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LETTER TO THE EDITOR

Definition, aims, and implementation of GA²LEN/HAEi Angioedema Centers of Reference and Excellence

To the Editor,

GA²LEN, the Global Allergy and Asthma European Network, and HAE international (HAEi), the global umbrella organization for the world's hereditary angioedema (HAE) patient groups, have launched their joint ACARE (Angioedema Center of Reference and Excellence) program, within GA²LEN's center of reference and excellence (CORE) initiative. Angioedema is a common, heterogeneous, often debilitating and chronic condition and is frequently a challenge for physicians and affected patients, especially patients suffering from recurrent attacks. Additionally, it can be a challenge for some patients to understand the underlying etiology of their angioedema (Table 1). GA²LEN's CORE networks, such as UCARE for urticaria and ADCARE for atopic dermatitis, help to improve the management of difficult-to-treat conditions. Here, we describe the aims, requirements, provisions, application process, audit, and accreditation protocol for GA²LEN/HAEi ACAREs. ACAREs aim to provide excellence in angioedema management, increase the knowledge of angioedema through research and education, and promote advocacy activities that raise angioedema awareness. To become a certified ACARE, angioedema centers must fulfill 32 requirements, defined by specific provisions that will be assessed during an audit visit. The ACARE program will result in a strong network of angioedema specialists, promote angioedema research and awareness, and harmonize and improve angioedema management globally. ACAREs will expand access to modern angioedema medicines in countries where they are available and help to bring them to countries where they are not.[1]

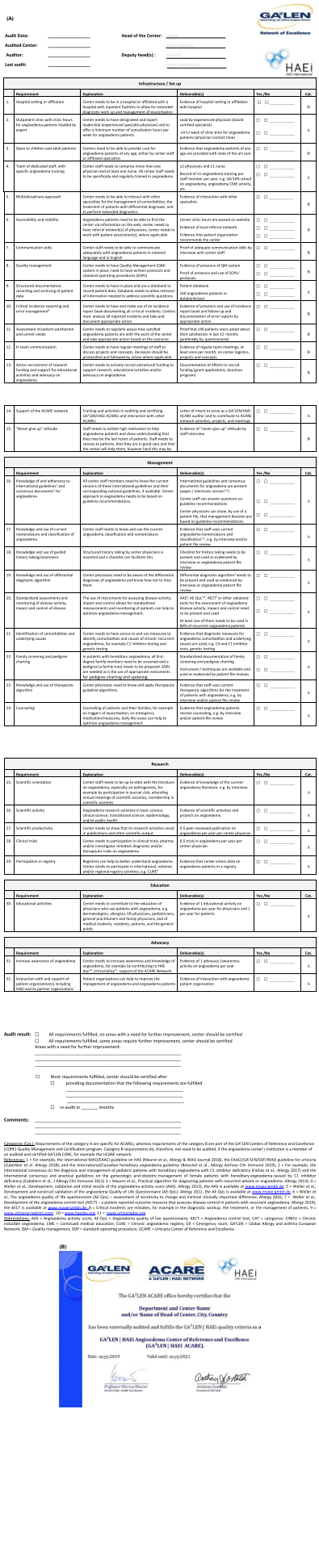
This document summarizes the aims of GA²LEN/HAEi Angioedema Centers of Reference and Excellence (ACAREs) and elaborates the requirements that ACAREs must fulfill to become certified. It also provides (see Appendix S1) background information on GA²LEN and HAEi, including HAEi member organizations and regional patient advocates, on why we need an Angioedema Center of Reference and Excellence (ACARE) program and network, and on the accreditation and certification process, governance and funding, and on the interaction with other GA²LEN networks of centers of reference and excellence. The protocols, aims, requirements, and provisions related to becoming a certified ACARE are based on (a) the experience of the GA²LEN UCARE network and (b) input from angioedema patients, general practitioners, and angioedema specialists.

What are the aims of GA²LEN/HAEi ACAREs? The aims of ACAREs are to set the global standard for excellence in comprehensive angioedema care through research, education, advocacy, and interaction among ACAREs. By serving as referral centers for the diagnosis and management of patients with angioedema, ACAREs will complement the local healthcare system. ACAREs aim to increase knowledge and awareness of angioedema.

