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Original Article

A Core Outcome Set for Efficacy of Acute Treatment of Hereditary Angioedema

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What is already known about this topic? Clinical trials investigating the acute treatment of hereditary angioedema attacks have used a large variety of outcomes to assess efficacy, limiting comparability of trial results.

What does this article add to our knowledge? A panel consisting of patients with hereditary angioedema, expert clinicians and researchers, pharmaceutical companies, and a regulatory body agreed on a core outcome set for the acute treatment of hereditary angioedema attacks, consisting of five key outcomes.

How does this study impact current management guidelines? The development, endorsement, and adoption of this core outcome set by participating stakeholders will provide a standardized framework for trial outcomes, facilitating more meaningful comparisons and interpretations of future study results.

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Abbreviations used
COS- Core outcome set
HAE- Hereditary angioedema
PROM- Patient-reported outcome measure

BACKGROUND: Clinical trials investigating drugs for the acute treatment of hereditary angioedema attacks have assessed many different outcomes. This heterogeneity limits the comparability of trial results and may lead to selective outcome reporting bias and a high burden on trial participants.
OBJECTIVE: To achieve consensus on a core outcome set composed of key outcomes that ideally should be used in all clinical efficacy trials involving the acute treatment of hereditary angioedema attacks.
METHODS: We conducted a Delphi consensus study involving all relevant parties: patients with hereditary angioedema, hereditary angioedema expert clinicians and clinical researchers, pharmaceutical companies, and regulatory bodies. Two Internet-based survey rounds were conducted. In round 1, panelists indicated the importance of individual outcomes used in clinical trials on a 9-point Likert scale. Based on these results, a core outcome set was developed and voted on by panelists in round 2.
RESULTS: A total of 58 worldwide panelists completed both rounds. The first round demonstrated high importance scores and substantial agreement among the panelists. In the second round, a consensus of 90% or greater was achieved on a core outcome set consisting of five key outcomes: change in overall symptom severity at one predetermined time point between 15 minutes and 4 hours after treatment, time to end of progression of all symptoms, the need for rescue medication during the entire attack, impairment of daily activities, and treatment satisfaction.
CONCLUSIONS: This international study obtained a high level of consensus on a core outcome set for the acute treatment of hereditary angioedema attacks, consisting of five key outcomes. **(J Allergy Clin Immunol Pract 2024;12:1614-21)**

Key words: *Acute treatment; Consensus; Core outcome set; Delphi; Hereditary angioedema; Randomized controlled trial; Outcome*

INTRODUCTION

Hereditary angioedema (HAE) is a condition caused by a group of rare genetic disorders characterized by recurrent episodes of cutaneous or submucosal swelling. Most cases of HAE are due to deficient or dysfunctional C1-inhibitor. The occurrence of angioedema attacks in HAE can be unpredictable and in rare cases even life-threatening when it affects the upper airways. Therefore, access to acute treatment to manage angioedema attacks remains vital for every patient with HAE, even when prophylactic treatment is used to reduce the attack frequency and burden of disease.[1,2]

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Conflicts of interest: R.S. Petersen has received speaking fees from Pharvaris and Astria. L.M. Fijen has received a conference travel grant from Ionis Pharmaceuticals, Inc and has acted as a consultant for Pharvaris in the past. C. Apfelbacher has received institutional funding from the Dr Wolff Group and Bionorica, and consultancy fees from the Dr Wolff Group, Sanofi, Bionorica, Rheacell, and LEO Pharma. M. Magerl has received personal fees from CSL Behring, Takeda-Shire, Pharming, BioCryst, Novartis, Octapharma, and KalVista. K. Weller has received research grant support and/or honoraria for educational lectures or consulting from BioCryst, CSL Behring, Moxie, Novartis, Pharvaris, and Takeda. W. Aberer has received speaking fees from BioCryst, CSL Behring, and Takeda. A. Adatia has received speaker/advisor fees, travel support, and/or research funding from Astria, BioCryst, Covis Pharma, CSL Behring, Ionis Pharmaceuticals, and Takeda. P. Audhya is an employee of KalVista and a shareholder of KalVista Pharmaceuticals Inc. N.-A. Bara has received grants, consulting fees, payments, honoraria for lectures, and presentations from CSL Behring, Shire/Takeda, Pharming, BioCryst, and KalVista. S. Betschel has received speaker/advisor fees and/or research funding from Astria, Canadian Blood Services, CSL Behring, Grifols, Ionis Pharmaceuticals, KalVista Novartis, Octapharma, Pharvaris, Sanofi, and Takeda. I. Boccon-Gibod has consulted/served as speaker for, engaged in research and educational projects with, or accepted travel grants from BioCryst, Takeda, CSL Behring, BioMarin, KalVista, and Pharvaris. L. Bouillet has consulted/served as speaker for, engaged in research and educational projects with, or accepted travel grants from BioCryst, CSL Behring, Takeda, Novartis, GSK, and Blueprint. Nicholas Brodszki has received speaker/consultancy fees from BioCryst, CSL Behring, and Shire-Takeda. P.J. Busse has received grant research support from Takeda, CSL Behring, and KalVista and consulting support from Takeda, CSL Behring, KalVista, BioMarin, Pharvaris, Novartis, Astria, CVS/Caremark, and ADARx. T. Buttgereit is or recently was a speaker and/or advisor for AstraZeneca, BioCryst, CSL-Behring, GSK, Hexal, KalVista, Medac, Novartis, Pharming, Roche, Sanofi, and Takeda, outside the submitted work. A. Bygum has received consulting fees from BioCryst, CSL Behring, and Takeda. M. Cancian has received grant research support and/or speaker/consultancy fees from BioCryst, CSL Behring, KalVista, Pharming, Shire-Takeda, and SOBI; and clinical trial/registry investigator fees from

