Challenges in identifying information to build economic evaluations in hereditary angioedema

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Introduction and objectives

- Hereditary angioedema (HAE) is a genetic disorder characterised by recurrent, typically painful, and potentially life-threatening attacks of swelling that affect various body parts.[1,2] Treatment of HAE aims to prevent occurrence of recurrent attacks (long-term prophylaxis; LTP) and to reduce morbidity associated with attack manifestations if attacks occur (on-demand treatment, ODT). An unmet need remains for additional efficacious, well-tolerated, and easily administered treatment options for both LTP and ODT for HAE.[3]
- A systematic literature review was performed with the objective to identify and appraise the available published economic evidence in HAE to support *de novo* early economic modelling of LTP and ODT for HAE, via the following research question:
  - **What is the existing economic evidence for HAE, and can this be used to support design (model structure and appropriate assumptions) and parameterisation of early economic modelling of LTP and ODT for HAE?**

Methods

- **The economic review captured three key components of evidence:**
  - Economic evaluations including full economic evaluations synthesising costs and health outcomes (cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis, and cost-consequence analysis, and partial economic evaluations including budget impact and cost-minimisation analysis);
  - Healthcare cost and resource use (HCRU) studies;
  - Health related quality of life (HRQoL) studies, and utility and mapping studies.
- The review was registered on PROSPERO: CRD42023470068 and searches were conducted in October 2023, including electronic databases, conference proceedings, and HTA websites.
- To identify evidence to answer the research question, eligibility criteria were defined using the Population(s), Interventions, Comparators, Outcomes, and Study designs of interest (PICOS) format (**Table 1**).

Table 1. Summary of PICOS (Population, Interventions, Comparators, Outcomes, Study design)

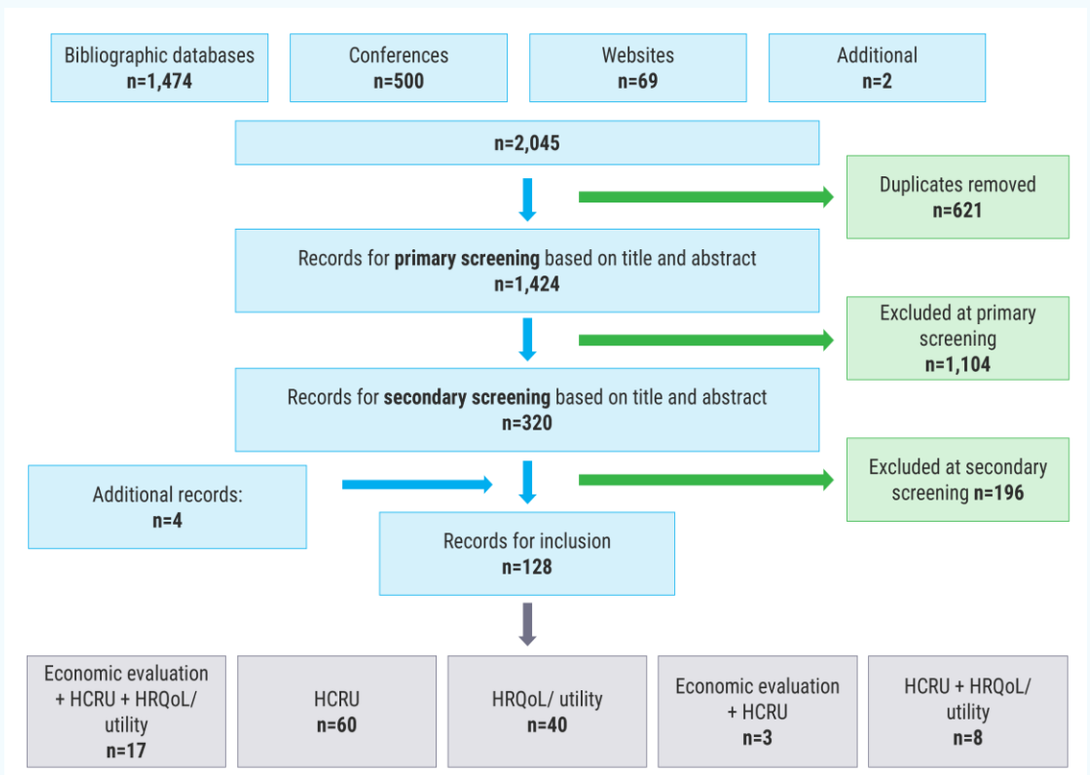
Criterion	Inclusion
Population	HAE patients of any age and caregivers of HAE patients.
Intervention & comparators	Any intervention and comparator.
Outcomes	Outcomes of interest vary by study type and included outcomes under the broader categories[a] • Economic evaluations (focus on cost-effectiveness model design and structural approaches) • Healthcare cost and resource use[b] • HRQoL including generic and disease-specific measures
Study design & publication types	• Economic evaluations and budget impact analyses • Healthcare resource use and costing studies • Studies reporting disease-specific resource use and cost-estimates • HRQoL and utility studies • Mapping algorithms
Limits	Date limits applied to conference proceedings which were included from 2021-2023, only. Healthcare resource use/ costing studies were eligible if published within the last 10 full years. No language limits.

a = Studies reporting 1, 2, or 3 types of economic evidence were eligible for inclusion; b = Studies that only report medication/pharmaceutical costs were excluded

Results

- In total, 128 records were included, of which 17 reported all three economic components (**Figure 1**).
  - HCRU evidence only was reported in 60 records; HRQoL/utilities evidence only was reported in 40 records; three records reported an economic evaluation as well as HCRU; and the remaining eight records reported HCRU as well as HRQoL/utilities.
- In total, 70 records presented data across HAE populations comprising patients receiving LTP and/or ODT. Evidence for patients receiving LTP only or ODT only was presented in 39 and 19 records, respectively.

