4 (0.8)
	n	*94*		*84*		*76*		*57*
	% Change	NA		**–27**		**–36**		**–56**
	p vs baseline	NA		0.0001		0.02		0.056
Perez-Calvo, 1997[110]	Mean (SD)	8.2 (8.7)	5.7 (7.5)	3.9 (7.0)		1.5 (2)		1.6 (2.8)
	n[b]	*18?*	*18?*	*18?*		*16?*		*11?*
	% Change	NA	**–31.5**	**–52.5**		**–82**		**–80.5**
	p vs baseline	NA	NR	NR		NR		NR
Zaizov, 1995[117]	Mean (SD)	12						7[c]
	n	*11*						*11*
	% Change	NA						**–42**
	p vs baseline	NA						NR

[a] Data read from graph.
[b] The number of patients at each time-point of Perez-Calvo was not explicit; the percentage change relates to the mean for all the patients measured at baseline.
[c] Mean follow-up 2.5 years.

TABLE 33 *Percentage change in liver volume or 'volume index' (by group or individual) with ERT*

Study	Liver volume (l)	Months of treatment					
		Baseline	**6**	**12**	**24**	**30**	**36 or > 36**
Altarescu, 2000[82] HD	Mean (SD)	2.29 (0.8)			2.0 (0.75)	1.68 (0.62)	1.67 (0.5)
	n	*12*			*12*	*12*	*12*
	% Change	NA			**–13.2**	**–26.9**	**–27.3**
	p vs baseline	*NA*			*NR*	*NR*	*NR*
Altarescu, 2000[82] LD	Mean (SD)	2.53 (1.1)	2.44 (0.98)	2.39 (1.05)			
	n	*32*	*32*	*32*			
	% Change	NA	**–3.4**	**–5.5**			
	p vs baseline	*NA*	*NR*	*NR*			
Barton, † 1991[84]	Mean (SD)	2.29 (0.83)		2.01 (0.74)[a]			
	n	*12*		*12*			
	% Change	NA		**–11**			
	p vs baseline	*NA*		*NR*			
Bembi, 1994[87b]	Mean (SD)	1.9 (1.1)	1.4. (1.0)				
	n	*12*	*12*				
	% Change	NA	**–16.9**				
	p vs baseline	*NA*	*NR*				

continued

TABLE 33 *Percentage change in liver volume or 'volume index' (by group or individual) with ERT (cont'd)*

Study	Liver volume (l)	Months of treatment					
		Baseline	**6**	**12**	**24**	**30**	**36 or > 36**
Dweck, 2002[72c]	Mean (SD)	3.8 (1.6)					3.5 (1.5)[d]
	n	*30*					*30*
	% Change	NA					**–8**
	p vs baseline	*NA*					*NR*
Ehlen, 1995[92]	Mean (SD)	2.75 (NR)		1.5 (NR)[e]			
	n	*7*		*7*			
	% Change	NA		**–46**			
	p vs baseline	*NA*		*NR*			
Elstein, 1998[93]	Mean (SD)	NR	NR	NR	NR		
	n	*–*	*25*	*23*	*16*		
	% Change	NA	**–5.5**	**–10.0**	**–18.1**		
	p vs baseline	*NA*	*NR*	*NR*	*NR*		
Fallet, 1992[95]	Mean (SD)	3.3 (1.4)	2.7 (1.1)[f]				
	n	*11*	*11*				
	% Change	NA	**–18.2**				
	p vs baseline	*NA*	*NR*				
Figueroa, 1992[96b]	Mean (SD)	3.15 (1.86)	2.53 (1.39)				
	n	*14*	*14*				
	% Change	NA	**–17.8**				
	p vs baseline	*NA*	*NR*				
Grabowski, 1995[61b]	Mean (SD)	2.7 (0.86)	2.4 (0.71)				
	n	*30*	*30*				
	% Change	NA	**–10.1**				
	p vs baseline	*NA*	*NR*				
Hollak, 1995[100]	Mean (SD)	3.3 (1.29)	NR				
	n	*25*	*21*				
	% Change	NA	**–12.2**				
	p vs baseline	*NA*	*NR*				
Hollak, 1997[99]	Mean (SD)	3.2 (1.26)	NR	NR			
	n	*30*	*26*	*26*			
	% Change	NA	**12**	**20**			
	p vs baseline	*NA*	*NR*	*NR*			
Hollak, 2001[75b]	Mean (SD)	2.9 (0.84)					2.92.0 (0.5)[g]
	n	*12*					*12*
	% Change	NA					29
	p vs baseline	*NA*					*NR*
Lorberboym, 1997[103]	Mean (SD)	NR					NR[h]
	n	*37*					*37?*
	% Change	NA					**–24.5**
	p vs baseline	*NA*					*<0.001*
Patlas, 2002[108i]	Mean (SD)	NR					NR
	n	*100*					*100?*
	% Change	NA					**30**
	p vs baseline	*NA*					*NR*
Schaison, 2002[114]	Mean (SD)	NR	NR	NR			
	n	*108?*	*108?*	*108?*			
	% Change	NA	**10**	**12**			
	p vs baseline	*NA*	*NR*	*NR*			

continued

TABLE 33 *Percentage change in liver volume or 'volume index' (by group or individual) with ERT (cont'd)*

Study	Liver volume (l)	Months of treatment						
		Baseline	**6**	**12**	**24**	**30**	**36 or > 36**	
Schiffmann, 2002[28]	Mean (SD)	3.41 (0.31)	2.73 (0.28)	2.42 (0.25)	2.48 (0.185)			
	n	*10*	*10*	*10*	*10*			
	% Change	NA	**–24.9**	**–40.8**	**–37.3**			
	p vs baseline	*NA*	*NR*	*NR*	*NR*			
	Mean (SD)[j]	3.16 (0.43)	3.0 (0.49)	2.7 (0.49)	2.48 (0.49)			
	n	*9*	*9*	*9*	*9*			
	% Change	NA	**–6.2**	**–17.2**	**–27.4**			
	p vs baseline	*NA*	*NR*	*NR*	*<0.001*			
Terk, 2000[81b]	Mean (SD)	NR					NR[k]	
	n	*32*					*32*	
	% Change	NA					**–11**	
	p vs baseline	*NA*					*NR*	
Weinreb, 2002[116]	Mean (SD)	NR			NR	NR	NR	NR[l]
	n	*NR*			*94*	*56*	*37*	*17*
With spleen	**% Change**	NA			**–29**	**–36**	**–38**	**–41**
	p vs baseline	*NA*			*NR*	*NR*	*NR*	*NR*
With no spleen	Mean (SD)[j]	NR			NR	NR	NR	NR
	n	*NR*			*35*	*21*	*11*	*10*
	% Change	NA			**–38**	**–41**	**–50**	**–47**
	p vs baseline	*NA*			*NR*	*NR*	*NR*	*NR*
Zimran, 1994[120]	Mean (SD)[m]	NR	NR	NR				
	n	*28*	*28*	*28*				
	% Change	NA	**–16.7**	**–25.9**				
	p vs baseline	*NA*	*NR*	*NR*				
Zimran, 1995[121b]	Mean (SD)	2.78 (0.76)	NR	NR				
	n	*10*	*10*	*10*				
	% Change	NA	**–9.5**	**–14.6**				
	p vs baseline	*NA*	*NR*	*NR*				
	Mean (SD)							
	n							
	% Change							
	p vs baseline							

[a] Median follow-up 10.75 months.
[b] Individual patient data.
[c] Volume index measure (patients all children).
[d] Follow-up 3–9 years.
[e] Follow-up 18 months.
[f] follow-up 8 months.
[g] Follow-up 4 years.
[h] Mean follow-up 31.6 months
[i] Percentage calculated from volume index determined by ultrasound follow-up 2–7 years.
[j] ERT + vitamin D analogue, data read from graph.
[k] Median follow-up 34 months.
[l] Data for 3 years and 4 years reported.
[m] Based on volume index measures.

TABLE 34 *Changes during ERT of spleen volume measured as extension beyond costal margin*

Study	Distance beyond costal margin (cm)	Months of treatment						
		Baseline	**6**	**12**	**18**	**24**	**30**	**36**
Alfonso, 2003[70]	Mean (SD)	14 (9.0)			8 (7.9)			
	n	*54?*			*54?*			
	% Change	NA			**–43%**			
	p vs baseline	*NA*			*NR*			
Giraldo, 2000[55a]	Mean (SD)	11.7 (1)		8.3 (1.2)		8 (1.7)		8.1 (2.0)
	n	*94*		*84*		*76*		*57*
	% Change	NA		**–29.1**		**–31.6**		**–30.7**
	p vs baseline	*NA*		0.0005		0.0009		0.0064
Perez-Calvo, 1997[110]	Mean (SD)	16.5 (11.7)	11.0 (9.7)	8.5 (8.7)		5.0 (8.6)		5.2 (10.5)
	n[b]	*18?*	*18?*	*18?*		*16?*		*11?*
	% Change	NA	**–33.3**	**–48.5**		**–69.7**		**–68.5**
	p vs baseline	*NA*	*NR*	*NR*		*NR*		*NR*
Zaizov, 1995[117]	Mean (SD)	7.8						2.4[c]
	n	*7*						*7*
	% Change	NA						**–73**
	p vs baseline	*NA*						*NR*

[a] Data read from graph.
[b] The number of patients at each time-point of Perez-Calvo was not explicit, the percentage change relates to the mean for all the patients measured at baseline.
[c] Mean follow-up 2.5 years.

Appendix 5

Results of ICGG Gaucher Registry Study by Weinreb (2002)[116]

The results in *Table 35* were read from graphs or tables reported in the Weinreb study[116] and reaggregated using a weighted mean procedure with assumed equal variance between subgroups.