However, evaluation of the efficacy of acute treatment of HAE attacks can be challenging because angioedema attacks differ in location, symptoms, severity, and duration among patients and even within individual patients. Whereas the assessment of disease burden and response to prophylactic treatment is well established in HAE by validated instruments such as the Angioedema Activity Score,[3] the Angioedema Control Test,[4] and the Angioedema Quality of Life Questionnaire,[5] consensus on the assessment of acute treatment efficacy does not exist. Reasons for this shortcoming could be that objective markers for assessing attack severity and response to acute treatment are lacking or have not yet been defined.[6] In addition, modern therapy is based on delegating the treatment to the patients, advocating home (self) treatment.[1] Therefore, the assessment of response to acute treatment has to rely on the use of patient-reported outcome measures (PROMs).

A recent systematic review identified 72 combinations of efficacy outcomes and outcome measures applied in 13 different clinical trials aimed to evaluate the efficacy of acute treatment of HAE attacks.[7] The use of many different outcomes and outcome measures leads to difficulties when findings from trials are compared and interpreted.[8] Moreover, measuring numerous outcomes in one trial can impose a high burden on participants and potentially lead to selective outcome reporting bias.[8] Another concern is the lack of clarity regarding which instrument best reflects efficacy of acute treatment. Thus, it is important to reach a general consensus on outcomes that ideally should be measured when assessing treatment efficacy of acute treatment of HAE attacks. Furthermore, unified criteria may assist in developing clinical guidelines, serving clinicians treating patients with HAE.

The Acute Treatment Outcomes in Hereditary Angioedema (AURORA) project aimed to develop a consensus-based core outcome set (COS) consisting of key outcomes that should be measured and reported in all clinical trials of acute treatment of HAE attacks.

METHODS

Study design

We conducted a Delphi process from February to June 2023, using the Welphi online survey Web platform (Decision Eyes, Lisbon, Portugal, 2019), and in accordance with the Core Outcome Set—Standards for Development and Core Outcome Set—Standards for Reporting guidelines.[9,10] The Delphi technique is a consensus-building method that uses successive anonymous survey rounds to gather input from a selected expert panel on a specific topic.[11] The study protocol was registered in the Core Outcome Measures in Effectiveness Trials database.[12] The AURORA project was not subject to the Dutch Medical Research Involving Human Subjects Act.

Delphi panel

This Delphi project was initiated by two Angioedema Centers of Reference and Excellence: the Amsterdam University Medical Center and the Charité University Hospital—Berlin. A steering