Figure 1. PRISMA diagram of the study selection process



Economic evaluation evidence:

- Economic evaluations were presented in four studies and 14 HTA appraisals that assessed interventions for ODT (four), LTP (nine), or both (one). The searches highlighted an overall paucity of economic evaluation evidence, particularly in interventions for ODT for which there was limited precedent and reporting of details of model structure and approach.

Three key studies reporting healthcare cost and resource use were identified:

- Jolles *et al.* (2014)[4] for patients receiving LTP and/or ODT, Longhurst *et al.* (2018)[5] for patients receiving ODT only, and Fijen *et al.* (2023)[6] for patients receiving LTP and/or ODT.
  - **Jolles *et al.* (2014)** described a national audit of 116 HAE patients in the UK assessing information on productivity losses in terms of missed days of school/work, or when activities of daily living could not be performed. Mean annual days missed of school/work was nine days.
  - **Longhurst *et al.* (2018)** reported real-world outcomes from patients enrolled in the Icatibant Outcomes Study at sites in the UK *versus* those enrolled in other countries. The key resource use outcome was number of hospitalisations per patient at baseline and follow-up; UK patients requiring five or more hospitalisations decreased from 4.4% of patients at baseline, to 1.9% of patients in the follow-up period.
  - **Fijen *et al.* (2023)** reported results of an online survey in 69 adult HAE patients in the Netherlands, providing a detailed breakdown of average visits/use of healthcare resource in the Dutch healthcare system. Total costs per patient per month ranged from €0.00 to €19,422.21, with a mean total monthly cost of €1,897.04.

Health related quality of life evidence:

- Two sources of utility values were identified that could potentially form base case or scenario HRQoL inputs of future economic models in HAE. This review also aimed to identify mapping algorithms for eliciting utility values from disease-specific PROMs, however none of relevance were identified.
  - **Nordenfelt *et al.* (2014)**[7] estimated health state disutilities for mild, moderate, and severe attacks in HAE patients from Sweden. These values were used as base case or scenario analyses in the majority of the LTP economic evaluations identified in this review.
  - **Lo *et al.* (2022)**[8] reported a UK-based time trade-off study aiming to elicit utility values specific to HAE attack body locations (facial, hand, abdominal, laryngeal), as well as estimating utility values for caregivers whilst caring for someone experiencing an attack.

Discussion

- The EQ-5D has not yet been validated in HAE, therefore other measures, for example use of the AE-QoL or HAE-QoL, may be more applicable for assessing HAE patient-relevant outcomes. However, angioedema-specific measures do not yet have value sets or mapping algorithms to convert scores into a utility value – this is a potential avenue for further data collection and research, especially in the ODT space.
- It may be applicable for future healthcare costs and resource use studies to mirror the Fijen *et al.* (2023) study in each country of interest, to capture comprehensive resource utilisation data in different groups of HAE patients.

Conclusion

This review highlighted evidence gaps that should be addressed to assist with the development of model structures and to allow parameterisation of comprehensive cost effectiveness models of LTP and ODT for HAE fully capturing the impact that attacks have on people living with HAE. Potentially useful HCRU and HRQoL parameter values were identified, however additional country-specific data are required to supplement this evidence.

Abbreviations: AE-QoL, angioedema quality of life questionnaire; EQ-5D, EuroQoL-5 dimensions; HAE, hereditary angioedema; HAE-QoL, hereditary angioedema quality of life questionnaire; HCRU, healthcare cost and resource use; HRQoL, health related quality of life; HTA, health technology assessment; LTP, long-term prophylaxis; ODT, on-demand treatment; PROMs, patient reported outcome measures.

Refs: 1. Betschel S, Banerji A, Busse PJ, et al. Hereditary Angioedema: A Review of the Current and Evolving Treatment Landscape. J Allergy Clin Immunol Pract. 2023;11(8):2315-2325. doi: 10.1016/j.jaip.2023.04.017; **2.** Busse P, Christiansen SC. Hereditary Angioedema. The New England Journal of Medicine. 2020;382(12):1136-1148; **3.** Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema -The 2021 revision and update. Allergy. Jul 2022;77(7):1961-1990. doi:10.1111/all.15214; **4.** Jolles S, Williams P, Carne E, et al. A UK national audit of hereditary and acquired angioedema. Clinical and experimental immunology. 2014;175(1):59-67. doi:https://dx.doi.org/10.1111/cei.12159; **5.** Longhurst HJ, Dempster J, Lorenzo L, et al. Real-world outcomes in hereditary angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom. Allergy Asthma Clin Immunol. 2018;14:28. doi:10.1186/s13223-018-0253-x; **6.** Fijen LM, Klein PCG, Cohn DM, Kanters TA. The Disease Burden and Societal Costs of Hereditary Angioedema. The journal of allergy and clinical immunology In practice. 2023;11(8):2468-2475.e2. doi:https://dx.doi.org/10.1016/j.jaip.2023.03.032; **7.** Nordenfelt P, Dawson S, Wahlgren C-F, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy and asthma proceedings. 2014;35(2):185-90. doi:https://dx.doi.org/10.2500/aap.2014.35.3738; **8.** Lo SH, Lloyd A, Elkhalifa S, Sisic Z, van Nooten FE. Time Trade-Off Utilities for Hereditary Angioedema Health and Caregiver States. PharmacoEconomics - open. 2022;6(2):231-239. doi:https://dx.doi.org/10.1007/s41669-021-00302-6.

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