# The Effectiveness and Cost-Effectiveness of Enzyme Replacement Therapies for the Treatment of Late onset Pompe Disease: Protocol

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## Plain English Summary

Late-onset Pompe disease is a rare inherited disorder which affects approximately 260 people in the UK. Late-onset disease can begin from early childhood or well into adulthood and is the result of a deficiency of an enzyme called acid alpha-glucosidase (GAA). In the absence of GAA, the body cannot break down glycogen - a complex sugar - which causes glycogen to build up in the body's cells. This can impair the functioning of organs and tissues, resulting in patients experiencing progressive muscle weakness, especially in the legs and the muscles which control breathing. Without treatment, people with late-onset Pompe disease usually die of respiratory complications.

The recommended treatments are medicines called enzyme replacement therapy (ERT); three different ERTs are recommended for use in the NHS by NICE (National Institute for Health and Care Excellence). However, ERTs are very expensive and may not represent a cost-effective use of NHS resources at their current price. To investigate this issue, we will perform a study to estimate the cost-effectiveness of ERTs when compared to the best supportive care therapies available on the NHS (such as mobility aids and supplemental oxygen to help with breathing). To do this we will identify and analyse all the data from relevant clinical trials and other research studies on late-onset Pompe disease. These data will be used in a health economic model to estimate the cost-effectiveness of ERTs.


## Abstract

**Aim:** To determine the clinical and cost-effectiveness of enzyme replacement therapy (ERT) in people with late-onset Pompe disease (LOPD)

**Background:** Pompe disease is a rare inherited genetic disorder classified under glycogen storage diseases and lysosomal storage disorders. It is caused by a deficiency of the enzyme acid alpha-glucosidase (GAA). This deficiency leads to the accumulation of glycogen in the body's cells, resulting in a progressive decline in muscle function, particularly in the muscles of the legs and those involved in breathing. Over time, this muscle deterioration may necessitate the use of mobility aids and respiratory support. Without treatment, people with LOPD usually die of respiratory complications.

The standard of care in the UK for the treatment of LOPD is alglucosidase alfa, an ERT. Alglucosidase alfa is very expensive, with drug acquisition costs exceeding £400,000 per annum for the average patient. Due to historical commissioning decisions, it is unclear whether alglucosidase alfa is cost-effective compared to best supportive care therapies. Recently, two new ERTs-avalglucosidase alfa and cipaglucosidase alfa with miglustat-have been approved by NICE for the treatment of LOPD under the single technology appraisal process. In line with standard NICE procedures, these appraisals focused on the clinical and cost-effectiveness of each new treatment compared to the long-established standard of care, alglucosidase alfa. They importantly did not include best supportive care therapies as a comparator. NICE processes have significant limitations in this context, and it is unclear if avalglucosidase alfa and cipaglucosidase alfa represent a cost-effective use of NHS resources.

**Methods:** A systematic review and individual participant data (IPD) synthesis will be conducted based on a prospectively agreed protocol and in accordance with recommended systematic review methods. Studies will be included in the review if they recruited juveniles or adults with LOPD and

evaluated the clinical effectiveness of either ERT or best supportive care therapies. IPD will be requested from all eligible randomised controlled trials (RCTs) included in the review .Risk of bias in included RCTs will be assessed using version 2 of the Cochrane Risk of Bias Tool. The risk of bias for other study types will be assessed using appropriate tools. For outcomes with sufficient comparative RCT evidence, quantitative synthesis will be undertaken using meta-analysis. Network meta-analysis will also be performed if feasible.

A decision-analytic model will be developed to estimate the cost-effectiveness of alternative therapy ERT treatments for LOPD compared to best supportive care therapies. The model will be developed in alignment with the NICE reference case. The formal conceptualisation of the economic model will take place following the completion of the cost-effectiveness review and will adopt a design-oriented approach, focusing on the feasibility of alternative model designs. The model is expected to focus on the progression of patient respiratory and mobility outcomes over a lifetime horizon and the impact of treatment on these outcomes.

**PPI:** To enhance our understanding, interpretation, and contextualisation of the findings from this project, we will collaborate with clinical experts, individuals who have lived experience of LOPD and third-sector organisations that advocate for the Pompe disease community.