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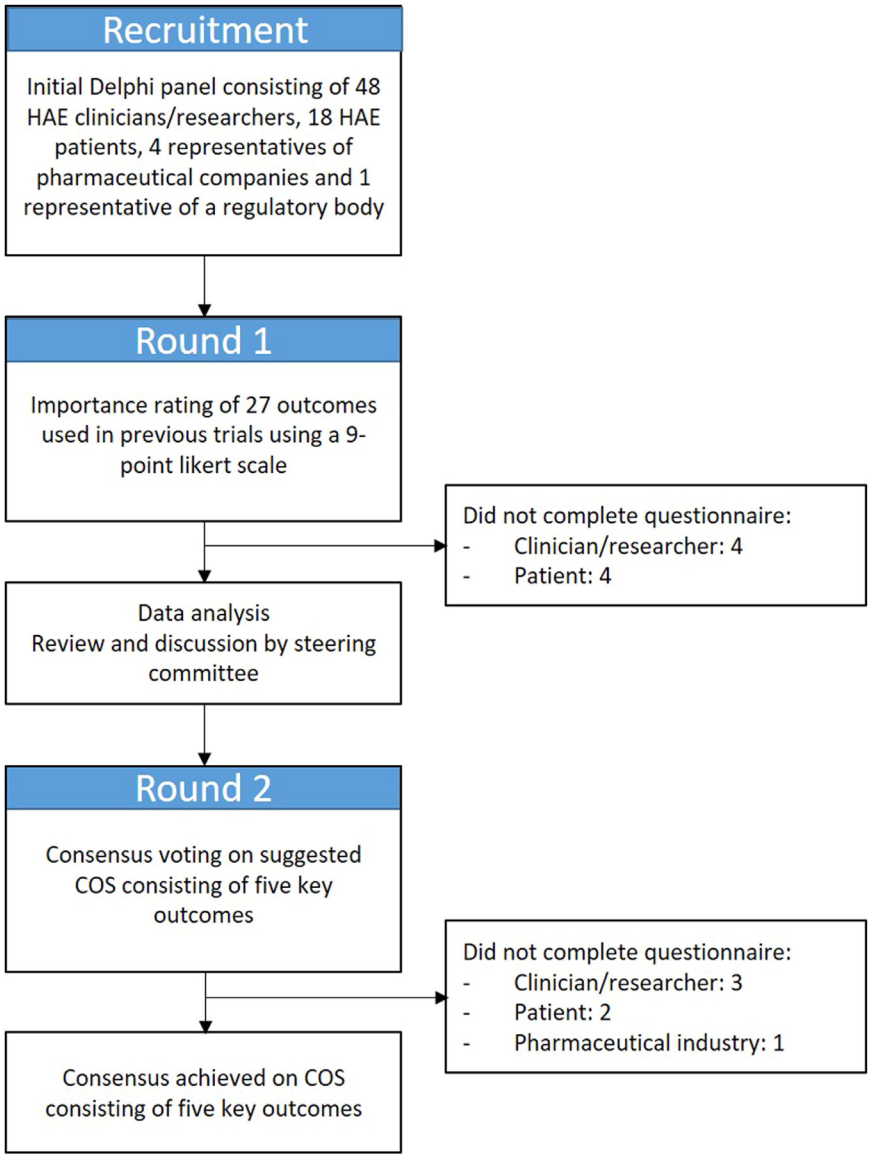

FIGURE 1. Flowchart of Delphi process to reach consensus on a core outcome set (COS) for measuring efficacy of acute treatment for hereditary angioedema (HAE).

group consisting of members from these initiative centers was formed, composed of six clinicians and clinical researchers (R.S.P, L.M.F., K.W., M. Magerl, M. Maurer, and D.M.C.) with experience in HAE care and research, two patient representatives from the international HAE patient organization (the chairman and the president of HAE International), and one methodologist (C.A.). The following representative groups were invited to participate as panelists: HAE clinicians and clinical researchers, patients with HAE, the pharmaceutical industry, and regulatory bodies. By consulting with these groups we aimed to include individuals experienced in designing, conducting, overseeing, and participating in clinical trials, and have them contribute personal wisdom to the development of the COS. All authors of the latest update of the international HAE guideline[13] were personally invited to participate, as were HAE clinicians attending the Bradykinin Symposium held in Berlin, Germany in 2022. Patients with HAE were personally approached via the network of the steering group members. All pharmaceutical companies with registered or investigational compounds for the acute treatment of HAE attacks were invited to appoint one representative as a panelist. Both the European Medicines Agency and the US Food and Drug Administration were asked to appoint one representative as a panelist. Participants were informed about the study and consented to participate. All panelists were required to be at least aged 18 years and able to communicate in English.

