



Identification of real-world data to study hereditary angioedema unmet need: a targeted literature review

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Introduction

- Hereditary angioedema (HAE) is a rare disease affecting 1 in 50,000 people globally.¹ Patients experience recurring, unpredictable, severe and potentially fatal swelling attacks, commonly affecting the hands, feet, stomach, face and throat.²
- Diagnosing HAE is complex, involving clinical assessment, blood tests, and in some instances genetic testing – potentially leading to underdiagnosis in routine clinical care.³
- There is a lack of granularity in diagnosis coding. ICD-10 D84.1 “Defects in the complement system” is often used, however its not specific enough, and may encompass other forms of C1 inhibitor deficiency, such as acquired angioedema.⁴
- The rarity of HAE, combined with its clinical complexity and the absence of highly specific diagnosis codes, poses significant challenges for conducting meaningful real-world evidence (RWE) studies using secondary real-world data (RWD).

Objective

- The primary objective was to conduct a targeted literature review (TLR) that identified secondary RWD sources for subsequent research on HAE attacks, healthcare resource utilization (HCRU), treatment patterns, quality of life (QoL), and adverse events in Europe.

Methods

Data landscape

- A search strategy combining HAE and data source specific terms was developed in PubMed for the period January 1st, 2015 – April 15th, 2025.
- Desk-based research was conducted to identify conference publications, disease-specific registries, HAE centers, claims data, and national health databases that may not have been published.
- Full-text review exclusion criteria included: geographical scope, lack of RWD and/or secondary data, or non-English publications.
- After screening, five RWD sources were selected for a pre-specified qualitative in-depth assessment based on their suitability for RWE generation in HAE.

Assessment of data sources

- Shortlisted RWD sources were selected due to: access to secondary European RWD; and inclusion of variables specific to HAE attacks, HCRU, treatment patterns, QoL, and adverse events.
- Pre-specified assessment framework was supplemented with interview-based discussions.
- Evaluation focused on the availability of key variables, patient counts, available follow-up, and operational aspects of conducting a future study (e.g., data access considerations).
- One of the five identified sources, ITACA, was excluded from the study as no response was available at the time for the pre-specified data source assessment framework.

Results

Data sources

A total of 98 sources of information were reviewed (**Figure 1**), from which 5 data sources were prioritized, and 4 completed the pre-specified qualitative in-depth assessment (**Table 1**, 2):

Chronic Angioedema Registry (CARE)

- A multinational registry of angioedema patients that collects patient-reported data through online questionnaires completed at each outpatient visit with an angioedema-treating physician.
- Provides detailed data on HAE attacks and patient QoL; however, limited follow-up hinders long-term characterization.

HARPE (Registre National de l'Angio-œdème Héritaire en France)

- A France-based registry specific to HAE. Uses a natural language processing (NLP) algorithm to convert unstructured medical notes from an HAE reference center into structured data.
- Transforms rich physician notes into structured datasets; follow-up length and coverage remain limited.