# 1 DECISION PROBLEM

## *1.1 Background*

Pompe disease, also known as glycogen disease type II, is a rare inherited genetic disorder that is classified under glycogen and lysosomal storage disorders. It is caused by a deficiency of the enzyme acid alpha-glucosidase (GAA), which is responsible for breaking down glycogen, a complex sugar molecule, into simpler forms in the body's cells. This deficiency results in glycogen accumulation within the lysosomes, leading to progressive muscle weakness and damage to various tissues, particularly in the organs and muscles.[1]

Pompe disease is classified into two forms: early- (infantile) onset Pompe disease (IOPD), with symptoms beginning in the first months of life, and late- (juvenile/adult) onset Pompe disease (LOPD), which can begin from early childhood to well into adulthood.[1] The severity of Pompe disease and age of onset varies widely and is determined by the degree of enzyme deficiency. Most individuals with LOPD undergo a gradual and continuous decline in muscle function, often starting in the trunk and lower limbs, and impacting respiratory muscles. Over the course of the disease, this progressive muscle deterioration may lead to the need to use mobility aids and respiratory support. Supportive treatment for Pompe disease varies considerably based on the severity of symptoms and the progressive nature of the disease. Patients are required to undergo regular assessments to determine the appropriate supportive treatment. These tests include assessment of muscle strength and function, and cardiac and respiratory function.

The standard of care in the UK for the treatment of LOPD is alglucosidase alfa, an enzyme replacement therapy (ERT).[2] ERT involves regular intravenous infusions of the deficient or malfunctioning GAA enzyme to help clear glycogen build up in cells, helping improve muscle tone, respiratory function, and quality of life [3, 4] Although there are currently no guidelines for the treatment and management of LOPD specific to the UK, clinical practice is consistent with the European Pompe Consortium 2017 guidelines.[5] Eligibility for treatment with ERT typically hinges on a set of criteria which includes a confirmed diagnosis, symptomatic presentation of the disease, retention of some level of skeletal and respiratory muscle function, and the absence of another advanced, life-threatening condition.

Alglucosidase alfa was the first established ERT to treat all types of Pompe disease and was commissioned directly by the National Health Service (NHS) Highly Specialised Services, becoming available for patients in 2006.This was prior to the formalisation of National Institute for Health and Care Excellence (NICE) processes for highly specialised technologies and therefore alglucosidase alfa has not been subject to a formal assessment and guidance by NICE.[6] The cost-effectiveness of alglucosidase alfa is therefore unknown. The drug acquisition costs associated with alglucosidase alfa are, however, very high (over £400,000 per annum for the average patient)[7] and there is a substantive risk that alglucosidase alfa is not a cost-effective use of NHS resources. Any comparison of a new treatment option with alglucosidase alfa, or to other comparators whose cost-effectiveness has been estimated relative to alglucosidase alfa, is therefore likely to generate a misleading estimate of cost-effectiveness and to overestimate the value of that treatment to the NHS significantly. NICE processes are not equipped to make decisions in this context, as they require comparisons to be made against current standard of care – which is assumed to be cost-effective relative to other options (e.g. supportive care).

Recently, avalglucosidase alfa and cipaglucosidase alfa with miglustat – new ERTs - have been approved by NICE for the treatment of late-onset Pompe disease under the single technology process.[8, 9] In line with standard NICE processes, these appraisals have focused on the clinical and cost-effectiveness of each respective alternative treatment compared with the long-established standard of care - alglucosidase alfa - and importantly do not include best supportive care (BSC) without ERT as a comparator. Alglucosidase alfa has been available on the NHS since 2006, having been commissioned by the National Specialised Commissioning Advisory Group[10] as part of the Lysosomal Storage Disorders Service,[11-13] which provided national funding for the diagnosis and treatment of lysosomal storage disorders across six UK centres. Alglucosidase alfa remains available for the treatment of LOPD through NHS service specifications for adult metabolic disorders.[14]