TABLE 35 *Results of ICGG Gaucher Registry study of Weinreb (2002)[116]*

		Platelets ($\times 10^3$ mm^{-3})			
	n	**Baseline**	**6 months**	**12 months**	**24 months**
Whole population	910	135.4 (82.9)			
All ERT population	238	70 (14.5)	90.6 (41)	108.5 (44.2)	119.4 (46.2)
Whole no-Spx population	643	92 (57)			
ERT no-Spx population	222	69.3 (12.4)	86.5 (42)	101.3 (41.1)	112.1 (43.7)
Whole Spx population	267	240 (125)			
ERT Spx population	16	82 (32)	148 (33)	208 (76)	220 (73)
		Liver volume ($\times$ normal)			
Whole population	496	1.93 (0.89)			
All ERT population	129	2.13 (0.71)	1.81 (0.47)	1.59 (0.44)	1.41 (0.33)
Whole no-Spx population	382	1.78 (0.70)			
ERT no-Spx population	94	1.84 (0.39)	1.64 (0.36)	1.44 (0.37)	1.30 (0.25)
Whole Spx population	114	2.43 (1.34)			
ERT Spx population	35	2.93 (1.21)	2.24 (0.69)	1.97 (0.59)	1.72 (0.48)
		Hb (g dl^{-1})			
Whole population	911	11.31 (1.77)			
All ERT population	184	9.81 (7.83)	11.45 (8.24)	12.03 (8.35)	12.22 (8.42)
Whole no-Spx population	642	11.1 (1.8)			
ERT no-Spx population	135	9.72 (7.87)	11.42 (8.17)	12.01 (8.28)	12.12 (8.37)
Whole Spx population	269	11.8 (1.7)			
ERT Spx population	49	10.05 (7.71)	11.51 (8.44)	12.07 (8.53)	12.47 (8.54)

Data are means (SD).
Spx, splenectomised.

Appendix 6

Spanish Gaucher's Disease Registry

Dr Pilar Giraldo and colleagues at the Miguel Servet University Hospital in Zaragoza, Spain, set up the Spanish Gaucher's Disease Registry in 1993.[55,155] At time of recruitment onto the registry (baseline) the following information is collected for each individual from the local/referring clinician:

Year of diagnosis
Family members affected with GD
Hospital name
Region of Spain
Type of disease (I, II or III)
Date of birth
Age at time of assessment
Age at diagnosis
Duration between diagnosis and treatment
Severity Score Index (SSI) (Zimran revised)
Disease scale (mild, moderate, severe devised from SSI)
SSI adjusted for age
Gender
Weight (kg)
Height (cm)
Liver size (cm) (hepatomegaly)
Spleen size (cm) (splenomegaly)
Lung disease (Y/N)
Heart disease (Y/N)
Kidney disease
CNS (Y/N)
Skin disease (Y/N)
Eye disease (Y/N)
Splenectomy (Y/N)
Time from diagnosis to splenectomy
Bone disease (description)
Chitotriosidase plasma
Iron amount in blood
Ferritin
Glutamic pyruvate transaminase
Glutamic oxalate transminase
Acid phosphate
Gamma-glutamyltransferase (GGT)
Bilirubin
High-density lipoprotein cholesterol (HDL)
Low-density lipoprotein cholesterol (LDL)
Triglycerides
Haemoglobin (anaemia)
Haemotocrit
Leucocytes
Platelets (thrombocytopenia)
Virus hepatitis B
Virus hepatitis C
AIDS
Lysozyme
Total proteins
Immunoglobin G (IgG)
Immunoglobin A (IgA)
Immunoglobin M (IgM)
Genotype
Start date of ERT
Year started ERT
ERT treatment (every week, every 2 weeks, or no treatment)
Dose (U kg^{-1})

Follow-up data are also recorded at 3, 6, 12, 18 months, and annually thereafter. The follow-up data consist of:

- liver size (cm) (hepatomegaly)
- spleen size (cm) (splenomegaly)
- haemoglobin
- platelets
- cholesterol
- chitotriosidase
- ferritin.

At January 2005, 278 individuals with Gaucher's disease in Spain were registered: 256 (92%) were classified as having type I, 14 (5%) as having type II and eight (3%) as having type III disease. Some individuals received an SF-36 Health Survey Questionnaire close to recruitment and approximately 2 years after commencing treatment or 2 years after initial assessment;[155] 60 individuals completed the SF-36 questionnaire at baseline and 51 individuals at follow-up. Seven individuals in the subgroup did not receive treatment, although they did complete a follow-up questionnaire. In total 80 individuals completed at least one of the SF-36 questionnaires, with 33 individuals completing both a baseline and a follow-up SF-36 questionnaire. Two out of these 33 individuals never started ERT treatment. During analysis the baseline SF-36 could be mapped approximately to the clinical data collected at the initial assessment, but it was less clear which clinical data the follow-up data should be matched to, owing to the lack of dates recorded.

TABLE 36 *Initial assessment characteristics*

	All	SF-36 subgroup
n	256	80
Age at diagnosis (years), mean (SD)[a]	28.0 (19.1)	25.8 (14.6)
Years between diagnosis and inclusion on the registry, mean (SD)[b]	7.3 (8.2)	7.6 (8.4)
Female (%)[c]	51	54
On ERT at initial assessment (%)	37	44
SSI, mean (SD)[d]	8.6 (4.1)	8.9 (3.8)
Splenectomy (%)[e]	23	24
Splenomegaly (%)[f]		
Mild (spleen size >0 to ≤ 3 cm)	12	11
Moderate (spleen size >3 to ≤ 8 cm)	27	24
Severe (spleen size >8 cm)	50	49
Hepatomegaly (%)[g]		
Mild (liver size >0 to ≤ 2 cm)	25	22
Moderate (liver size >2 to ≤ 10 cm)	38	38
Severe (liver size >10 cm)	11	16
Anaemia (%)[h]	29	27
Thrombocytopenia (%)[i]		
Mild (≥ 60 to $<120 \times 10^3$ mm^{-3})	51	46
Moderate (≥ 30 to $<60 \times 10^3$ mm^{-3})	18	18
Severe ($<30 \times 10^3$ mm^{-3})	6	7
Bone crisis (%)[j]	55	68
Bone necrosis (%)[k]	20	23
Genotype mutations (%)[l]		
N370S/N370S	13	9
N370S/other	80	82
Other	7	9

[a] 33 (13%) missing; [b] 42 (16%) missing; [c] 4 (2%) missing; [d] 113 (44%); [e] 68 (27%) missing; [f] 83 (32%) missing; [g] 83 (68%); [h] 80 (32%) missing; [i] 71 (28%) missing; [j] 78 (30%) missing; [k] 78 (30%) missing; [l] 53 (21%) missing.

Table 36 provides a summary of the individuals with type I Gaucher's disease at the time of initial assessment for inclusion onto the registry.

Statistical analysis

Regression analysis was undertaken to describe the relation between:

- Zimran severity score (1992), and patient and clinical characteristics
- SF-6D score quality of life, and patient and clinical characteristics.

The results from these analyses are reported *Tables 37* and *38*.

A statistically significant (at the 5% level) positive relationship was observed between Zimran severity score (1992)[17] and duration between diagnosis and initial assessment and chitotriosidase, suggesting that the Zimran score increases with longer duration between diagnosis and initial assessment, and higher levels of chitotriosidase. A positive relationship was also observed between Zimran severity score and the presence of anaemia, hepatomegaly, bone crisis and bone necrosis, and also treatment with ERT. There was a statistically significant (at the 5% level) negative relationship between Zimran severity score (1992) and age at diagnosis.

A statistically significant (at the 5% level) positive relationship was observed between SF-6D score and the presence of anaemia and treatment with ERT. There was a statistically significant negative relationship between SF-6D score (1992) and age at diagnosis, and duration between diagnosis and initial assessment. An increase in SF-6D was also observed for genotype 'other' (i.e. not N370S/N370S or N370S/other), which included the mutation L444P/L444P, compared with N370S/N370S.

Graphs

Error bars, plot of means and 95% confidence intervals are presented in *Figures 15–21*, showing the relationship between different variables in the registry.

TABLE 37 *Univariate analysis: Zimran severity score regressed against individual variables*

	Coefficient	95% CI	*p*	R^2
Age at diagnosis	–0.046	–0.89 to –0.003	0.037*	0.03
Duration between diagnosis and initial assessment (years)	0.142	0.061 to 0.224	0.001*	0.08
Chitotriosidase	0.000	0.0000 to 0.000	0.008*	0.06
SF-6D score	3.453	–2.872 to 9.779	0.278	0.03
Genotype (N370S/N370S base category)				0.00
N370S/other	0.767	–1.672 to 3.204	0.535	
Other	1.856	–1.526 to 5.237	0.279	
Anaemia	1.765	0.229 to 3.301	0.025*	0.04
Thrombocytopenia ('no' base category)				0.07
Mild	–2.190	–3.894 to –0.486	0.012*	
Moderate	0.246	–1.834 to 2.326	0.815	
Severe	–0.145	–2.923 to 2.632	0.918	
Hepatomegaly ('no' base category)				0.19
Mild	2.812	0.799 to 4.826	<0.001*	
Moderate	4.082	2.352 to 5.812	<0.001*	
Severe	5.383	2.977 to 7.789	<0.001*	
Splenomegaly ('no' base category)				0.04
Mild	3.083	–2.248 to 8.415	0.251	
Moderate	0.216	–3.707 to 4.138	0.912	
Severe	1.083	–2.687 to 4.853	0.566	
Bone crisis	3.362	2.120 to 4.604	<0.001*	0.18
Bone necrosis	2.101	0.530 to 3.671	0.009*	0.05
On ERT	1.810	0.288 to 3.331	0.020*	0.05

* Significant at the 5% level.

TABLE 38 *Univariate analysis: SF-6D score regressed against individual variables*

	Coefficient	95% CI	*p*	R^2
Age at diagnosis	–0.006	–0.008 to –0.003	<0.001*	0.25
Duration between diagnosis and initial assessment (years)	–0.007	0.002 to 0.012	0.008*	0.12
Chitotriosidase	0.000	0.000 to 0.000	0.273	0.03
Zimran score	0.007	–0.006 to 0.021	0.278	0.03
Genotype (N370S/N370S base category)				0.13
N370S/other	–0.051	–0.184 to 0.082	0.445	
Other	–0.236	–0.420 to –0.051	0.013*	
Anaemia	0.112	0.007 to 0.218	0.038*	0.08
Thrombocytopenia ('no' base category)				0.02
Mild	–0.042	–0.158 to 0.075	0.473	
Moderate	–0.024	–0.162 to 0.114	0.731	
Severe	–0.082	–0.278 to 0.114	0.403	
Hepatomegaly ('no' base category)				0.011
Mild	0.008	–0.133 to 0.150	0.909	
Moderate	0.044	–0.093 to 0.182	0.521	
Severe	0.009	–0.150 to 0.168	0.911	
Splenomegaly ('no' base category)				0.19
Mild	0.300	–0.156 to 0.756	0.173	
Moderate	0.117	–0.187 to 0.420	0.412	
Severe	0.156	–0.156 to 0.467	0.290	
Bone crisis	0.048	–0.054 to 0.151	0.348	0.02
Bone necrosis	0.042	–0.081 to 0.165	0.494	0.01
On ERT	0.122	0.027 to 0.217	0.013*	0.13

* Significant at the 5% level.

