Systematic literature reviews to identify clinical and economic outcomes in adults with Pompe disease

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Introduction and objectives

- Pompe disease is a rare, progressive neuromuscular disease. Irreversible muscle damage in adults with Pompe disease may cause muscle weakness, mobility impairment and respiratory insufficiency.[1]
- The current standard of care for Pompe disease is enzyme replacement therapy (ERT) in addition to supportive care, such as mechanical ventilation.[2]
- Alglucosidase alfa (alg), avalglucosidase alfa (aval), and cipaglucosidase alfa plus miglustat (cipa+mig) are treatments for late-onset Pompe disease (LOPD) that have been approved for use in Europe (2006, 2022 and 2023, respectively)[3–6] and the United States (US; 2010, 2021, and 2023, respectively).[7–10]
- Here, the objective was to identify published (i) clinical evidence for LOPD therapies ('clinical systematic literature review [SLR]') and (ii) economic evidence, including health-related quality of life (HRQoL) and cost and resource use, ('economic SLR') in adults with Pompe disease, from a global perspective.

Conclusions

- These robust SLRs were designed to provide a comprehensive overview of the clinical and economic evidence for currently available therapies in adults with Pompe disease.
- Characteristic of rare diseases, few studies were identified for inclusion in the SLRs. While there is a reasonable volume of evidence on the clinical efficacy and safety of LOPD therapies, most of the clinical data were derived from interventional non-randomised controlled trials (non-RCTs) and observational studies, which generally carry a higher risk of bias than RCTs.
- Despite the rarity of Pompe disease, observational studies with up to 283 participants were identified.[32]
- The lack of standardisation of outcome measures for motor function, muscle function and HRQoL/utilities limit comparability of study results within the SLRs and with other conditions.
- There is a paucity of recent studies reporting on the costs, resource use, and cost-effectiveness of treatments for this population. This emphasises the need for more current health economic research in Pompe disease.

Methods

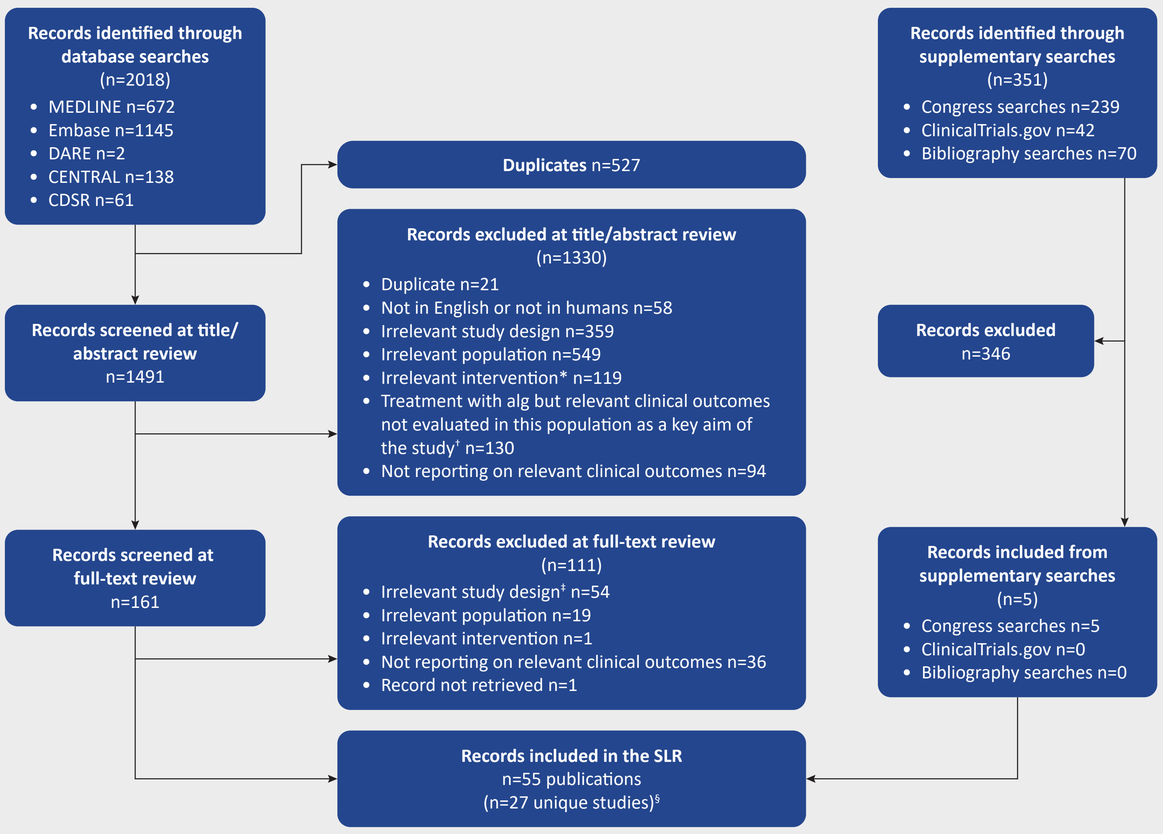
- Both SLRs were conducted following best practice, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Collaboration guidelines.[11, 12] Both SLRs were also performed in accordance with pre-specified protocols.
- Databases and grey literature sources (as shown in **Figure 1** [clinical SLR] and **Figure 2** [economic SLR]) were searched from inception to June 2022. Key conference proceedings from 2020 to 2022 and SLR and meta-analysis bibliographies were searched.
- Search terms and eligibility criteria were selected to identify records reporting on:
  - Clinical SLR: key clinical outcomes in interventional or observational studies of LOPD therapies
  - Economic SLR: economic evaluations, HRQoL, utilities, costs, and healthcare resource use.
- Titles and abstracts, and subsequently full texts, were assessed for inclusion in the SLRs by two independent reviewers. Included full texts were extracted into pre-specified data extraction tables with an independent reviewer verifying the extracted information.
- The risk of bias of included studies was assessed by one individual and verified by a second individual using the following tools:
  - RCTs: University of York Centre for Reviews and Dissemination quality assessment tool[12]
  - Interventional non-RCT and observational studies: Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I)[13]
  - Economic evaluations: Drummond checklist.[14]