As highlighted above, NICE processes have significant limitations in this context with important consequences for decision making. Firstly, when expensive treatments are approved outside the agreed upon value assessment framework it breaks the conceptual basis of incremental decision making and increases the risk associated with individual reimbursement decisions. Specifically, it is likely to lead to the NHS overpaying for new treatments. In the context of Pompe disease, this has non-negligible budget consequences. The precise number of patients with Pompe disease is unknown. Prevalence is reported as 1:256,000 in recent Belgian study,[15] extrapolating this to UK population there would be 260 patients with LOPD, the majority of whom will be in receipt of ERT. Annual spending for this patient cohort, based on the list price of avalglucosidase, will therefore be in excess of £60 million. Secondly, comparisons against a non-cost-effective comparator distort incentives and can lead to scenarios where the NHS is willing to pay less for more effective treatments; this is because more effective treatments lead to improved survival which increases total drug acquisition costs. This has the potential to discourage investment in new treatment options. To address this problem a clinical and cost-effectiveness analysis should be undertaken which is not limited by the scope of NICE methods and which can address not only the cost-effectiveness of new technologies but also existing technologies including BSC without ERT.

## *1.2 Purpose of the decision to be made*

The purpose of this assessment is to evaluate the clinical and cost-effectiveness of ERT treatment for patients with LOPD. A systematic review of clinical and cost-effectiveness evidence will be conducted to inform the conceptualisation of the economic model and to assess key subgroups that can influence effectiveness. This assessment will include an individual patient data (IPD) meta-analysis to compare efficacy outcomes across the different ERT treatment options for LOPD.

## *1.3 Interventions*

This assessment will evaluate whether the existing ERT options represent a clinical and cost-effective means of managing and treating LOPD in comparison to best supportive care (BSC).

### 1.3.1 Alglucosidase alfa

Alglucosidase alfa is a recombinant acid alpha-glucosidase (GAA) replacement enzyme that helps break down glycogen, preventing abnormal build-up in cells. Alglucosidase alfa is administered as an infusion of 20 mg per kilogram of body weight given once every two weeks. Alglucosidase alfa has been approved and given as a first-line treatment to patients with all types of Pompe disease, and was until recently the only approved treatment for Pompe disease.[2] Alglucosidase alfa has been found to be more effective compared to placebo, at 78 weeks, in improving both the distance patients could walk in six minutes and their lung function (NCT00158600).

### 1.3.2 Avalglucosidase alfa

Avalglucosidase alfa is an alternative, next-generation ERT that works in the same way as alglucosidase alfa but is designed to deliver the enzyme to cells more efficiently. Avalglucosidase alfa received approval from the Medicines and Healthcare products Regulatory Agency (MHRA) and NICE guidance in 2022 as an alternative standard treatment for all types of Pompe disease. Avalglucosidase alfa is given through intravenous infusion once every two weeks, at a dose of 20mg/kg of body weight.

### 1.3.3 Cipaglucosidase alfa with miglustat

Cipaglucosidase alfa is a next-generation ERT which works in a similar way to alglucosidase alfa and avalglucosidase, as a recombinant human GAA enzyme with optimised carbohydrate structures to enhance uptake into muscle cells. Miglustat binds to, stabilises, and decreases the inactivation of cipaglucosidase alfa within the bloodstream.

Cipaglucosidase alfa with miglustat received a NICE recommendation in 2023 for the treatment of adults aged 18 years and older with LOPD. Administration of CIPA is via intravenous infusion of 20 mg/kg over approximately four hours, every other week. Miglustat is administered orally alongside CIPA i.e., every other week, and dosage is also dependent on body weight; recommended doses are 4 capsules of 65 mg (260 mg) for adults with LOPD weighing ≥50 kg, and 3 capsules of 65 mg (195 mg) for patients weighing ≥40 kg to <50 kg.[16]

## *1.4 Comparators*

### 1.4.1 Best supportive care

Although standard care for Pompe disease involves administering lifelong ERT, there is also supportive treatment for patients consisting of respiratory support, ambulatory support, physiotherapy, and/or dietary treatment.[2] Patients may need to consult with specialists, including pulmonologists, cardiologists, and physical therapists, to effectively manage the different symptoms associated with the condition.