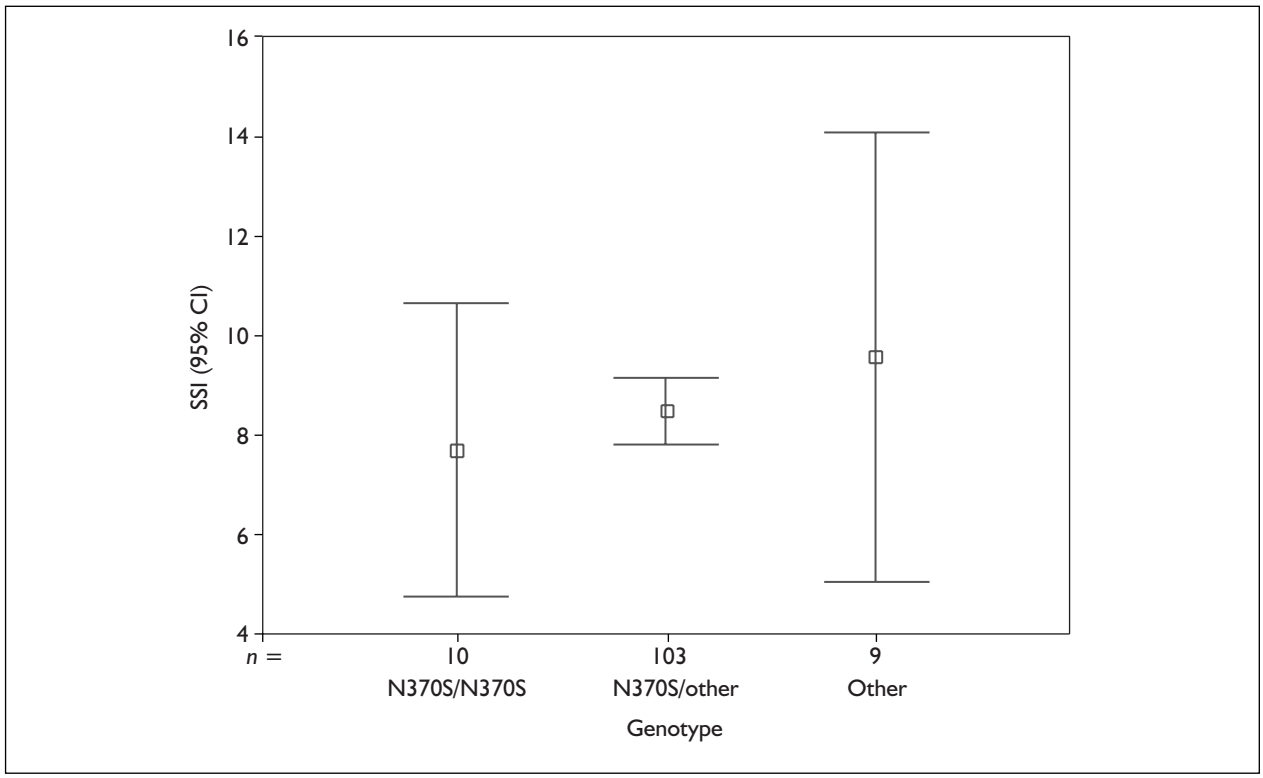

FIGURE 15 *SSI versus genotype mutations*

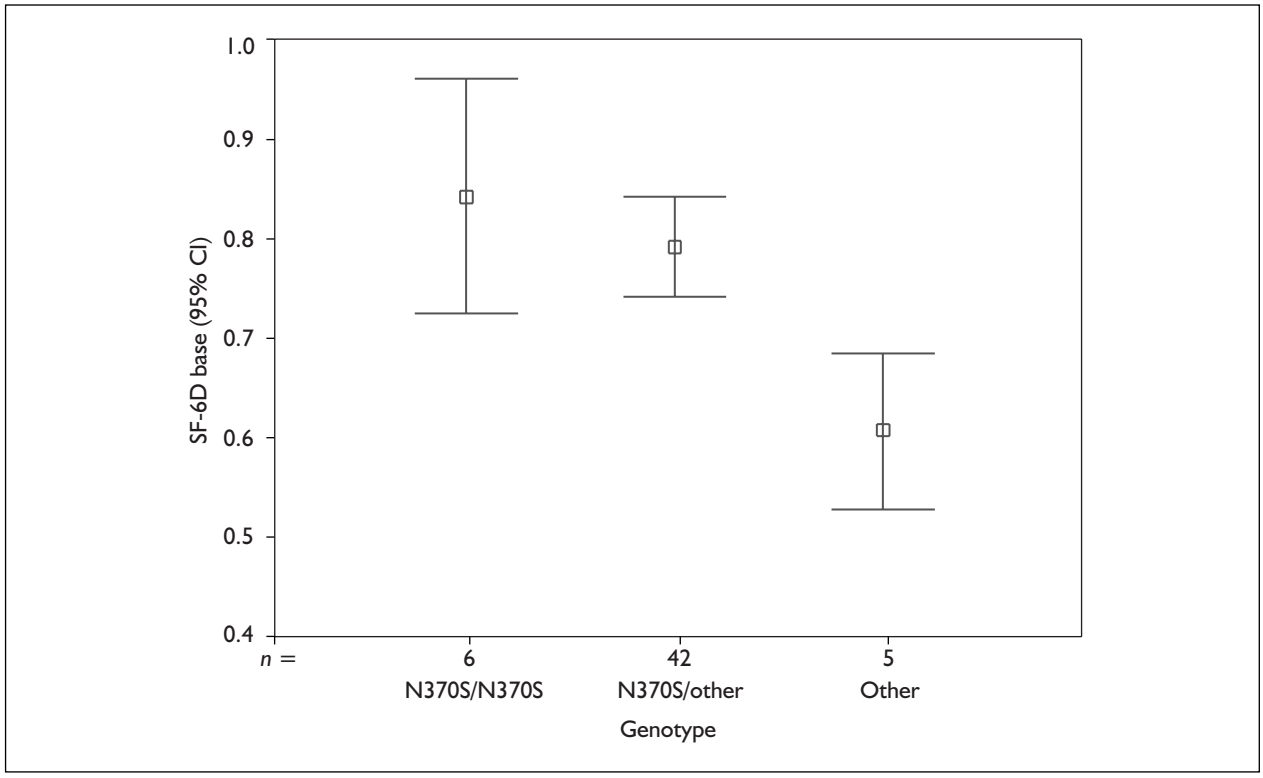

FIGURE 16 *SF-6D versus genotype mutations*

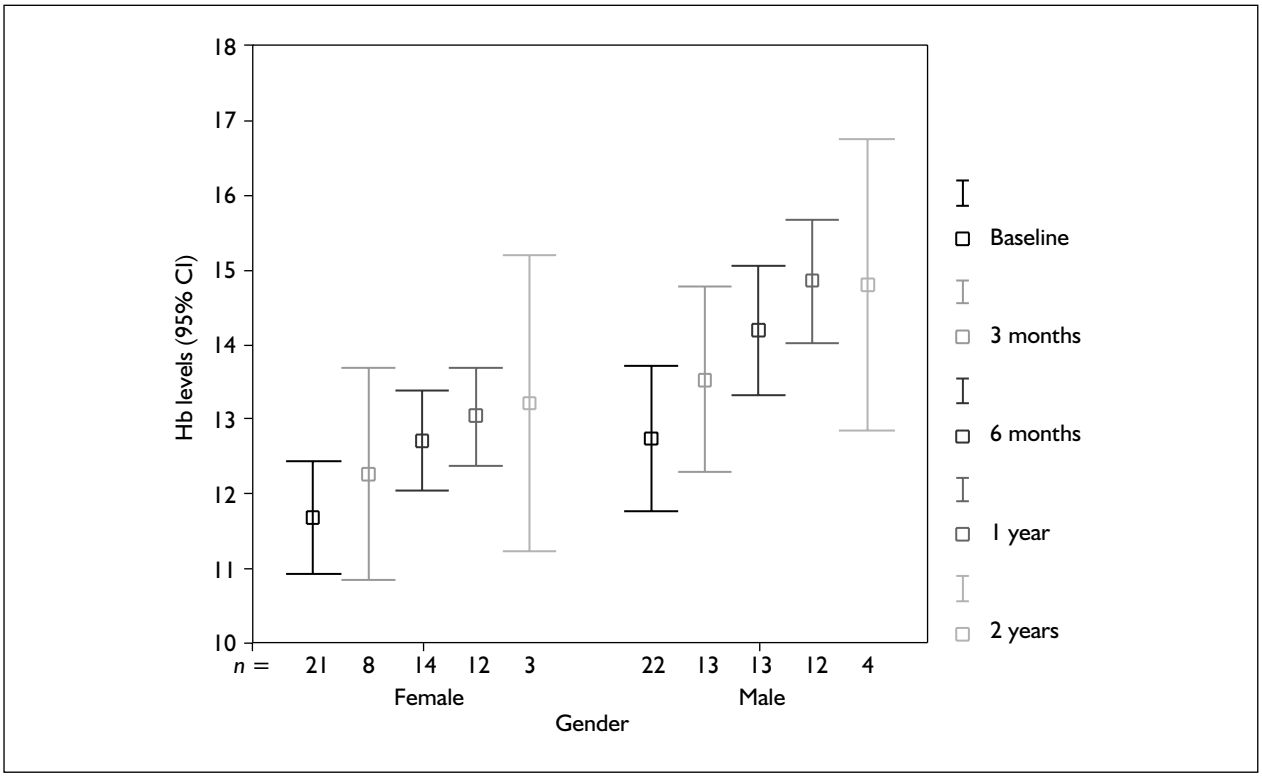

FIGURE 17 *Haemoglobin levels of adult patients on treatment by gender at different periods from baseline to 2 years*