Results

Clinical SLR results

- Of 2369 records identified in the clinical SLR searches, 27 unique studies were included[15–42] (**Figure 1**).

Figure 1. PRISMA diagram for the clinical SLR



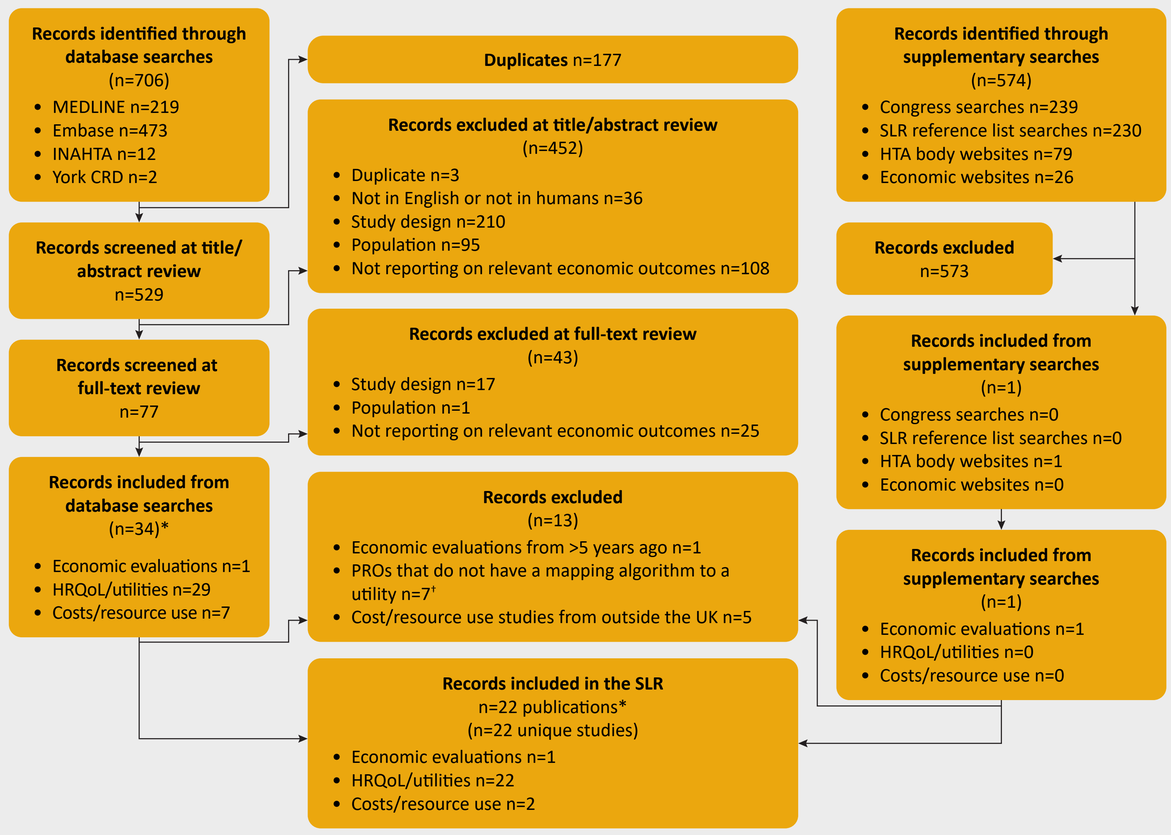
*Interventions of interest were cipa+mig, alg and aval. Interventions not of interest included other ERT interventions and non-ERT interventions such as respiratory muscle training; †Studies in which patients were treated with alg but the effects of this intervention were not evaluated as a key aim of the study were excluded; ‡Retrospective studies and case reports/series were excluded *post hoc* to ensure only the most robust literature were included in the SLR; §The NEO1/NEO-EXT study was associated with two primary references.[38, 39] CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Database of Abstracts of Reviews of Effects.