# 2 OBJECTIVES

This project aims to determine the clinical and cost-effectiveness of ERT in people with late-onset Pompe disease, specifically the three technologies described in Section **Error! Reference source not found.**. To achieve this, the following objectives are proposed:

**Clinical effectiveness**

- To perform a systematic review of the clinical impact of ERTs for the treatment and management of LOPD, including evaluating studies of both short- and long-term effectiveness and safety, and studies which help to establish the relative effectiveness of ERT compared to BSC (in the absence of ERT).
- To obtain individual patient data (IPD) from all randomised controlled trials evaluating ERT for the treatment of LOPD.
- To perform network meta-analyses to compare and rank all treatments for LOPD, incorporating any IPD collected, in combination with published aggregate data where IPD is not available.

**Cost-effectiveness**

- To perform a systematic review of published cost-effectiveness studies of the use of ERT for the treatment and management of adult patients with LOPD.
- To develop a decision-analytic model to estimate the cost-effectiveness of ERT compared to ERTs compared to each other and BSC for the treatment and management of patients with LOPD. The cost-effectiveness of ERT will be expressed in terms of incremental cost per quality-adjusted life year and/or net health (or monetary) benefits.

# 3 METHODS FOR SYNTHESISING EVIDENCE OF CLINICAL EFFECTIVNESS

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement.[17]

## *3.1 Search strategy*

The aim of the searches will be to systematically identify published and unpublished studies on late-onset Pompe disease. Comprehensive searches of electronic databases and trial registers will be undertaken along with reference checking of included studies and any relevant systematic reviews.

An Information Specialist (HF) will develop an initial search strategy in Ovid MEDLINE with input from the review team. The strategy will include terms for Pompe disease with a choice of subject headings and free-text terms. The MEDLINE strategy will be adapted as necessary for the other databases and sources searched. No restrictions in terms of study design will be applied to any of the searches. Searches will be date-limited from 2000 onward and limited to English language studies. The MEDLINE strategy will be peer reviewed by a second Information Specialist (MH) with adjustments and corrections made as necessary. A draft search strategy for Ovid MEDLINE is included in Appendix 1. Update searches will be conducted 3 months prior to the end of the project to ensure that we identify any recently published studies.

The following databases will be searched to identify relevant studies: MEDLINE via Ovid; EMBASE via Ovid; KSR Evidence via Ovid; EconLit via Ovid; NHS Economic Evaluations Database (NHS EED) via CRD; Cochrane Database of Systematic Reviews (CDSR) via Wiley; Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley; and the International HTA database via https://database.inahta.org/. The Embase strategy will be designed to find relevant studies from 2000 onward as well as conference proceedings from 2020 onward.

The following resources will be searched for any unpublished, ongoing, or completed studies: ClinicalTrials.gov; European Union Clinical Trials Register; and WHO International Clinical Trials Registry Platform (WHO ICTRP).

References will be deduplicated in EndNote 21 (Clarivate Analytics, US).

## *3.2 Study selection*

All references identified from the electronic searches will be uploaded into EPPI-reviewer (systematic review software) and prioritised screening will be used to identify relevant titles and abstracts. In this process, which is based on text-mining and machine learning technologies, the software 'learns' to recognise records which are likely to be included and excluded, based on how screening criteria have been applied. Titles and abstracts will be screened by two reviewers independently until a stable

plateau in the number of included studies is reached i.e. no new includes are found, despite continued screening. To provide reassurance that it is unlikely that any further eligible studies remain in the unscreened records we will use EPPI-Reviewer's clustering tool to identify any patterns in the unscreened citations and single screen any cluster that looks potentially relevant. All records will be double-screened if a stable plateau in the number of included studies is not reached.

Full-texts of included titles and abstracts will be obtained where possible and independently screened by two reviewers according to the inclusion criteria listed below. Any disagreements will be resolved through discussion and, where necessary, consultation with a third reviewer.

## *3.3 Inclusion criteria*

### 3.3.1 Population

The population of interest is juveniles or adults with LOPD. Subgroups will be considered based on the presence or absence of prior treatment with ERT. Until recently, alglucosidase alfa was the only ERT available to patients with LOPD. The availability of avalglucosidase alfa and cipaglucosidase alfa with miglustat presents the opportunity for sequential use of alternative ERTs. Subgroups will therefore be considered based on the presence or absence of prior treatment with ERT.