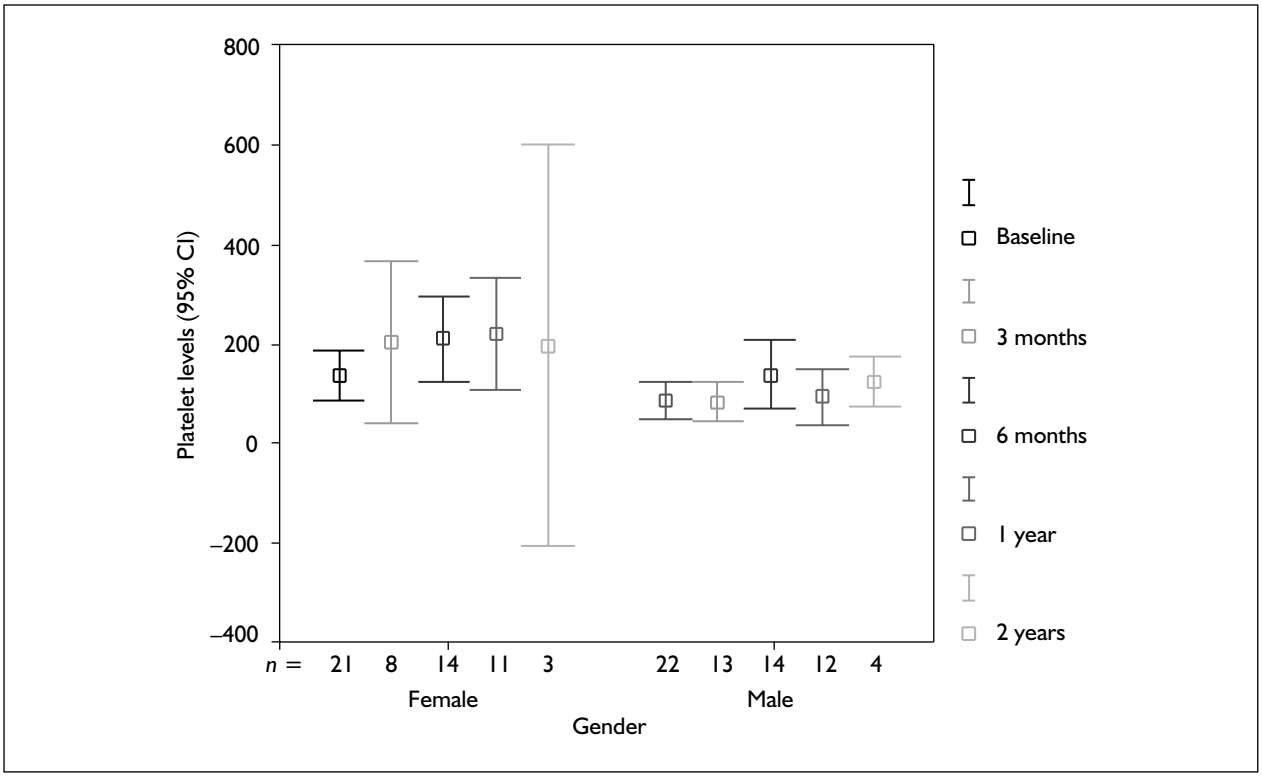

FIGURE 18 *Platelet levels of adult patients on treatment by gender at different periods from baseline to 2 years*

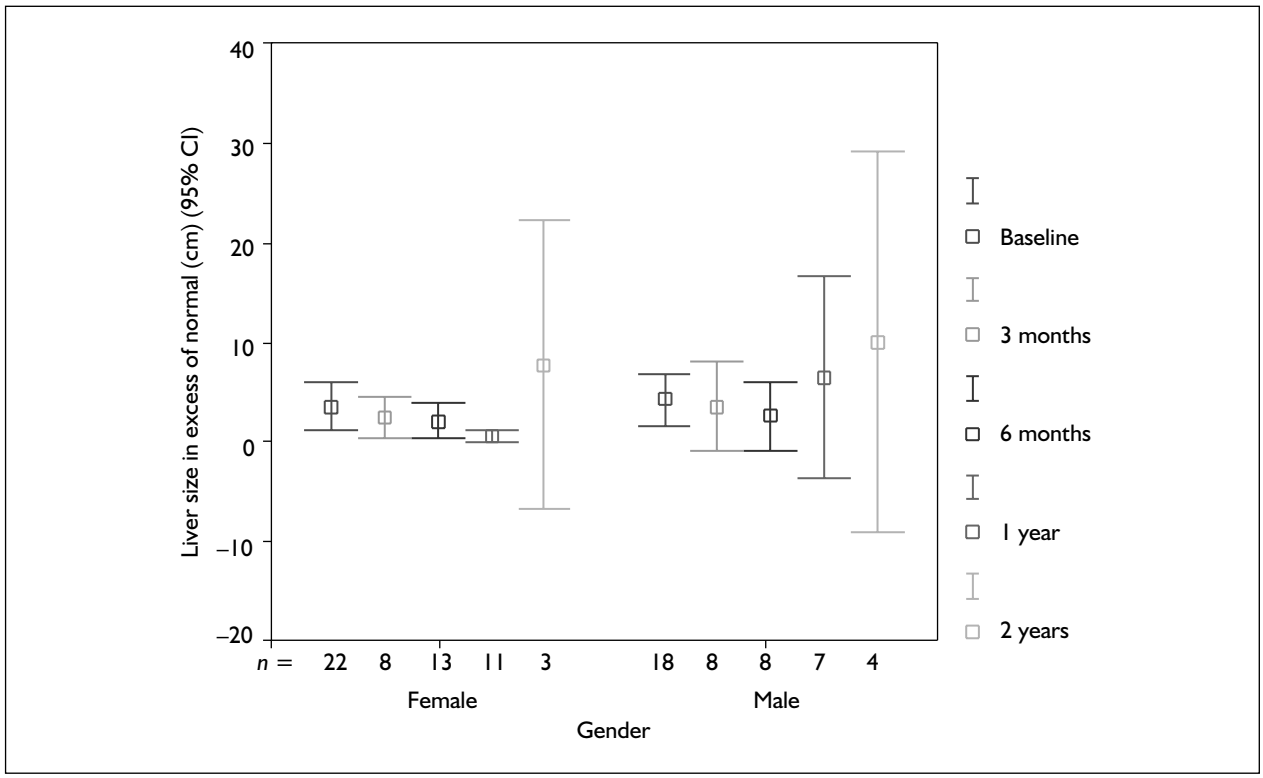

FIGURE 19 *Hepatomegaly levels of adult patients on treatment by gender at different periods from baseline to 2 years*

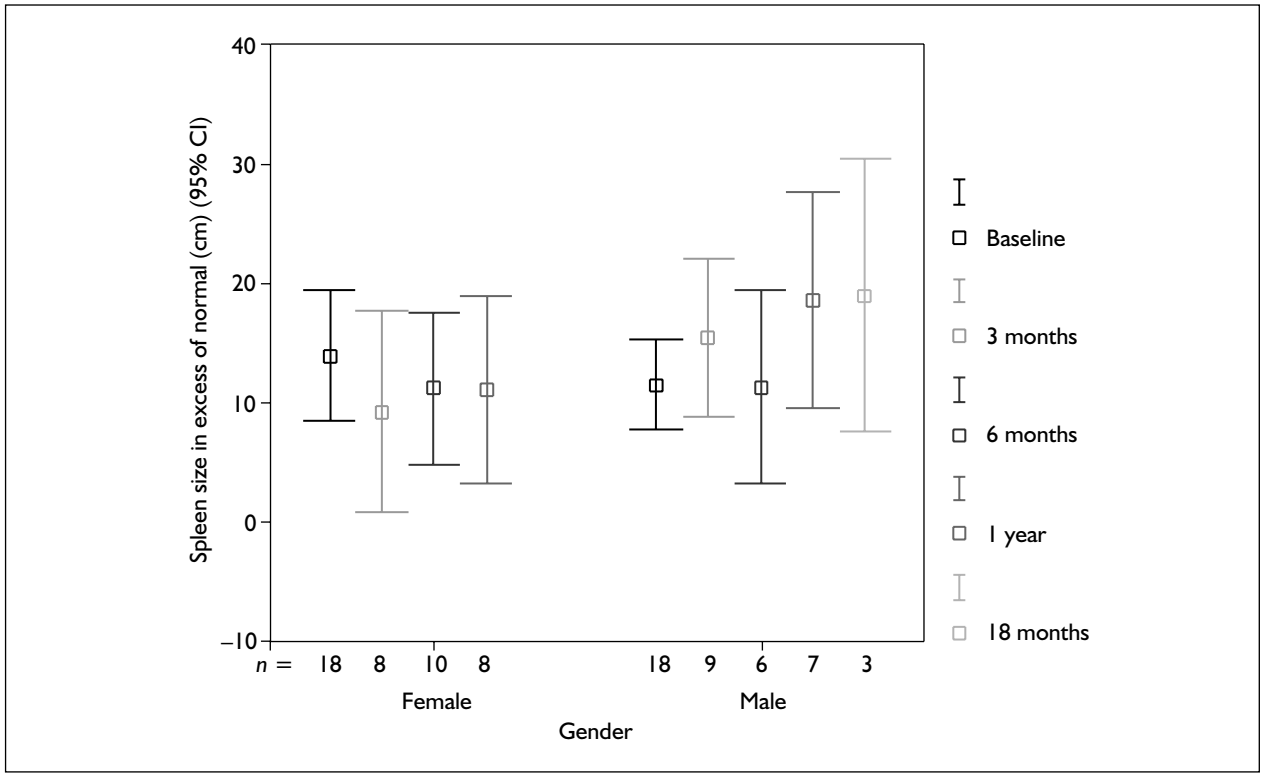

FIGURE 20 *Splenomegaly levels of adult patients on treatment by gender at different periods from baseline to 18 months*