- 3/27 studies were RCTs,[21, 31, 42] 4/27 were interventional non-RCTs[15, 38–41] and 20/27 were observational studies.[16–20, 22–30, 32–37]
- The studies, some of which reported on ≥1 treatment, reported on alg (20/27 studies),[18–23, 26–36, 40–42] an unspecified recombinant human acid α-glucosidase (5/27 studies),[16, 17, 24, 25, 37] aval (2/27 studies)[31, 38, 39] and cipa+mig (2/27 studies).[15, 21]
- The studies ranged in sample size from 5 to 283 participants (median: 40 participants).
- 23/27 studies reported on lung function,[15–26, 28, 30, 31, 34–42] 23/27 studies on motor function[15–19, 21–29, 31, 34–42] and 13/27 on muscle function.[16, 18, 21–24, 26, 30, 31, 35, 40–42]
- Forced vital capacity was a consistently utilised measure for lung function, facilitating comparability between studies. Conversely, motor and muscle function were assessed across a range of measures, limiting comparability across studies. Most consistently used were the 6-minute walk test; the Gait, Stair, Gowers' manoeuvre, Chair test; and hand-held dynamometry test.
- RCTs generally had low risk of bias. Among interventional non-RCTs and observational studies, 9/24 had moderate risk of bias, and 15/24 had serious risk of bias, with bias due to confounding often being serious and bias in outcome selection and reporting generally being low.

Economic SLR results including HRQoL, cost and resource use

- Of 1280 records identified in the economic SLR searches, 22 unique studies were identified.[33, 35, 36, 43–61] Of these 22 studies, all reported HRQoL or utility outcomes, 2 reported on costs and/or resource use[48, 61] and 1 reported on an economic evaluation[55] (**Figure 2**).

Figure 2. PRISMA diagram for the economic SLR



*Several records were relevant to multiple streams and therefore the total number of records is not equal to the sum of records included in each individual stream; †All PROs that did not have a mapping algorithm to a utility were excluded from the SLR, aside from records reporting on R-PAct, due to its relevance to Pompe disease. CRD, Centre for Reviews and Dissemination; HTA, health technology assessment; INAHTA, International Network of Agencies for Health Technology Assessment; PROs, patient-reported outcomes; R-PAct, Rasch-built Pompe-specific activity; UK, United Kingdom.

- A variety of HRQoL methods, general measures and disease-specific measures were used to measure HRQoL across included studies: 36-Item Short Form Survey, Short Form 6 Dimension, R-PAct scale, Patient-Reported Outcome Measurement Information System, EQ-5D, EQ-VAS, Nottingham Health Profile and time trade-off.[43–61] Only eight of the included studies used EQ-5D,[50, 52–57, 61] a generally well-accepted and commonly used HRQoL measure across disease areas.
- The only identified cost and resource use data were published over a decade ago, in 2004 and 2012, and utilised questionnaires and retrospective health service use data, respectively.[48, 61]
- The single identified cost-utility study (Kanters *et al*, 2017) employed a patient-level simulation model to evaluate the cost-effectiveness of alg compared with supportive care from a Dutch healthcare system and societal perspective over a lifetime horizon.[55] Risk of bias assessment found inadequate reporting of comparator definitions, disaggregated resource use, and cost quantities and price adjustments.