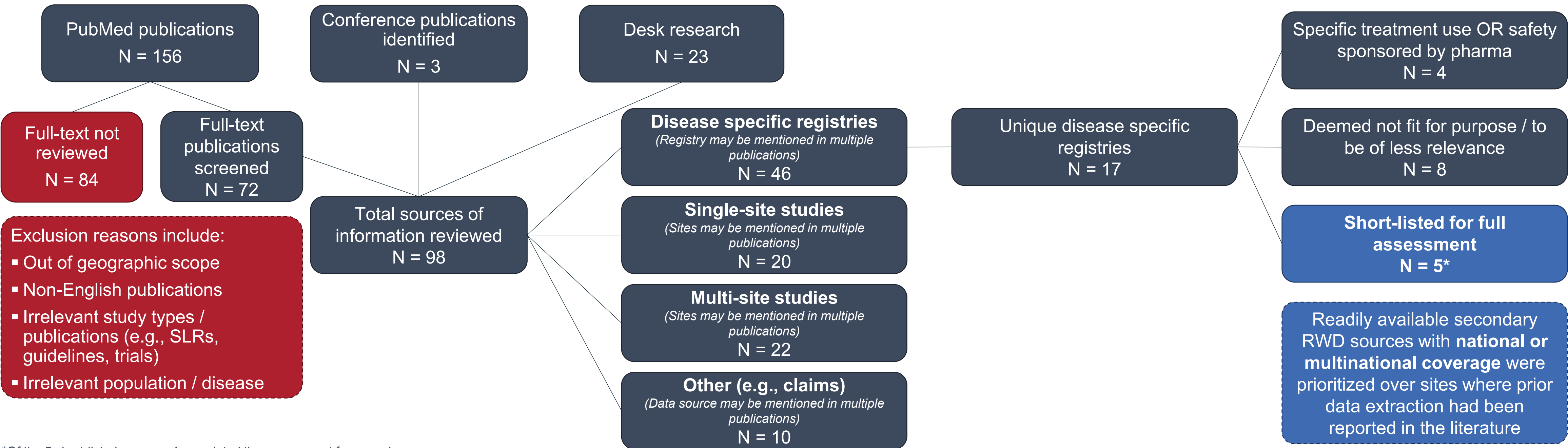
Sweha-reg (Swedish Hereditary Angioedema Registry)

- A national cohort of HAE patients in Sweden, each with a clinician-confirmed diagnosis. Can be linked to administrative data from national registers via a unique patient identifier.
- Enables comprehensive analysis of healthcare use, costs, and treatment patterns via national register linkage; attack identification limited to hospitalizations and excludes in-hospital therapy details.

PHARMO Data Network

- Electronic medical records from both primary and secondary healthcare settings in the Netherlands.
- Links data across care settings for broad healthcare insights; lacks national coverage and misses data from the main Dutch HAE reference center.

Figure 1. Data landscaping results



*Of the 5 short-listed sources, 4 completed the assessment framework

Table 1. Assessment of variable availability among selected data sources

Data type	Data variable	CARE	HARPE	Sweha-reg linked to Swedish national registries	PHARMO Data Network
Demographics	Age				
	Sex				
HAE clinical characteristics	Ethnicity	Patient reported	Not recorded	Not recorded	Not recorded
	HAE diagnosis	Reported by patients, confirmed by physician	Confirmed by physician	Confirmed by physician	Identifiable based on treatment
	HAE type	Confirmed by physician	Confirmed by physician	Confirmed by physician	Possibly identifiable based on lab data
	HAE attack	Patient reported for the 3 months prior to consultation (inc. home & hospital)	Extracted from patients' medical notes (inc. home & hospital)	Attacks requiring hospitalization identified via attack related codes	Attacks requiring hospitalization identified via attack related codes
	HAE attack frequency	Patient reported for the 3 months prior to consultation	Available in ~50% of cases via extraction from medical notes	Attacks requiring hospitalization identified via attack related codes	Attacks requiring hospitalization identified via attack related codes
	HAE attack duration	Patient reported for untreated or late treated episodes	Available in ~35% of cases via extraction from medical notes	Not recorded	Not recorded
	HAE attack location	Patient reported for the most recent attack	Available in ~95% of cases via extraction from medical notes	Not recorded	Not recorded
	HAE attack severity	Not recorded	Available in ~60% of cases via extraction from medical notes	Not recorded	Not recorded
	HAE attack triggers	Patient reported symptoms and frequency 1-12 hours prior to attack	Available in ~50% of cases via extraction from medical notes	Not recorded	Not recorded
Labs	C1-INH values	Sites where patients are treated can optionally add laboratory results to patients record	Available in ~40% of cases via extraction from medical notes	Possibly via linkage to lab register	Lab data coverage: ~20% of network
	Plasma prekallikrein values	Not recorded	Not recorded		Not performed in the Netherlands
Treatments	On-demand HAE therapies	Based on the last 3 months prior to outpatient visit	Detailed posology information available in ~99% of cases, extracted from patients' medical notes	Treatments administered in hospital are not recorded.	Both out- & inpatient treatment records recorded
	Prophylactic HAE therapies				LTPs recently approved & primarily administered in specialized centers
	Concomitant medication	Not recorded	Only mention of treatment with no detailed posology	Identifiable via outpatient pharmacy records	Identifiable via out & in-patient pharmacy records
HCRU & costs	Outpatient visits	Patient reported for the 12 month prior to consultation	Not recorded		
	Outpatient specialty		Not recorded		
	Inpatient visits				
	ER admissions	HAE related ER visits	HAE related ER visits	All ER visits related to the patient	All ER visits related to the patient
	Procedures	Not recorded	Some procedures are captured via extraction from medical notes	All out- & inpatient procedures are recorded	All out- & inpatient procedures are recorded
	Length of hospital stay	Not recorded	Not recorded	Recorded for all inpatient stays	Recorded for all inpatient stays
	Costs	Not recorded	Not recorded	Based on local tariff codes	Based on local tariff codes
Safety & adverse events	Safety and adverse events	Patient reported	Available in ~40% of cases	Based on hospitalizations	Based on hospitalizations
Quality of Life (QoL)	QoL	Patient reported AE-QoL ^a and AECT ^b for the 3 months prior to consultation	HAE sick days available in ~40% of cases	Not recorded	Not recorded