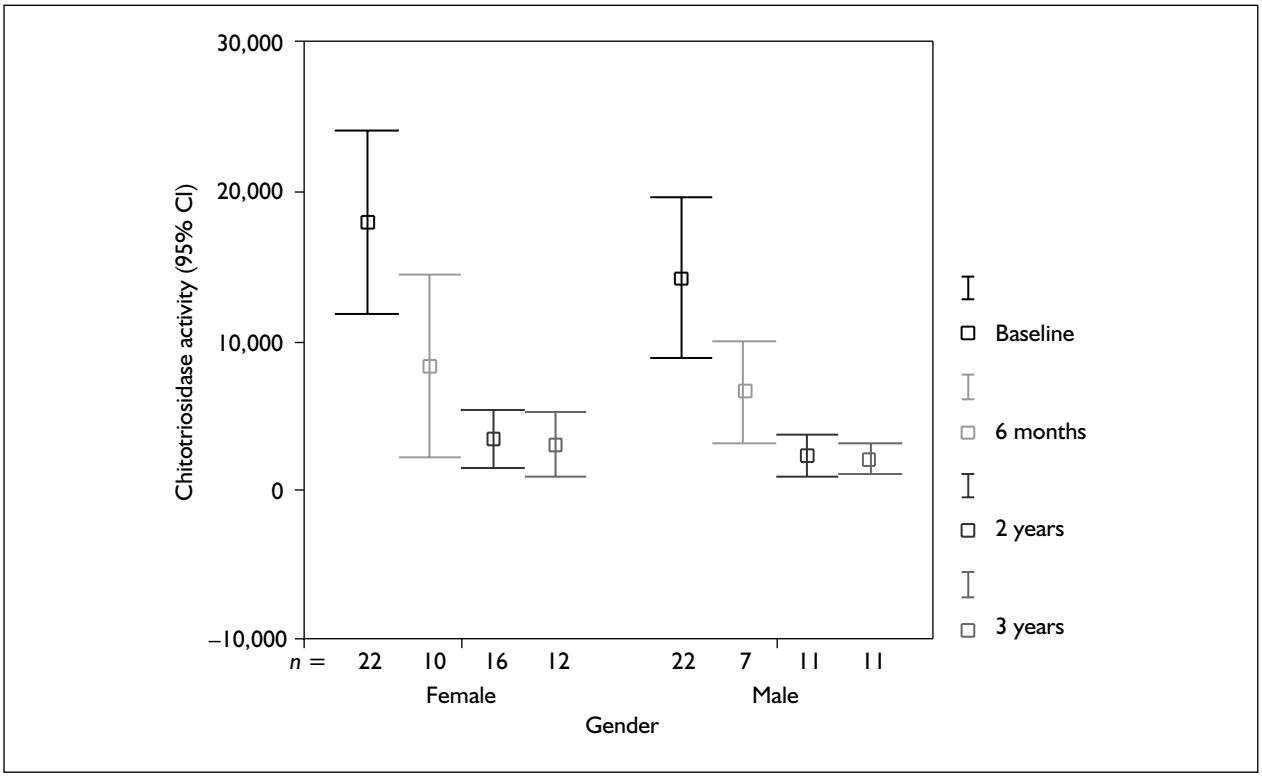

FIGURE 21 *Chitotriosidase activity levels of adult patients on treatment by gender at different periods from baseline to 3 years*

Appendix 7

ICGG Gaucher Registry

By the end of 2003 the ICGG Gaucher Registry had data on over 3337 patients with Gaucher's disease in 44 countries, of whom approximately 90% (3016) had type I disease. UK patients account for approximately 3% of all patients, and genotype data are available for 68% of type I patients. This registry is sponsored by Genzyme Corporation and data requests must be made via the International Collaborative Gaucher Group (ICGG) to their biostatisticians.

Data requested

Data requested of the ICGG Gaucher Registry were designed to facilitate the development and parameterisation of a cost-effectiveness decision model based on the Zimran SSI (1992).[17] This request consisted of three sections.

The first section considered the distribution of patients across the 29 states formed by the distinct scores of the SSI at entry onto the registry, and for those who received ERT at time of initiation of therapy. These analyses were requested first for all patients on the registry and second for only UK patients. Within each of these populations, in addition to an overall analysis, analyses stratified by gender, time period, age at diagnosis and genotype were also requested.

The second section requested data on the SF-6D utility score[165] by each of the 29 SSI states; this included the number of patients in the state, the mean, variance and sum of squares. The latter would ensure that the variance associated with an amalgamation of some of the 29 states into much broader health states as proposed by Zimran in 1992[17] could be estimated.

The third section consisted of the transition matrix for patient movement between the 29 health states defined by the SSI and death. Separate matrices were requested depending on whether patients were on or off treatment, and stratified by the different populations defined in the first part of the request.

Data received

Data were received on seven dimensions of the SSI: anaemia, thrombocytopenia, splenomegaly, hepatomegaly, skeletal pain, bone crises and skeletal imaging manifestations. No UK patients had complete data for all seven SSI components, and only 37 patients who were untreated and 127 who were treated had all seven components complete at baseline. These numbers reduced to three untreated and 42 treated patients at 5 years. The distribution of data points for the intervening years assumed that patients could contribute to any year.

Age distributions showed the mean/median (SD) age at diagnosis and initiation of therapy for all patients to be 18.7/13.0 (17.4) and 29.9/29 (19.6), respectively, while for UK patients these results were 14.2/8.5 (11.9) and 24.4/25 (15.8), respectively.

The prevalence of the seven clinical components for each year since diagnosis (for untreated patients) or years on ERT for treated patients, was reported separately for all patients, and just for UK patients, for up to 5 years. *Tables 39–42* report each of the seven clinical components separately for each year; patients can contribute to these tables if any of the seven clinical components are reported, but perhaps more crucially the tables only report the annual prevalence of the seven components, and not longitudinal patient movement between the levels of each component. Thus, these tables provide neither information on the levels of association between the seven components nor the transitions that would be likely to occur in Gaucher's disease.

The prevalence of the clinical symptoms represented by the seven components is summarised for all patients at baseline and at 5 years for treated and untreated patients in *Table 43*.

Subsequently, data were provided for patients who had at least six out of seven components and

TABLE 39 *Clinical parameters for all type I patients at diagnosis*

	Years since diagnosis (while not on ERT) for all type I patients					
	0	**1**	**2**	**3**	**4**	**5**
1. Anaemia	*n* = 289	*n* = 82	*n* = 70	*n* = 40	*n* = 42	*n* = 25
No (%)	186 (64)	61 (74)	44 (63)	24 (60)	29 (69)	17 (68)
Yes (%)	103 (36)	21 (26)	26 (37)	16 (40)	13 (31)	8 (32)
2. Thrombocytopenia	*n* = 286	*n* = 82	*n* = 66	*n* = 40	*n* = 41	*n* = 25
No (%)	97 (34)	31 (38)	27 (41)	13 (33)	15 (37)	7 (28)
Mild (%)	148 (52)	32 (39)	24 (36)	21 (53)	25 (61)	13 (52)
Moderate (%)	34 (12)	14 (17)	15 (23)	6 (15)	1 (2)	3 (12)
Severe (%)	7 (2)	5 (6)	0 (0)	0 (0)	0 (0)	2 (8)
3. Splenomegaly	*n* = 151	*n* = 38	*n* = 31	*n* = 23	*n* = 25	*n* = 13
No (%)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mild (%)	20 (13)	2 (5)	3 (10)	1 (4)	0 (0)	1 (8)
Moderate (%)	64 (42)	22 (58)	13 (42)	9 (39)	12 (50)	5 (38)
Severe (%)	66 (44)	14 (37)	15 (48)	13 (57)	12 (50)	7 (54)
Splenectomy (P/F)	0	0	0	0	1	0
4. Hepatomegaly	*n* = 135	*n* = 38	*n* = 35	*n* = 24	*n* = 23	*n* = 15
No (%)	22 (16)	3 (9)	3 (8)	2 (8)	1 (4)	3 (20)
Mild (%)	20 (15)	5 (13)	5 (14)	1 (4)	4 (17)	2 (13)
Moderate (%)	74 (55)	24 (63)	20 (57)	17 (71)	15 (65)	9 (60)
Severe (%)	19 (14)	6 (16)	7 (20)	4 (17)	3 (13)	1 (7)
5. Bone pain	*n* = 270	*n* = 75	*n* = 48	*n* = 37	*n* = 32	*n* = 23
No (%)	173 (64)	49 (65)	33 (69)	22 (59)	14 (44)	9 (39)
Yes (%)	97 (36)	26 (35)	15 (31)	15 (41)	18 (56)	14 (61)
6. Bone crisis	*n* = 266	*n* = 72	*n* = 45	*n* = 35	*n* = 28	*n* = 18
No (%)	225 (85)	67 (93)	45 (100)	30 (86)	24 (86)	14 (78)
Yes (%)	41 (15)	5 (7)	0 (0)	5 (14)	4 (14)	4 (22)
7. Skeletal imaging manifestations	*n* = 234	*n* = 55	*n* = 38	*n* = 33	*n* = 41	*n* = 23
Moderate						
No (%)	52 (22)	8 (15)	4 (11)	6 (18)	6 (15)	6 (26)
Yes (%)	182 (78)	47 (85)	34 (89)	27 (82)	35 (85)	17 (74)
Severe						
No (%)	207 (88)	46 (84)	31 (82)	29 (88)	33 (80)	15 (65)
Yes (%)	27 (12)	9 (16)	7 (18)	4 (12)	8 (20)	8 (35)

P, partial; F, full.

patients who had at least five out of seven components. However, the tables only included patients who contributed data to that year and the preceding years. Consequently, for untreated patients, no patients had all seven components beyond diagnosis, and of the 56 who had six or more components at baseline only two had data at the following year. For 5 out of 7 components, 124 patients had baseline data, but again only two had data at the following year, and none had data for subsequent years. For UK patients, only one treated patient had six or more components at baseline and had no data for the following year. Four untreated UK patients had five or more components at baseline, but none for the following year. For treated UK patients 13 had five or more components at baseline, with only one patient having five or more components up to 2 years after initiation of therapy.

TABLE 40 *Clinical parameters for all type I patients on ERT*

	Years on ERT for all type I patients					
	0	**1**	**2**	**3**	**4**	**5**
1. Anaemia	*n* = 1562	*n* = 1290	*n* = 988	*n* = 799	*n* = 722	*n* = 473
No (%)	901 (58)	1124 (87)	892 (90)	723 (90)	650 (90)	422 (89)
Yes (%)	661 (42)	166 (13)	96 (10)	76 (10)	72 (10)	51 (11)
2. Thrombocytopenia	*n* = 1564	*n* = 1293	*n* = 986	*n* = 796	*n* = 717	*n* = 473
No (%)	637 (41)	844 (65)	700 (71)	570 (72)	527 (74)	351 (74)
Mild (%)	624 (40)	324 (25)	226 (23)	186 (23)	161 (22)	106 (22)
Moderate (%)	244 (16)	97 (8)	54 (5)	37 (5)	26 (4)	13 (3)
Severe (%)	59 (4)	28 (2)	6 (1)	3 (0)	3 (0)	3 (1)
3. Splenomegaly	*n* = 518	*n* = 521	*n* = 338	*n* = 251	*n* = 253	*n* = 154
No (%)	1 (0)	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Mild (%)	56 (11)	121 (24)	95 (29)	71 (30)	89 (38)	63 (43)
Moderate (%)	211 (42)	262 (52)	176 (54)	138 (58)	125 (53)	77 (52)
Severe (%)	230 (46)	116 (23)	53 (16)	30 (12)	23 (10)	7 (5)
Splenectomy (P/F)	20	21	14	11	16	7
4. Hepatomegaly	*n* = 646	*n* = 671	*n* = 438	*n* = 334	*n* = 322	*n* = 206
No (%)	62 (10)	115 (17)	102 (23)	84 (25)	106 (33)	71 (34)
Mild (%)	87 (13)	161 (24)	123 (28)	106 (32)	105 (33)	71 (34)
Moderate (%)	364 (56)	369 (55)	201 (46)	139 (42)	110 (34)	62 (30)
Severe (%)	133 (21)	26 (4)	12 (3)	5 (1)	1 (0)	2 (1)
5. Bone pain	*n* = 867	*n* = 750	*n* = 614	*n* = 526	*n* = 471	*n* = 371
No (%)	408 (47)	488 (65)	412 (67)	359 (68)	316 (67)	237 (64)
Yes (%)	459 (53)	262 (35)	202 (33)	167 (32)	155 (33)	134 (36)
6. Bone crisis	*n* = 809	*n* = 731	*n* = 581	*n* = 520	*n* = 454	*n* = 362
No (%)	659 (81)	705 (96)	563 (97)	504 (97)	447 (98)	352 (97)
Yes (%)	150 (19)	26 (4)	18 (3)	16 (3)	7 (2)	10 (3)
7. Skeletal imaging manifestations	*n* = 604	*n* = 518	*n* = 317	*n* = 300	*n* = 326	*n* = 179
Moderate						
No (%)	84 (14)	59 (11)	48 (15)	49 (16)	62 (19)	38 (21)
Yes (%)	520 (86)	459 (89)	269 (85)	251 (84)	264 (81)	141 (79)
Severe						
No (%)	464 (77)	406 (78)	252 (79)	251 (84)	270 (83)	141 (79)
Yes (%)	140 (23)	112 (22)	65 (21)	49 (16)	56 (17)	38 (21)