### 3.3.2 Interventions

The assessment will appraise the clinical effectiveness of ERT, administered at their UK-licensed doses, for the treatment and management of LOPD. The ERT options considered in this assessment are:

- Alglucosidase alfa
- Avalglucosidase alfa
- Cipaglucosidase alfa with miglustat

### 3.3.3 Comparators

Eligible comparator or best supportive care therapies will include one or more of:

- Respiratory support (supplemental oxygen)
- Ambulatory support
- Physiotherapy
- Dietary treatment

These therapies must be evaluated in the absence of a concomitant ERT. Studies of non-ERT patients which do not evaluate a specific comparator therapy (or specific combination of therapies), but which report a review outcome will also be eligible providing that some patients are receiving one or more of the above comparator therapies (i.e. natural history studies).

### 3.3.4 Outcomes

Outcomes to be considered will cover a range of endpoints relevant to LOPD, which include motor and respiratory function, muscle strength, and patient-reported outcomes.

To be included, studies must report one or more of the following outcomes:

- Change in motor function (assessed using the six-minute walk test [6MWT])

- Change in respiratory function (assessed using forced vital capacity [FVC] % predicted, slow vital capacity [SVC], or maximal inspiratory pressure [MIP])
- Change in muscular function (assessed using manual muscle testing and the Gait, Stairs, Gowers' manoeuvre, and Chair [GSGC] assessments, MRC grading scale, quantitative muscle testing (QMT), quick motor function test (QMTF))
- Health-related quality of life (HRQoL)
- Adverse effects from treatments and treatment discontinuation due to adverse events
- Ambulation and ventilator status / support, including time on ventilator (TOV))
- Mortality

Outcomes will be considered at clinically relevant time points, such as 6 and 12 months post treatment, and annually thereafter from studies reporting extended follow-up.

#### 3.3.5 Study design

For studies of ERTs: any randomised trial or extended follow up study of a RCT cohort will be eligible. Prospective single-group studies, including registry studies, will also be eligible, providing they include 10 or more LOPD patients and report results for individual ERTs (i.e. they must not report results for only a mixed ERT group).

Evidence for best supportive care therapies will also be sought from clinical trials and also from observational studies with 10 or more patients.

### *3.4 Data Extraction*

#### 3.4.1 Published data

A data extraction form will be developed and piloted. Data will be extracted by one reviewer and independently checked by a second reviewer. Discrepancies will be resolved by discussion, with the involvement of a third reviewer where necessary.

Data obtained from relevant studies having multiple publications will be consolidated and presented as a single study. The most recent or most complete publication will be used where the possibility of overlapping populations cannot be excluded.

#### 3.4.2 Individual Participant Data

While it is anticipated that the main objectives of this project, i.e. to establish the clinical and cost-effectiveness of ERT compared to BSC in people with late-onset Pompe disease via a network meta-analysis and decision-analytic model can be achieved using published data alone, IPD will be requested from eligible RCTs to allow a wider range of methods to be used and for subgroups based on presence or absence of prior treatment with ERT for assessment of clinical and cost-effectiveness.

Sponsors of eligible RCTs will be contacted either directly or via data-sharing platforms such as Vivli, Inc or ClinicalStudyDataRequest.com, depending on the data sharing process of the sponsor.

First and/or corresponding authors of all eligible RCTs identified in the systematic review will be contacted and invited to collaborate in the project by contributing anonymised individual participant data for inclusion in the IPD meta-analysis. If appropriate, a collaborative group will be formed who will contribute to the interpretation of results, and in whose name the IPD meta-analysis will be

conducted. On setting up the collaboration, a data sharing and data transfer agreement will be put in place with the contributing authors.

Related documents such as clinical trial protocols, statistical analysis plans, case report forms and clinical study reports will also be requested from authors or sponsors (herein referred to as data providers).

If a data provider is unable to provide IPD, the quoted reason of why IPD could not be made available will be recorded and any published aggregate data related to the outcomes of interest of this review will be requested.