^aAngioedema quality of life questionnaire; ^bAngioedema control test

Table 2. Feasibility of future research objectives based on the limitations observed in the assessed sources

Research objectives	CARE	HARPE	Sweha-reg linked to Swedish national registries	PHARMO Data Network
HAE Attack characterization (Home)	Limited follow-up / longitudinality. Currently only 33% of patients have at least one follow up data point.	Data on HAE attacks is extracted from information provided by physicians during follow up consultations where patients describe the attacks suffered, leading to incomplete data in some key variables (e.g., attack duration).	No information on attacks occurring outside of a hospital setting recorded.	No information on attacks occurring outside of a hospital setting recorded.
HAE Attack characterization (Hospital)			HAE attacks requiring hospitalization may be identified by using proxies.	HAE attacks requiring hospitalization may be identified by using proxies.
HAE burden & cost of illness	Lacking data on procedures, length of stay, costs, and relying on patient reported healthcare resource use.	Little information recorded on patients' healthcare resource use, limited to HAE related events, and no cost information		
Drug utilization (DUS) for LTP therapies / treatment patterns	Limited follow-up / longitudinality. Reliant on patient reported treatment information.		Hospital-administered drugs not captured.	LTPs recently approved & primarily administered in specialized centers
Safety and adverse events	Limited follow-up / longitudinality. Reliant patient reported adverse events to treatments.	Only for adverse events reported in physicians' medical notes.	Based on hospitalizations, outpatient visits and procedures recorded in national patient register. Able to supplement with chart extraction.	Based on hospitalizations, outpatient visits and procedures. Able to supplement with chart extraction.
QoL	Limited follow-up / longitudinality.	Limited information recorded, primarily on HAE caused absenteeism and only in some cases	Not recorded	Not recorded

CONCLUSIONS

This targeted literature review and assessment highlighted a scarcity of mature secondary data sources for conducting HAE research in Europe.

The qualitative assessments for the four data sources reflect the nature and content of each database at the time of the study. Consequently, the findings from our assessment are subject to change as each database evolves and grows in the coming years.

Each data sources had its own strengths and limitations. When designing RWE studies, it is essential to evaluate these pros and cons — including factors such as data maturity, follow-up duration, and the presence or absence of key HAE-specific variables (e.g., attack frequency, duration, location, severity, triggers) — to ensure robust and meaningful study design.

In the evolving field of HAE research, new databases continue to be developed, expanding the landscape of potential RWD sources. Findings from this study underscore the ongoing need to enhance the availability and depth of secondary data to better support future research and evidence generation.

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