TABLE 41 *Clinical parameters for UK type I patients at diagnosis*

	Years since diagnosis (while not on ERT) for UK type I patients					
	0	**1**	**2**	**3**	**4**	**5**
1. Anaemia	*n* = 18	*n* = 1	*n* = 2	*n* = 1	*n* = 3	*n* = 2
No (%)	9 (50)	1 (100)	2 (100)	1 (100)	2 (67)	1 (50)
Yes (%)	9 (50)	0 (0)	0 (0)	0 (0)	1 (33)	1 (50)
2. Thrombocytopenia	*n* = 17	*n* = 1	*n* = 2	*n* = 1	*n* = 3	*n* = 2
No (%)	7 (41)	1 (100)	1 (50)	0 (0)	1 (33)	1 (50)
Mild (%)	8 (47)	0 (0)	1 (50)	1 (100)	2 (67)	0 (0)
Moderate (%)	2 (12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)
3. Splenomegaly	*n* = 1	*n* = 0	*n* = 0	*n* = 0	*n* = 0	*n* = 0
No (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mild (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Moderate (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe (%)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Splenectomy (P/F)	0	0	0	0	0	0
4. Hepatomegaly	*n* = 0	*n* = 0	*n* = 1	*n* = 1	*n* = 0	*n* = 0
No (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mild (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Moderate (%)	0 (0)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)
Severe (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5. Bone pain	*n* = 12	*n* = 1	*n* = 2	*n* = 2	*n* = 3	*n* = 3
No (%)	7 (58)	1 (100)	1 (50)	1 (50)	1 (33)	0 (0)
Yes (%)	5 (42)	0 (0)	1 (50)	1 (50)	2 (67)	3 (100)
6. Bone crisis	*n* = 8	*n* = 1	*n* = 1	*n* = 2	*n* = 2	*n* = 3
No (%)	8 (100)	1 (100)	1 (100)	2 (100)	2 (100)	0 (0)
Yes (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)
7. Skeletal imaging manifestations	*n* = 8	*n* = 1	*n* = 2	*n* = 0	*n* = 0	*n* = 3
Moderate						
No (%)	6 (75)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Yes (%)	2 (25)	1 (100)	2 (100)	0 (0)	0 (0)	3 (100)
Severe						
No (%)	8 (100)	1 (100)	1 (50)	0 (0)	0 (0)	0 (0)
Yes (%)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	3 (100)

TABLE 42 *Clinical parameters for UK patients on ERT*

	Years on ERT for UK type 1 patients					
	0	**1**	**2**	**3**	**4**	**5**
1. Anaemia	*n* = 47	*n* = 34	*n* = 18	*n* = 10	*n* = 5	*n* = 1
No (%)	28 (60)	30 (88)	16 (89)	7 (70)	4 (80)	1 (100)
Yes (%)	19 (40)	4 (12)	2 (11)	3 (30)	1 (20)	0 (0)
2. Thrombocytopenia	*n* = 47	*n* = 34	*n* = 18	*n* = 10	*n* = 5	*n* = 1
No (%)	22 (47)	26 (76)	14 (78)	9 (90)	4 (80)	1 (100)
Mild (%)	14 (30)	5 (15)	2 (11)	0 (0)	0 (0)	0 (0)
Moderate (%)	10 (21)	3 (9)	2 (11)	1 (10)	1 (20)	0 (0)
Severe (%)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3. Splenomegaly	*n* = 3	*n* = 5	*n* = 1	*n* = 0	*n* = 1	*n* = 0
No (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mild (%)	0 (0)	2 (40)	0 (0)	0 (0)	1 (100)	0 (0)
Moderate (%)	1 (33)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Severe (%)	2 (67)	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)
Splenectomy (P/F)	0	0	0	0	0	0
4. Hepatomegaly	*n* = 8	*n* = 7	*n* = 0	*n* = 0	*n* = 0	*n* = 0
No (%)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)
Mild (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Moderate (%)	7 (88)	5 (71)	0 (0)	0 (0)	0 (0)	0 (0)
Severe (%)	1 (12)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)
5. Bone pain	*n* = 29	*n* = 23	*n* = 10	*n* = 9	*n* = 4	*n* = 2
No (%)	15 (52)	13 (57)	8 (80)	5 (56)	2 (50)	2 (100)
Yes (%)	14 (48)	10 (43)	2 (20)	4 (44)	2 (50)	0 (0)
6. Bone crisis	*n* = 22	*n* = 14	*n* = 4	*n* = 4	*n* = 7	*n* = 3
No (%)	17 (77)	12 (86)	4 (100)	4 (100)	7 (100)	3 (100)
Yes (%)	5 (23)	2 (14)	0 (0)	0 (0)	0 (0)	0 (0)
7. Skeletal imaging manifestations	*n* = 26	*n* = 17	*n* = 5	*n* = 1	*n* = 2	*n* = 3
Moderate						
No (%)	5 (19)	1 (6)	0 (0)	0 (0)	1 (50)	0 (0)
Yes (%)	21 (81)	16 (4)	5 (100)	1 (100)	1 (50)	3 (100)
Severe						
No (%)	16 (62)	8 (47)	3 (60)	0 (0)	2 (100)	3 (100)
Yes (%)	10 (38)	9 (53)	2 (40)	1 (100)	0 (0)	0 (0)

TABLE 43 *Prevalence of clinical components at baseline and 5 years for untreated and treated patients with Gaucher's disease*

Clinical component	**Baseline**		**5 years post-baseline**	
	Untreated	**Treated**	**Untreated**	**Treated**
Anaemia (yes)	289 (36)	1562 (42)	25 (32)	473 (11)
Thrombocytopenia (moderate and severe)	286 (14)	1564 (20)	25 (20)	473 (4)
Splenomegaly (severe)	151 (44)	518 (46)	13 (54)	154 (5)
Hepatomegaly (moderate and severe)	135 (69)	646 (77)	15 (67)	206 (31)
Bone pain (yes)	270 (36)	867 (53)	23 (61)	371 (36)
Bone crisis (yes)	266 (15)	809 (19)	18 (22)	362 (3)
Skeletal manifestations (severe)	234 (12)	604 (23)	23 (35)	179 (21)

Data are shown as *n* (%).

Appendix 8

Summary of existing economic analyses

All studies used an assumed quality of life gain to calculate the QALY increment as a result of ERT. No study applied a sophisticated modelling approach to estimate the cost-effectiveness of treatment. *Table 44* describes the key cost-effectiveness results.

Hallam and Bryant (1996)[41] (sections 1 and 2)

This study applied a simple cost per QALY calculator assuming that total treatment costs of Gaucher's disease are £60,000 (low dose) to £400,000 (high dose) a year (assuming four patients with Gaucher's disease in a population of one million people). The analysts use the Index of Health-Related Quality of Life (IHQL) scale of to assume that patients with mild symptoms could have a quality of life of 0.9 and those with severe symptoms a quality of life of between 0.4 and 0.5. It is not clear how the link is made between the clinical outcomes of a patient with mild and severe disease and the estimated quality of life on the IHQL scale. Using these quality of life estimates it is then further assumed that treatment with Ceredase will return the patient to near-normal activity or mild symptoms, thus a gain of 0.4–0.5 QALY per patient. The analysts also assume that only patients with severe Gaucher's disease will be treated; however, it is not clear how severe cases are being defined. These assumptions lead to an estimated cost per QALY of £30,000 (low dose) to £400,000 (high dose). It is clear from these estimates that the cost per QALY is particularly sensitive to the dose level.

In section 2 of the Hallam and Bryant report, a QALY ready-reckoner approach is applied assuming a QALY gain as a result of Ceredase treatment of 0.25, 0.5 and 0.75 QALY per patient per year. These QALY gains are based on estimates alone. For four (prevalent) patients per million the QALYs per million per year are then estimated. The analysts also use different dose regimens on the basis of information from the literature to test the impact on the cost per QALY estimate. This results in a cost per QALY estimate of between £7666 (low dose) and £169,333 (high dose) assuming that 0.75 QALY is gained per patient per year, or £23,000 (low dose) and £508,000 (high dose) assuming that 0.25 QALY is gained per patient per year. Although the report contains interesting data with respect to the rate of splenectomy, bone-marrow transplants and associated mortality risks, many of the assumptions incorporated in the QALY ready reckoner approach are based on estimates alone.

Beutler and Garber (1994)[156]

The costs of three separate alglucerase dosage regimens are estimated:

1. 60 U kg^{-1} administered every 2 weeks (standard NIH regimen)
2. 30 U kg^{-1} administered every 2 weeks
3. 2.3 U kg^{-1} administered three times weekly.