### 3.4.3 Data checking and quality assurance

All IPD will be checked on receipt. Data will be examined for internal consistency and integrity of randomization (e.g. temporal distribution of randomisations, baseline balance of important prognostic factors). Patterns of missing data will be examined. Baseline data will be tabulated and compared with the trial publication. The analysis of the primary outcome of each individual trial will also be replicated and compared with corresponding published analyses. One researcher will run data checks and note inconsistencies for discussion with senior members of the research team. Discrepancies may be easily explained, if for example previously excluded participants have been reinstated in the analyses, or additional follow up is provided within IPD compared to published analyses. Any data issues or inconsistencies which cannot be explained or resolved by the research team will be passed back to the responsible trial investigator for explanation and discussion.

### 3.4.4 Data provision and coding

Data providers will be invited to supply data in a standardized comma-separated value (csv) format that will be developed. However, data will be accepted in any reasonable format and re-coded as necessary by the research team. Data will be requested for all randomised participants, including any who were excluded from the original study analyses.

Data checking and coding will be conducted using R[18]or Stata statistical software[19] depending on the format of IPD provided and the software within data sharing platforms, if applicable.

### 3.4.5 Data storage and confidentiality

All IPD provided directly to the research team will be transmitted through secure means, such as a secure File Transfer Protocol (FTP) or encrypted email. All original data provided will be maintained in an anonymous format and stored in a password-protected section of the CRD server. No attempts will be made to trace back the identity of participants, and in the unlikely case in which re-identification is possible, confidentiality will be maintained.

### 3.4.6 Monitoring of IPD requests

The project plans 6 months following registration of the protocol to identify, request and receive IPD to maximise the opportunity to obtain all relevant IPD.At regular intervals, the research team will meet to discuss progress in obtaining IPD. If we reach 6 months, we will review the status of any outstanding requests and the benefits/risks of proceeding to obtain any outstanding IPD.

Decisions on how to proceed with IPD collection will be made based on the proportion of the total trials IPD has been received for and the responsiveness of data providers to communications regarding the provision of IPD at the time of the research team meeting.

The process of IPD collection including how IPD is requested (e.g. by contacting trialists or via data sharing platforms) and documentation required (e.g. research proposals, data sharing agreements, data dictionaries), the extent of requested IPD provided and the extent of data cleaning required and the time taken for each stage of the IPD collection and preparation process will be documented as part of a wider project within the Centre of Reviews and Dissemination at the University of York around time, resources and challenges associated with collecting IPD for research projects.

## *3.5 Quality assessment strategy*

Risk of bias in the RCTs will be assessed using version 2 of the Cochrane risk of bias tool. Risk of bias will be assessed based on published articles, as well as any additional information provided within IPD requests (e.g., data provided for unpublished outcomes, or for patients excluded from published analyses). It is anticipated that the observational studies of best supportive care therapies will not have comparator groups - any which do will be assessed using the ROBINS-I tool. The applicability of observational studies to the NHS setting will be evaluated using an adapted AHRQ approach.[20]

Quality assessments will be performed by one reviewer and independently checked by a second reviewer. Any disagreements will be resolved through discussion and, where necessary, consultation with a third reviewer.

Where IPD is available, we will follow PRISMA-IPD guidance on this aspect of the study. Where possible, we will check randomisation sequences and allocation patterns for any indications that these may not have been random, and we will also check for any important imbalances in factors which may be prognostic of outcomes. Obtaining full study protocols and clinical study reports, together with direct contact with study investigators, may also enhance risk of bias assessments.

## *3.6 Methods of analysis / synthesis*

All study characteristics and quality assessment results will be tabulated and summarised narratively.

### 3.6.1 Meta-analysis

For outcomes with sufficient comparative RCT data available, fixed-effect (also known as common effect) meta-analysis and random-effects meta-analysis will be conducted. If fewer than 5 studies are included, a Bayesian random-effects meta-analysis will be considered, using a semi-informative prior distribution for the between-study heterogeneity.[21]

For outcomes where meta-analyses are performed and a sufficient number of studies is available, heterogeneity will be assessed visually by inspecting forest plots and by examining between-study heterogeneity estimates, such as $I^2$ statistic and the between-study standard deviation, and if feasible, by performing meta-regression or separate meta-analyses in different subgroups of participants, such as people who have received prior treatment with ERT.

If multiple single arm studies (i.e. non-comparative studies or studies of long-term effectiveness and safety outcomes) of the same ERT or of best supportive care with sufficiently homogenous study and participant characteristics are identified, meta-analysis of individual study arms will be considered if

appropriate. If meta-analysis is not deemed appropriate, results of single arm studies will be synthesised narratively.