References

1. Cabello JF *et al. Orphan Drugs: Res Rev* 2017:1–10.
2. Stevens D *et al. Curr Treat Options Neurol* 2022;24:573–88.
3. European Medicines Agency (EMA). Nexviadyme© (avalglucosidase alfa). 2022.
4. European Medicines Agency (EMA). Pombiliti© (cipaglucosidase alfa). 2023.
5. European Medicines Agency (EMA). Myozyme© (alglucosidase alfa). 2023.
6. European Medicines Agency (EMA). Opfolda© (miglustat). 2023.
7. US Food and Drug Administration. Nexviazyme© (avalglucosidase alfa-ngpt): highlights of prescribing information. 2021.
8. US Food and Drug Administration. Lumizyme© (alglucosidase alfa): highlights of prescribing information. 2010.
9. US Food and Drug Administration. Opfolda© (miglustat): highlights of prescribing information. 2023.
10. US Food and Drug Administration. Pombiliti© (cipaglucosidase alfa-atga): highlights of prescribing information. 2023.
11. Moher D *et al. Int J Surg* 2010;8:336–41.
12. University of York Centre for Reviews and Dissemination (CRD). Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009.
13. Sterne JA *et al. BMJ* 2016;355.
14. Drummond MF *et al*. Methods for the economic evaluation of health care programmes. 4th ed., Oxford University Press 2015.
15. Byrne B *et al*. Poster presented at the Muscular Dystrophy Association conference 2022; Poster number 92.
16. Ravaglia S *et al. Front Cell Dev Biol* 2022;10.
17. Ravaglia S *et al. J Inherit Metab Dis* 2010;33:737–45.
18. Regnery C *et al. J Inherit Metab Dis* 2012;35:837–45.
19. Ripolone M *et al. Neuropathol Appl Neurobiol* 2018;44:449–62.
20. Schneider I *et al. Wien Med Wochenschr* 2013;163:40–4.
21. Schoser B *et al. Lancet Neurol* 2021;20:1027–37.
22. Semplicini C *et al. J Inherit Metab Dis* 2020;43:1219–31.
23. Strothotte S *et al. J Neurol* 2010;257:91–7.
24. Wenninger S *et al. J Neurol* 2021;268:2943–50.
25. Witkowski G *et al. Neurol Neurochir Pol* 2018;52:465–69.
26. Anderson LJ *et al. J Inherit Metab Dis* 2014;37:945–52.
27. Angelini C *et al. J Neurol* 2012;259:952–8.
28. Angelini C *et al. Muscle Nerve* 2012;45:831–4.
29. Bembi B *et al. J Inherit Metab Dis* 2010;33:727–35.
30. De Vries JM *et al. Orphanet J Rare Dis* 2012;7.
31. Diaz-Manera J *et al. Lancet Neurol* 2021;20:1012–26.
32. Güngör D *et al. Orphanet J Rare Dis* 2013;8.
33. Güngör D *et al. J Inherit Metab Dis* 2016;39:253–60.
34. Harlaar L *et al. Neurology* 2019;93:e1756–67.
35. Kuperus E *et al. Neurology* 2017;89:2365–73.
36. Kuperus E *et al. PLoS ONE* 2018;13:e0208854.
37. Masat E *et al. Sci Rep* 2016;6:36182.
38. Pena LDM *et al. Neuromuscul Disord* 2019;29:167–86.
39. Schoser B *et al. Eur J Neurol* 2020;27:486.
40. van der Ploeg AT *et al. Mol Genet Metab* 2016;119:115–23.
41. van der Ploeg AT *et al. Mol Genet Metab* 2012;107:456–61.
42. van der Ploeg AT *et al. N Engl J Med* 2010;362:1396–406.
43. Aslan GK *et al. Lung* 2016;194:555–61.
44. Boentert M *et al. J Clin Sleep Med* 2016;12:1623–32.
45. Boentert M *et al. Eur J Neurol* 2015;22:369–76.
46. Favejee MM *et al. Arch Phys Med Rehabil* 2015;96:817–22.
47. Güngör D *et al. Mol Genet Metab* 2013;109:371–6.
48. Hagemans MLC *et al. Neurology* 2004;63:1688–92.
49. Harfouche M *et al. J Patient-Rep Outcomes* 2020;4:1–11.
50. Hu J *et al. Intractable Rare Dis Res* 2021;10:190–7.
51. Jones HN *et al. Neuromuscul Disord* 2020;30:904–14.
52. Kanters TA *et al. J Inherit Metab Dis* 2011;34:1045–52.
53. Kanters TA *et al. Qual Life Res* 2015;24:837–44.
54. Kanters TA *et al. Orphanet J Rare Dis* 2015;10:112.
55. Kanters TA *et al. Orphanet J Rare Dis* 2017;12:179.
56. Malottki K *et al. Value Health* 2022;25:S173.
57. Pollissard L *et al. Neuromuscul Disord* 2021;31:S111.
58. Sechi A *et al. Orphanet J Rare Dis* 2020;15:143.
59. Simon N-J *et al. J Patient-Rep Outcomes* 2019;3:1–10.
60. Vaeggemose M *et al. PeerJ* 2021;9.
61. Wyatt K *et al. Health Technol Assess* 2012;16.

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