Assuming that the drug has the effect of increasing survival from immediate death with no treatment to survival with certainty and with perfect quality of life for the duration of therapy, the cost-effectiveness of each dosage regimen is estimated. After 2 years of treatment, the cost-effectiveness of regimens 1, 2 and 3 is estimated to be US$147,000, US$75,000 and US$49,000 respectively, per QALY saved. The analysts assume that the initial dose will be reduced by 50% each year until it reaches 25% of the initial level, but it is not clear how realistic this assumption is. There is no evidence to suggest that patients with Gaucher's disease will immediately die; however, the authors acknowledge that the intention is to estimate the lower boundary for the cost-effectiveness ratio. The source of the drug cost estimates is unclear. The cost of infusion is taken to be between published estimates of home- and office-based infusions (US$100) and it is likely that the UK cost of infusions differs from US estimates. This analysis does, however, raise the issue of the impact of dose assumptions on the resulting cost-effectiveness estimations. The authors also acknowledge that the analysis does not include the adverse effects of treatment.

TABLE 44 *Summary of existing economic analyses of ERT for Gaucher's disease*

Study details	Hallam and Bryant, 1996[41] (section 1)	Hallam and Bryant, 1996[41] (section 2)	Beutler and Garber, 1994[156]	WMHTAC, 2004[38] (rapid review)
Time horizon	1 year	1 year	10 years	Lifetime
Objective	Costing analysis of Ceredase	Costing analysis of Ceredase	To calculate the cost-effectiveness of alternative dosage regimens by placing a lower boundary on the cost-effectiveness ratio	Cost-effectiveness of ERT vs no specific treatment. Cost-effectiveness of different dose regimens
Source of effectiveness information	Source not reported. IHQL scale applied to illustrate range of cases. Link from clinical outcomes to QoL scale not explained or illustrated	Estimates: presents three QALY gain possibilities	Assumes perfect QoL as a result of introduction of drug	Three studies reporting individual patient data identified
Costs	Source: Gauchers Association for News for Doctors. Cost of Ceredase for one adult patient reported. Total costs estimated on basis of four patients with Gaucher's disease in population of 1 million	Source: Gaucher's Association for News for Doctors. Costs estimated for HD and LD regimens and for varying frequency based on estimates from literature	Source: NR. Costs estimated for three separate dose regimens: (1) 60 U kg^{-1} every 2 weeks; (2) 30 U kg^{-1} every 2 weeks; (3) 2.3 U kg^{-1} three times weekly	UK cost of Cerezyme taken from Office of Fair Trading report. It is estimated that 17.3% of the UK cost for Cerezyme is taken to represent the average cost per unit for home delivery and home care services
Health outcomes reported	IHQL scale	NR	NR	SF-36, energy levels
Outcome analysis	Link between clinical outcomes and IHQL scale not clear		Link costs with assumed QALY gain	Three methods adopted: literature review, EQ-5D mapping, and public preference utilities. To estimate the ICERs, the utility gains estimated from the EQ-5D mapping exercise are applied
Economic outcomes	QALYs	QALYs (estimator)	QALYs (assumed gain)	QALYs
Model type	Cost per QALY calculator. Total costs per assumed QALY gain	Cost per QALY calculator	Cost per QALY calculator	Cost per QALY calculator
Model assumptions	Treatment assumed to be only for severe cases. Treatment assumed to return patients to near normal activity, giving a treatment gain of 0.5 QALY	Assumes average age of diagnosis is 20 years. Assumes 0.5, 0.75 and 0.25 QALY gained per patient per year	Assumes drug increases survival from immediate death with no treatment to survival with certainty and perfect quality of life. Assumes infusion costs US $100 (average home/office-based cost). Assumed initial dose reduced by 50% each year until reached 25% of the initial level	Ignored the first 2–3 years' extra cost incurred during treatment initiation

continued

TABLE 44 *Summary of existing economic analyses of ERT for Gaucher's disease (cont'd)*

Study details	Hallam and Bryant, 1996[41] (section 1)	Hallam and Bryant, 1996[41] (section 2)	Beutler and Garber, 1994[156]	WMHTAC, 2004[38] (rapid review)
Discount rate	Not applied	Not applied	5% (costs and benefits)	3.5% (costs and benefits)
Uncertainty around cost-effectiveness ratio expressed	No	No	No	
Sensitivity analysis	Cost per QALY expressed for different dosage regimens	Cost per QALY expressed for different dosage regimens	Cost per QALY expressed for different dosage regimens	Assuming utility value of 0 for patients with Gaucher's disease and a utility of 1 for treated patients produces an ICER of £123,000 per QALY
Results	Cost per QALY: £30k (low dose) to £200k (high dose)	Cost per QALY: 0.75 QALY gain: £800–23,000 (LD); 0.25 QALY gain: £169,000–508,000 (HD)	For regimens after 2 years of treatment: (1) US$147,000, (2) US$75,000, (3) US$49,000 per QALY saved	If gain in utility from treatment is: 0.26 = £473,000 per QALY, 0.36 = £342,000 per QALY

West Midlands Health Technology Assessment Collaboration (WMHTAC) (unpublished rapid review, 2004)[38]

The analysts compare the cost-effectiveness of ERT versus no specific treatment for patients with Gaucher's disease and compare different dosage regimens. They state that complex modelling was not possible owing to time restrictions and lack of availability of timely data from the ICGG Gaucher Registry. To obtain utility-based quality of life data, three separate methods are adopted: a literature review, mapping to EuroQol 5 Dimensions (EQ-5D) and estimation of public preference utilities. The literature review identified three studies that reported economic evaluations,[155,156] all of which produced very high ICERs despite optimistic assumptions being applied (lower prices than available in the UK and high estimates of effectiveness). Using cohort studies to assess the quality of life of an average patient with Gaucher's disease aged between 40 and 49 years, an increment to quality of life is estimated from treatment of ERT. This is done using the EQ-5D framework. The analysts know from the literature that an average patient with type I Gaucher's disease probably has no problem self-caring, but some problems with mobility, usual activities, pain/discomfort and anxiety/depression. So, using a 1993 UK survey, it is estimated that this health state will produce a utility score of 0.62. The public preference utilities are measured with a utility panel using the SG instrument. The health states are defined as evidence based, but the descriptions are not provided. A detailed outline of the costs of Cerezyme is provided. The ICER is calculated using only the utility values estimated from the EQ-5D exercise. No justification is provided as to why the estimates from the literature or the utility panel are not applied. The authors point out that even when the most generous assumptions about potential in cost savings are applied, the ICER still exceeds £200,000 per QALY.

It is clear that the analysts had difficulty accessing timely data from the ICGG Gaucher Registry, which might have allowed for a more complex modelling approach. Owing to the limitations in the data, the authors recognise that no consideration is given to treatment of asymptomatic patients, effect of immune reaction, effect of disease and ERT on different phenotypes, compliance and drug holidays, mortality, comparative treatment effects and the potential for preventing more serious manifestations.

Whittington and Goa (1995)[157]

This is a review paper that provides a summary of the pharmacoeconomic considerations of Gaucher's disease and alglucerase. One section is devoted to a discussion of cost-appraisal studies. The paper reviews the work conducted by Beutler and Garber[156] and states that although useful, the cost per QALY calculations require a more extensive analysis to establish the true cost-effectiveness of alglucerase.

Internal validity

When estimating the cost per QALY of ERT, only one study considered offsetting potential cost savings from the replaced service. It is plausible that symptomatic treatment of a patient with Gaucher's disease i.e. rate of splenectomy, liver transplantation, bone-marrow transplantation, etc.) may be altered as a result of ERT treatment and this is only discussed in the Hallam and Bryant analyses[41] (section 2) and not considered in any of the other analyses. In all of the final cost calculations, the incremental cost of ERT (compared with no ERT) assumes that symptomatic treatment costs will not be altered as a result of ERT being used. However little information exists about the treatment of an average patient with Gaucher's disease and given the heterogeneity of the disease this is difficult to estimate. It is also unlikely that high cost treatment such as splenectomy, bone-marrow transplantation and liver transplantation are used with any rate of frequency to have significant impact on the incremental costs of ERT treatment.

In all of the studies, the quality of life effect from ERT treatment is assumed. Three studies assume that treatment with ERT will return patients to near-normal activity, and have estimated the quality of life gain accordingly (Hallam and Bryant section 1,[41] Beutler and Garber,[156] and WMHTAC[38]). Hallam and Bryant[41] section 2 simply surmised the degree to which ERT improves the quality of life of patients with Gaucher's disease and presented costs per QALY for these different assumptions. All studies report that there is no utility-based evidence on the quality of life of patients with Gaucher's disease either on ERT or on symptomatic treatment.

External validity (generalisability)

Three of the four reviewed studies are UK based; however, in all cases the effectiveness of the drug

(in terms of impact on quality of life) is based on assumptions so questions of patient group selection are not relevant. Resource-use costs (with respect to the symptomatic treatment cost estimates) for the Hallam and Bryant studies[41] are based on relatively old data (from the early 1990s). The WMHTAC review presents the most up-to-date estimates of cost and likely service provision.

Appendix 9
Model parameters

TABLE 45 *Parameter values used in the base-case analysis*

Parameter description	Mean value	Type of distribution	Parameters of distribution	Source
Costs				
Unit cost of ERT	2.975	None		BNF, 2004[37]
Mean units per annum	2395	None		National Gaucher's Registry
Blood transfusion	76	None		NHS reference costs, 2003[166]
Cost of splenectomy	2751	Normal	(SE = 32)	NHS reference costs, 2003[166]
Cost of hip replacement	4660	Normal	(SE = 5)	NHS reference costs, 2003[166]
Cost of nursing per week	496	None		Curtis and Netten, 2004[162]
Annual cost of bisphosphonates (Alendronate)	301	None		Stevenson *et al.*, 2005[163]
Cost per annum in mild SSI	912			
Cost per annum in moderate SSI	3144.25			
Cost per annum in severe SSI	7857			
QALYs				
Organomegaly with blood disorders	0.82	Beta	(a = 290, b = 64)	Clarke *et al.*, 1997[153]
Bone pain with blood disorders	0.86	Beta	(a = 158, b = 26)	Clarke *et al.*, 1997[153]
Bone crises (decrement)	0.18	Beta	(a = 18, b = 84)	ICGG Gaucher Registry
QALY mild	0.82			
QALY moderate	0.70			
QALY severe	0.58			
Probabilities				
SSI regression				
Natural log of age	0.921	Multivariate normal	See variance–covariance matrix (*Table 46*)	Review of natural history (Chapter 4)
Splenectomy	4.872	Multivariate normal		
(d) Other	4.447	Multivariate normal		
(b) L444P/other	6.827	Multivariate normal		
(c) N370S/other	5.428	Multivariate normal		
Distribution of patients by genotype				
(a) N370S/N370S	0.20	Correlated beta	(n = 249, R = 49)	National Gaucher's Registry
(b) L444P/other	0.25	Correlated beta	(n = 249, R = 63)	National Gaucher's Registry
(c) N370S/Other	0.38	Correlated beta	(n = 249, R = 99)	National Gaucher's Registry
(d) Other	0.17	Correlated beta	(n = 249, R = 101)	National Gaucher's Registry
Annual risk of splenectomy				
N370S/N370S	0.021	None		Review of natural history (Chapter 4)
Others	0.013	None		Review of natural history (Chapter 4)
Size of cohort	200	None		Assumption
20% of patients present with skeletal involvement	0.2	Beta	(a = 1.4, b = 5.7)	Assumption
30% probability of above occurring	0.3	None		
Annual risk (30 years) of skeletal involvement if on ERT	0.002			Clinical opinion

TABLE 46 *SSI regression variance–covariance matrix*

	Splenectomy	(d) Other	(b) L444P/other	(c) N370S/other	Natural log of age
Splenectomy	0.3693	–0.0524	–0.1043	–0.1719	–0.0247
(d) Other	–0.0524	0.4019	0.1461	0.2262	–0.0547
(b) L444P/other	–0.1043	0.1461	0.4317	0.1984	–0.0362
(c) N370S/other	–0.1719	0.2262	0.1984	0.7357	–0.0549
Natural log of age	–0.0247	–0.0547	–0.0362	–0.0549	0.0208

Covariances of coefficients for linear regression as shown in *Table 19*. (d), (b), (c) refer to possible genotypes.