### 3.6.2 Network meta-analysis

Fixed-effect and random-effects network meta-analysis will also be performed if feasible using comparative RCT data. If fewer than 5 studies are included and the network is sparse, a Bayesian approach will be considered, again using a semi-informative prior distribution for the between-study heterogeneity if appropriate. Heterogeneity will be assessed by comparing study and participant characteristics within and across trials in the network and by examining the between-study standard deviation. If appropriate, treatments with the network will be ranked for each outcome.

If feasible, network meta-regression or separate network meta-analysis will be performed in different subgroups of participants, such as people who have received prior treatment with alglucosidase alfa and people who have not received prior treatment with alglucosidase alfa. Network meta-regression will also be considered if any important imbalances in participant baseline characteristics are observed across trials in the network.[22]

If at least one connected loop is present within the network, inconsistency will be assessed globally and/or locally as appropriate, for example using an unrelated mean effects model or by node-splitting.[23]

### 3.6.3 Approach to synthesis and data analysis

For meta-analysis and for network meta-analysis of comparative RCT data, continuous outcomes will be summarised as mean difference, dichotomous outcomes will be summarised as risk ratio and time-to-event outcomes will be summarised as hazard ratio, all with corresponding 95% confidence intervals or credible intervals if Bayesian approaches as used. If meta-analyses of single arm studies are feasible, continuous outcomes will be summarised as mean difference (i.e. mean change from baseline) and dichotomous outcomes will be summarised as proportions, with corresponding 95% confidence intervals or credible intervals.

IPD will be used for meta-analysis and network meta-analysis where available. In the event that IPD are available for a subset of included trials and relevant published outcome data can be extracted for other trials without IPD available, a synthesis approaches which combines IPD and aggregate data in a two stage approach will be considered.[22, 24]

Synthesis will be performed in statistical software, for example using the metafor,[25] bayesmeta[26] and/or multinma[27] packages in R or the metan[28] or ipdmetan[29] and/or network[30] packages in Stata, depending on the format of data available and the software within data sharing platforms if applicable.

# 4 METHODS FOR SYNTHERSISING EVIDENCE OF COST-EFFECTIVENESS

Relevant cost-effectiveness evidence on the use of ERT for the treatment of LOPD in adults (≥18 years of age) will be systematically identified using the search strategies outlined in Section 3. This review will assess any available studies that analyse the cost-effectiveness of alternative ERT options when compared to comparators, including the best supportive care without ERT. The findings from these studies will help identify key concerns and areas of uncertainty that can subsequently guide the

development of a decision-analytic model. The economic model will aim to inform the cost-effectiveness of ERT in the NHS.

## *4.1 Identifying and systematically reviewing published cost-effectiveness studies*

The results of the comprehensive literature searches carried out to identify all studies relating to the use of the ERT will be used to identify any relevant studies of the cost-effectiveness of the technologies in people with LOPD. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside clinical trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison within the text of the report. In particular, information will be extracted on the comparators, study population and setting, main analytic approaches (e.g. patient-level analysis/ decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis). Quality assessment will be undertaken using the Cheers checklist.[31]

The review will examine existing decision-analytic models in detail, to identify important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. The review will also note, records of discussions from NICE appraisal to provide insights into the acceptability and validity of alternative modelling assumptions. This review will be used to identify the central issues associated with adapting existing decision models to address the current decision problem and assist in the development of a new decision model that addresses issues identified in the clinical and cost-effectiveness review.

## *4.2 Development of a health economic model*

A decision-analytic model will be developed to estimate the cost-effectiveness of alternative ERT treatments for LOPD in comparison to best supportive treatment. The population, interventions and comparator are as set out in Section 1.4, and outcomes to be considered include those set out in Section 3.3.4. The model will be developed in alignment with the NICE reference case. The perspective will be that of the National Health Service and Personal Social Services, health benefits will be expressed in terms of quality-adjusted life years (QALYs) and both costs and QALYs will be discounted at a rate of 3.5% per annum.