ROUND 1

In round 1, panelists were requested to score the importance of all efficacy outcomes used in clinical trials investigating acute treatments of HAE attacks published before April 2021, as identified in a recent systematic review.[7] Panelists indicated their level of agreement on whether each outcome should be included

TABLE I. Summary of Delphi round 1: importance rating of 27 outcomes using 9-point Likert scale

Outcome (n = 63)	Score, medians (interquartile ranges)	Unable to score
Symptom change (symptom-based outcomes)		
Overall change in symptom severity at 1 h after treatment with study medication	8.00 (7.00-9.00)	3%
Overall change in symptom severity at 2 h after treatment with study medication	7.00 (6.00-8.00)	3%
Overall change in symptom severity at 3 h after treatment with study medication	7.00 (6.00-8.00)	3%
Overall change in symptom severity at 4 h after treatment with study medication	7.00 (6.00-9.00)	3%
Overall change in symptom severity at 24 h (1 d) after treatment with study medication	8.00 (6.25-9.00)	2%
Change in symptom severity at primary attack location at 4 h after treatment with study medication	7.00 (6.00-8.00)	3%
Change in symptom severity at primary attack location at 24 h after treatment with study medication	7.00 (6.00-8.00)	3%
Laryngeal, abdominal, or facial symptom improvement at 30 min after treatment with study medication	9.00 (7.00-9.00)	10%
Laryngeal, abdominal, or facial symptom improvement at 4 h after treatment with study medication	8.00 (7.00-9.00)	10%
Percentage of participants with treatment outcome score of ≥50 or 70 at 4 h after treatment with study medication	8.00 (6.00-8.00)	13%
Symptom change (time-based outcomes)		
Time to first onset of symptom relief	9.00 (8.00-9.00)	3%
Time to 50% symptom severity reduction	7.00 (6.00-8.00)	5%
Symptom resolution		
Time to complete resolution of all symptoms.	8.00 (7.00-9.00)	5%
Symptom recurrence		
New or emerging symptoms during entire attack	7.00 (5.00-8.00)	0%
Worsened intensity at 2 h after treatment with study medication	8.00 (6.00-9.00)	2%
Maintenance of significant overall improvement through 24 h after treatment with study medication	8.00 (6.00-8.00)	2%
Rebound angioedema symptoms within 24 h after complete resolution of previous angioedema symptoms	8.00 (7.00-9.00)	3%
Therapeutic failure, defined as any of: (1) beginning of relief of symptoms at >4 h after treatment with study medication, (2) increase in VAS score after initial symptom relief, (3) overall VAS score >0 until 4 h after treatment with study medication for any location that had an overall VAS score of 0 when study medication was administered, (4) use of rescue medication, pain medication, or antiemetics before beginning of relief of symptoms	8.00 (7.00-9.00)	5%
Symptom severity		
Absolute symptom severity at 1 h after treatment with study medication	7.00 (5.00-8.00)	5%
Absolute symptom severity at 8 h after treatment with study medication	6.00 (5.00-8.00)	3%
Resource use		
Need for medical intervention(s) during entire attack	8.00 (7.00-9.00)	5%
Need for rescue medication during entire attack	8.00 (8.00-9.00)	0%
Need for rescue medication before first onset of symptom relief	8.00 (6.00-8.00)	0%
Need for rescue medication at 4 h after treatment with study medication	8.00 (6.00-8.00)	2%
Need for rescue medication at 12 h after treatment with study medication	7.00 (5.25-8.00)	2%
Need for rescue medication at 48 h (2 d) after treatment with study medication	6.00 (4.00-7.00)	2%
Adverse events		
Vomiting episodes at 4 h after treatment with study medication	5.00 (3.00-7.25)	5%

VAS, Visual Analogue Scale.

in the COS using a 9-point Likert scale (1-3 = limited importance; 4-6 = important but not critical; 7-9 = critical,; and unable to score, for panel members lacking the required experience or knowledge regarding specific outcomes). Panelists were free to provide comments on each outcome and to suggest additional outcomes. Median responses and interquartile ranges were calculated for each outcome. These results, together with anonymized comments, were shared with the panelists prior to the start of round 2.

Round 2

Only panelists who completed round 1 were invited to participate in round 2. Based on the results of round 1, the steering committee suggested five key outcomes for inclusion in the COS. These five outcomes were chosen based on comments and suggestions provided by the panelists in round 1. In round 2, panelists were requested to indicate whether they agreed or disagreed with the selection of each of these individual outcomes in the COS and with the proposed COS as a whole. Panelists were also able to indicate abstain from voting if they were unable to decide, and could provide comments on each outcome and the COS as a whole. Consensus was defined as greater than 75% of all panelists in agreement with the inclusion of the selected key outcome or the COS as a whole.