Appendix 10

National Gaucher's Registry

The National Gaucher's Registry was set up by the NSCAG as part of the Gaucher's disease – Diagnosis and Management advice service, which was designated in 1997. The four centres designated to provide this service are:

- Addenbrooke's Hospital, Cambridge
- Royal Free Hospital, London (Children)
- Great Ormond Street Hospital, London
- Royal Manchester Children's Hospital

At the time of recruitment onto the register (baseline), the following information is collected for each individual:

Type of disease (I, II or III)
Date of birth
Age at referral
Age at diagnosis
Gender
Genotype
Severity Score Index (SSI) (baseline only)
General health scale
Nose-bleeds
Bruising
Abdominal distension
Failure to thrive
Bone pain
Infections
Breathlessness
Splenectomy
Date of splenectomy
Blood transfusions
Pregnancy
Smoking status
Medications
Ceredase dosage
Cerezyme dosage
Bone-marrow transplant
Surgery
Pallor
Cyanosis
Jaundice
Skin pigmentation
Clubbing
Height (cm)
Weight (kg)
Head circumference
Spinal deformity
Liver size and volume (hepatomegaly)
Spleen size and volume (splenomegaly)
Gaze palsy
Ataxia
Intention tremor
Muscle tone
Reflexes
Fundoscopy
Blood pressure
Systolic blood pressure
Diastolic blood pressure
Lymphadenopathy
Bone/joint pain/deformity
Pubertal status
Menarche
Verbal intelligence quotient (IQ)
Overall IQ
Performance IQ
Nucleated cells
Haemoglobin (anaemia)
Haematocrit
Mean cell volume (MCV)
Mean corpuscular haemoglobin (MCH)
Platelets (thrombocytopenia)
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Erythrocyte sedimentation rate (ESR)
Prothrombin time (PT)
Activated partial thromboplastin time (APTT)
Reticulocyte count
IgG
IgA
IgM
Electrophoresis
Red cell folate
Vitamin B_{12}
Serum iron
Transferrin
% Saturation
Ferritin
Coagulation factor deficiencies
Sodium
Potassium
Glucose
Urea
Creatinine
Albumin
Corrected calcium
Inorganic phosphate

Total bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
GGT
Angiotensin-converting enzyme (ACE)
Total acid phosphatase
C-reactive protein (CRP)
Aspartate aminotransferase (AST)
Haemoglobin A_{1c} (%)
Total cholesterol
Triglyceride
β-Glucose activity
Plasma chitotriosidase
Thyroid-stimulating hormone (TSH)
25-Hydroxy-vitamin D
Parathyroid hormone (PTH)
Luteinising hormone (LH)
Follicle-stimulating hormone (FSH)
Lumbar spine bone density
Femoral neck (hip) bone density
Wrist bone density
Nuclear medicine bone scintigram, whole body
Chest X-ray
Full skeletal X-ray survey
Liver size by ultrasound
Abdominal ultrasound
Spleen size by ultrasound
MRI skeletal/viscera
MRI liver volume
MRI spleen volume
Peak expiratory flow rate (PEFR)
Transfer factor (TCO)
Total lung capacity (TLC)
Residual volume (RV)
Forced expiratory volume in 1 second (FEV1)
Echocardiography
Brainstem auditory evoked potentials (AEPs)
Eye movement studies
Electroencephalogram (EEG)
Enzyme dose (IU kg^{-1} per month)

Depending on the severity of their disease, individuals are followed-up at 3-, 6- or 12-monthly intervals. Similar data to those listed above are also collected and recorded on the register at the follow-up assessments, although not all the information is collected at every visit.

At the time of writing (January 2005), the register consisted of 124 individuals with Gaucher's disease in the UK. Type of Gaucher's disease is recorded for 98 individuals on the register, of whom 94 (96%) are classified as having type I disease (zero type II and four type III). *Table 47* provides a summary of the individuals with type I Gaucher's disease at the time of initial referral onto the register.

Although data are recorded at each follow-up visit, the authors acquired access to only data collected at the last follow-up visit (*Table 48*). Given more

TABLE 47 *Summary statistics of data collected at time of referral to the register*

n	**94**
Age at diagnosis (years), mean (SD)[a]	22.8 (16.2)
Years between diagnosis and inclusion on the register, mean (SD)[b]	14.3 (14.3)
Female (%)[c]	59
SSI, mean (SD)[d]	9.0 (5.2)
Splenectomy (%)[e]	63
Surgery (%)[f]	65
Chitotriosidase, mean (SD)[g]	5530.0 (5146.9)
Anaemia (%)	30
Thrombocytopenia (%)[h]	
Mild	35
Moderate	16
Severe	4
Bone pain (%)	86
Easy bruising (%)[i]	62
Genotype mutations (%)[j]	
N370S/N370S	16
N370S/other	68
Other	16

[a] 10 (11%) missing; [b] 11 (12%) missing; [c] 1 (1%) missing; [d] 52 (55%) missing; [e] 7 (7%) missing; [f] 22 (23%) missing; [g] 72 (77%) missing; [h] 23 (24%) missing; [i] 20 (16%) missing; [j] 75 (79%) missing.

TABLE 48 *Summary statistics of data collected at last follow-up recorded on the register*

n	**94**
Duration of follow-up (years), mean (SD)[a]	8.0 (3.3)
Dose of ERT (U kg^{-1}), mean (SD)[b]	31.0 (20.8)
Total monthly dose of ERT, mean (SD)[c]	2364.2 (1084.8)
Chitotriosidase, mean (SD)[d]	1927.1 (1997.0)
Anaemia (%)[e]	17
Thrombocytopenia (%)[f]	
Mild	11
Moderate	2
Severe	2
Easy bruising (%)[g]	9

[a] 29 (31%) missing; [b] 29 (31%) missing; [c] 27 (29%) missing; [d] 15 (16%) missing; [e] 11 (12%) missing; [f] 10 (11%) missing; [g] 16 (17%) missing.

time and familiarity with the register database, data recorded at intervening time-points would probably be extractable.

Role of cytokines in the Osseous Complications of Gaucher's Disease study

This clinical research study has been funded by the Gaucher's Association with the main objective to understand more about the manifestations of Gaucher's disease, especially with regard to the bone complications of the disease, and in particular osteoporosis and bone crises. The study began in September 2003 and is a 3-year study. It is a multicentre study, with individuals being recruited from the four National Gaucher's centres across the UK:

- Addenbrooke's Hospital, Cambridge
- Royal Free Hospital, London (Children)
- Great Ormond Street Hospital, London
- Royal Manchester Children's Hospital.

At the time of writing (January 2005), 49 individuals had been recruited into the study. The following data are recorded for each individual at baseline:

Date of birth
Date of baseline measurements
Is the patient in the National Gaucher's Register?
History of avascular necrosis
Age at first attack
Current number of joints involved
EQ-5D
Pain inventory
Splenectomy
Age at splenectomy
History of fragility fracture
Number of fragility fractures
Age at first fracture
Loss of adult height
Residual deformity
History of joint replacement surgery
Joint revision surgery
Osteomyelitis
Liver disease
Pulmonary disease
Neuronopathil features
Clinical features of platelet function defect
ERT
Date commenced ERT
Current dose of ERT
Bisphosphonates
Date commenced bisphosphonates
Current dose of bisphosphonates
Vitamin D/calcium therapy
Date commenced vitamin D/calcium therapy
Current dose of vitamin D/calcium therapy
Height (cm)
Weight (kg)
Body mass index
Body surface area
Joint flexion (hips, knees, shoulders)
Joint extension (hips, knees, shoulders)
Joint abduction (hips, knees, shoulders)
Joint adduction (hips, knees, shoulders)
Joint internal rotation (hips, knees, shoulders)
Joint external rotation (hips, knees, shoulders)
Gait impairment
Hepatomegaly (cm)
Splenomegaly (cm)
Erlenmeyer flask deformity
Joint deformity
Type and number of non-vertebral fracture

Fracture deformity
Vertebral deformity
Lytic lesions
MRI: osteonecrosis
MRI: marrow fat signal
MRI: liver volume (ml)
MRI: spleen volume (ml)
Bone densitometry (hip, forearm, vertebrae)
Chitotriosidase
Angiotensin-converting enzyme
Acid phosphatases
PARC (PARC/CCL18, a recently discovered Gaucher's-specific biomarker)
Prothrombin time
Activated partial thromboplastin time (APTT)
Specific coagulation factor deficiency
Platelet function test
Vitamin D
Parathyroid hormone
Haemoglobin
Platelet
White cell count
Mean cell volume
Sodium
Potassium
Urea
Creatinine
Alanine aminotransferase (ALT)
Alkaline phosphatase
Albumin
Total bilirubin
Corrected calcium
Inorganic phosphate
IgG
IgA
IgM
Serum protein electrophoresis
Type of paraproteinaemia
Size of paraprotein band

Similar data are also collected at follow-up, which coincides with an individual's routine assessment. At both baseline and follow-up individuals are asked to complete an EQ-5D to assess their self-reported quality of life.

The data collected as part of the Osseous Complications of Gaucher's Disease study will be incorporated into the National Gaucher's Register and, once completed, will provide a rich source of information for future evaluations of ERT.

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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