### 4.2.1 Modelling approach

Formal conceptualisation of the economic model will be conducted following the completion of the cost-effectiveness review. With guidance from our clinical experts, the review will be used to assess the suitability of current models and will inform the model structure adopted in the new economic model. We will also utilise clinical experts to identify key outcomes most relevant to patient health-related quality of life as well as other clinical factors and issues relevant to patient experience, which will guide the overall structure of the economic decision model. The model conceptualisation process will adopt a design-orientated approach focusing on the feasibility of alternative model designs. It is anticipated that the model will focus on the evolution of patient respiratory and mobility progression over a lifetime horizon, and the impact of treatment on these outcomes.

If feasible, an individual simulation approach will be used. Such an approach allows increased flexibility over Markov modelling and makes it simpler to model respiratory and mobility progression simultaneously incorporating the fact that costs and quality of life are a function of both dimensions. It also simplifies the inclusion of natural history into a patient's progression and so is better able to reflect disease pathology. Where appropriate data are available, a simulation approach can also be used to link patient characteristics to model outcomes, such that the model appropriately reflects heterogeneity in disease pathology and patient outcomes.

Inputs will be based on results of the systematic clinical and cost-effectiveness reviews, and other sources of data to inform key input parameters such as utility values and cost data. Longer-term outcomes will also be considered that cover aspects such as disease severity (in terms of deterioration of mobility and respiratory function), adverse effects of treatment, follow-up consultations, hospitalisations, and mortality. To identify and appraise additional evidence required to inform the economic evaluation, pragmatic supplementary reviews of primary and secondary data (including existing systematic reviews) will be undertaken. The exact nature of these supplementary reviews will depend on the extent of the identified literature in clinical and cost-effectiveness reviews, and the requirements of the economic model.

Patient access schemes are in place for both avalglucosidase alfa and cipaglucosidase alfa. Therefore, the list prices of these treatments do not accurately reflect the amounts paid by the NHS. Since these discounts are confidential, the economic analysis will be unable to incorporate them. To address this limitation and thoroughly assess the cost-effectiveness of avalglucosidase alfa and cipaglucosidase alfa, we will conduct scenarios considering alternative price discounts. Additionally, threshold analysis will be employed to illustrate the price at which each treatment would become cost-effective, based on typically adopted willingness-to-pay thresholds.

# 5 STAKEHOLDER INVOLVEMENT

Throughout this project, we aim to ensure that relevant perspectives are properly considered. During protocol development, we have incorporated comments and feedback from two content experts. As part of the process of understanding, interpreting and contextualising the findings of this review, we will continue to work with a selection of specialist researchers and clinicians involved in the care of people with this disorder, as well as people with lived experience of the disorder and the third sector organisations that advocate for and support them. We will also approach key organisations including the Association for Glycogen Storage Disease (AGSD), Pompe Support Network, Pompe UK, Genetic Alliance, Lysosomal Storage Disorders Collaborative, Metabolic Support UK, Muscular Dystrophy UK, Specialised Healthcare Alliance.

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# 7 APPENDIX 1 – MEDLINE SEARCH STRATEGY

Database: Ovid MEDLINE(R) ALL <1946 to November 21, 2023>

Search Strategy:

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1 glycogen storage disease type II/ (1973)

2 (pompe or pompe's or LOPD or LO-PD).ti,ab. (2472)

3 ((alpha glucosidase* or alpha-glucosidase* or "4-glucosidase*" or "4 glucosidase*" or maltase or gaa) adj2 (deficien* or disease*)).ti,ab. (670)

4 (gsdii or gsd ii or gsd2 or "gsd 2" or gsdtwo or gsd two).ti,ab. (218)

5 generali?ed glycogenos?s.ti,ab. (58)

6 (glycogenos?s adj2 (ii or "2" or two)).ti,ab. (300)

7 (glycogen storage adj2 (disease* or disorder*) adj2 (ii or "2" or two)).ti,ab. (433)

8 or/1-7 (3344)

9 exp animals/ not humans.sh. (5173875)

10 8 not 9 (3173)

11 editorial/ or news/ or exp historical article/ (1286295)

12 10 not 11 (3118)

13 limit 12 to yr="2000 -Current" (2380)

14 remove duplicates from 13 (2370)

15 limit 14 to english language (2191)