Development of the consensus report

The consensus report was developed based on the results of rounds 1 and 2 and shared with the panelists, together with responses to panelists' comments by the steering group. Feedback

TABLE II. Results of Delphi round 2: consensus on a core outcome set to measure efficacy of acute treatment for hereditary angioedema attacks

Outcomes	Agree	Unable to answer
Change in overall symptom severity at one predetermined point between 15 min and 4 h after treatment (n = 57*)	95%	2%
Time to end of progression of all symptoms (n = 58)	95%	3%
Need for rescue medication during entire attack (n = 58)	95%	2%
Impairment of daily activities (n = 58)	95%	0%
Treatment satisfaction (n = 58)	90%	3%
Core outcome set consisting of these five outcomes (n = 57*)	91%	4%

*One panelist did not answer this question.

from this review was included in a second version of the report, which was shared with and approved for submission by all authors.

Statistical analysis

All statistical analyses and visualizations were performed with R Studio (4.2.1) (R Core Team, Vienna, Austria) and the *Likert* package.[14]

RESULTS

AURORA panel composition

Figure 1 shows a flowchart displaying the Delphi process. A panel consisting of 58 participants from 23 countries completed both Delphi rounds, 42 of whom were clinicians and researchers (72%), 12 were patients (21%), three were representatives of pharmaceutical companies (5%), and one was a representative of a regulatory body (European Medicines Agency) (2%). A total of 19 clinicians and researchers, three patients, two pharmaceutical companies, and one regulatory body (US Food and Drug Administration) refrained from participation. Response rates were 89% (63 of 71) and 92% (58 of 63) in rounds 1 and 2, respectively.

Importance scores of outcomes used in previous trials

Table I lists the scores of the 27 outcomes used in published clinical trials assessing the acute treatment of HAE attacks. A high degree of agreement was observed among the panelists, with the vast majority of outcomes receiving a median score of 7 or higher, indicating that most panelists deemed them of critical importance. The prespecified criterion for wide consensus regarding critical importance of an outcome (lower quartile $\geq$7) was met by 33% of the outcomes (9 of 27), as shown in Table I. Several additional outcomes were suggested by two or more panelists: impairment of everyday activities owing to angioedema; end of progression of angioedema; change in symptom severity at a primary attack location at 1, 2 and 3 hours; treatment satisfaction; and quality of life.

PROTOCOL CHANGE AND CONSENSUS ON FIVE KEY OUTCOMES

According to the original protocol, all nine outcomes that reached wide consensus regarding its critical importance (defined as a lower quartile ranking $\geq$7) would be adopted in the COS, and the 18 outcomes that did not reach consensus regarding importance (defined as a interquartile range including 4-6) would be modified and presented to the panelists in round 2, alongside with seven new outcomes suggested by two or more panelists. The steering committee deemed that this approach would not result in a concise and applicable COS. Hence, a protocol amendment was made. As a result of this protocol amendment, a COS of five key outcomes, suggested by the steering committee, was presented to the panelists in round 2. Consensus regarding this suggested COS was achieved in this second round. The five key outcomes and their respective rates of agreement are listed in Table II. The vast majority of the panelists (>90%) agreed with the selection of each individual key outcome and with the entire COS.

Change in overall symptom severity

The change in overall symptom severity at one predetermined point between 15 minutes and 4 hours after treatment provides useful information about the effect of the study medication. In the suggested COS, the steering committee advised measuring this outcome 1 hour after the administration of study medication, to reflect the need for fast improvement, especially for laryngeal or abdominal attacks. Notably, the panelists suggested that any point between 15 minutes and four hours after treatment can be selected, considering the agent's pharmacodynamics and trial characteristics.

This outcome received 95% agreement. There were some disagreements among panelists regarding the optimal timing of the measurement of this outcome.

Time to end of progression

Patients emphasized the importance of recognizing the very first effects of their acute treatment. To capture the earliest signs, the outcome time to the end of progression of all angioedema symptoms reached a consensus as a key outcome for the COS. Trial participants can be asked to indicate when the angioedema symptoms have ceased progression, therefore reaching a state of stability. Such stabilization may occur simultaneously with an improvement of symptoms.

Including this outcome in the COS received 95% agreement. One panelist voiced the concern that it could be challenging for patients to indicate the exact time to the end of symptoms, and another panelist warned that the reliability of this outcome might be influenced by the late administration of acute treatment.

Need for rescue medication

Analyzing the need for rescue medication during an entire attack reflects the inability of a study medication to provide effective treatment. Trial participants will use rescue medication if they perceive that their symptoms are worsening, improving insufficiently, or lingering even after an initial improvement.

Of all responding panel members, 95% agreed with the inclusion of this outcome. Nonetheless, two panelists advised that this outcome should be time restricted to distinguish between rescue medication used for the same attack or for a subsequent attack. Two others panelists highlighted several factors that could affect the evaluation of this outcome, including contact with the study staff or treating physician, as well as rescue medication costs, availability, convenience, and tolerance. These aspects need to be considered when selecting a measuring instrument.

Impairment of daily activities

Several panelists suggested impairment of daily activities to be an important efficacy outcome. This outcome assesses the capability of study treatments to attenuate the impact of the attack on a patient's daily life activities. Despite interpersonal and intrapersonal variations in the perception of impairment, effective treatment should substantially diminish, and ideally eliminate, the interference of HAE attacks with the ability of patients to maintain daily activities, therefore meeting the recommended treatment goal of leading a normal life.[15]

The inclusion of this outcome in the COS received 95% agreement. Still, two panelists were concerned about the subjectiveness of this outcome. Another panelist noted that a concise HAE-specific PROM focusing on impairment of daily living is required.

Treatment satisfaction

Treatment satisfaction provides important insight into a patient's overall experience with the acute treatment and holds a particular value in guiding patients and physicians for optimal treatment choices in light of the development and availability of acute treatment options and administration routes (ie, oral, subcutaneous, intravenous).

This outcome received 90% agreement. Comments from panelists included concerns that this outcome could be too subjective and that instruments measuring treatment satisfaction specifically for acute treatment are lacking. A comment from a steering committee member underscored that treatment satisfaction mirrors patients' experiences rather than the health status. Consequently, this outcome should be measured by a patient-reported experience measure rather than a PROM.

DISCUSSION

This consensus study achieved a high level of consensus on a COS for measuring the efficacy of the acute treatment of HAE attacks. The panel agreed on five critical outcomes: (1) change in overall symptom severity at one predetermined point between 15 minutes and 4 hours after treatment; (2) time to end of progression of all angioedema symptoms; (3) need for rescue medication; (4) impairment of daily activities; and (5) treatment satisfaction.

The Delphi design allowed for the engagement of a large number of panelists spanning across six continents and 23 countries. In addition, high response rates were observed and consensus was attained by two Delphi rounds, highlighting remarkable agreement among panelists. Although primarily created for outcome assessment in clinical trials, we suggest that the selected COS can be used in a wider range of future studies.

Although all participating groups were represented in this study, it is important to acknowledge that the groups were not equal in size, with an overrepresentation of clinicians and researchers. This disparity might have led to a skewed end result. The high scores provided by panelists for the outcomes presented in the first round show that most outcomes which were applied in past clinical trials are considered valid measures of efficacy in clinical trials assessing acute treatment of HAE attacks. Yet, these high scores also led to a protocol amendment, because the steering committee foresaw that following the original protocol would lead to a COS containing many outcomes that would be too extensive and inapplicable. We further acknowledge that a COS is not exhaustive, and depending on each pharmaceutical compound and specific trial characteristics, additional outcomes may be selected in future trials.

Achieving consensus marks an initial step toward harmonizing trial outcomes for evaluating acute treatment for HAE attacks. Yet, further efforts lie ahead. Although this COS offers valuable guidance on the required outcomes, it does not specify the optimal instruments to measure these outcomes. This requires the use of existing tools or the development and validation of new measurement instruments. Analysis of data from current clinical trials that employ such instruments will yield crucial insights into their validity, reliability, and utility.[16,17] Even greater insights can be gained from studies that directly compare the validity and psychometric properties of multiple instruments.[18] Further collaboration across the clinician, research, and regulatory communities to define the methods for the development, validation, and psychometric properties that any instrument must fulfill would lead to an overarching harmonization, which in turn would facilitate the adoption of this COS, because the approach to clinical outcome assessments has not been unified so far. Ideally, one instrument would be selected for every outcome in the COS, and this instrument would be endorsed by regulators, showcasing the harmonization of efficacy assessment in acute HAE treatment.[19]

This Delphi consensus study achieved a high degree of agreement on a COS consisting of five key outcomes that should be applied to future clinical studies with acute treatment for HAE. The adoption of this COS will allow more meaningful comparison and interpretation of future studies without imposing an excessive burden on trial participants.

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