TABLE 1 Classification of angioedema

Bradykinin-mediated angioedema				Mast cell mediator-mediated angioedema		Unknown mediator
C1-INH deficiency/ defect		C1-INH normal		IgE mediated	Non-IgE mediated	
Inherited	Acquired	Inherited	Acquired			
HAE-1 HAE-2	AAE-C1-INH	HAE nC1-INH (HAE-FXII, HAE-ANGPTI, HAE-PLG, HAE-KNG1, HAE-UNK)	AE due to medication that interferes with BK degradation, eg ACEi	Angioedema with or without wheals in patients with urticaria Anaphylaxis	Angioedema with or without wheals in patients with urticaria	Idiopathic AE

Abbreviations: AAE-C1-INH, acquired angioedema due to C1-inhibitor deficiency; ACEI-AE, angiotensin-converting enzyme inhibitor-induced angioedema; BK, bradykinin; HAE nC1-INH, hereditary angioedema with normal C1-inhibitor levels, either due to a mutation in factor XII (*F12*), angiopoietin-1 (*ANGPT1*), plasminogen (*PLG*), kininogen-1 (KNG1), or unknown (UNK) (HAE-FXII, HAE-ANGPTI, HAE-PLG, HAE-KNG1, HAE-UNK); HAE-1, hereditary angioedema due to C1-inhibitor deficiency; HAE-2, hereditary angioedema due to C1-inhibitor dysfunction.



(A)

GA²LEN Network of Excellence

Audit Date: _____ Head of the Center: _____
Audited Center: _____
Auditor: _____ Deputy head(s) : _____
Last audit: _____

HAEi

	Requirement	Explanation	Deliverable(s)	Yes /No	Cat.
Infrastructure / Set-up					
1.	Hospital setting or affiliation	Center needs to be in a hospital or affiliated with a hospital with inpatient facilities to allow for extended diagnostic work up and management of exacerbation	Evidence of hospital setting or affiliation with hospital	☐ ☐ _____	B
2.	Outpatient clinic with clinic hours for angioedema patients headed by expert	Center needs to have designated and expert leadership (experienced specialist physician) and to offer a minimum number of consultation hours per week for angioedema patients	Lead by experienced physician (board certified specialist) ≥4 h/week of clinic time for angioedema patients (physician contact time)	☐ ☐ _____ ☐ ☐ _____	A
3.	Open to children and adult patients	Centers need to be able to provide care for angioedema patients of any age, either by center staff or affiliated specialists	Evidence that angioedema patients of any age are provided with state of the art care	☐ ☐ _____	B
4.	Team of dedicated staff, with specific angioedema training	Center staff needs to comprise more than one physician and at least one nurse. All center staff needs to be specifically and regularly trained in angioedema	≥2 physicians and ≥1 nurse Record of ≥1 angioedema training per staff member per year, e.g. GA²LEN school on angioedema, angioedema CME activity, etc.	☐ ☐ _____ ☐ ☐ _____	A
5.	Multidisciplinary approach	Center needs to be able to interact with other specialties for the management of comorbidities, the treatment of patients with differential diagnoses, and to perform extended diagnostics	Evidence of interaction with other specialties	☐ ☐ _____	B
6.	Accessibility and visibility	Angioedema patients need to be able to find the center via information on the web; center needs to have referral network(s) of physicians; center needs to work with patient association(s), where applicable	Center clinic hours are posted on website Evidence of local referral network Evidence that patient organization recommends the center	☐ ☐ _____ ☐ ☐ _____ ☐ ☐ _____	B
7.	Communication skills	Center staff needs to be able to communicate adequately with angioedema patients in national language and in English	Proof of adequate communication skills by interview with center staff	☐ ☐ _____	B
8.	Quality management	Center needs to have Quality Management (QM) system in place, need to have written protocols and standard operating procedures (SOPs)	Evidence of presence of QM system Proof of presence and use of SOPs/ protocols	☐ ☐ _____ ☐ ☐ _____	B
9.	Structured documentation, recording and archiving of patient data	Center needs to have in place and use a database to record patient data. Database needs to allow retrieval of information needed to address scientific questions	Patient database ≥50 angioedema patients in database/year	☐ ☐ _____ ☐ ☐ _____	A
10.	Critical incidence reporting and error management[1]	Center needs to have and make use of an incidence report book documenting all critical incidents. Centers must analyze all reported incidents and take and document appropriate action	Evidence of presence and use of incidence report book and follow up and documentation of error reports by appropriate action	☐ ☐ _____	B
11.	Assessment of patient satisfaction and unmet needs	Center needs to regularly assess how satisfied angioedema patients are with the work of the center and take appropriate action based on the outcome	Proof that ≥90 patients were asked about their satisfaction in last 12 months (preferably by questionnaire)	☐ ☐ _____	B
12.	In-team communication	Center needs to have regular meetings of staff to discuss projects and concepts. Decisions should be protocolled and followed by action where applicable	Evidence of regular team meetings, at least once per month, on center logistics, projects and concepts	☐ ☐ _____	B
13.	Active recruitment of research funding and support for educational activities and advocacy on angioedema	Center needs to actively recruit extramural funding to support research, educational activities and/or advocacy on angioedema	Documentation of efforts to recruit funding (grant applications, donation program)	☐ ☐ _____	B
14.	Support of the ACARE network	Training and activities in auditing and certifying GA²LEN/HAEi ACAREs and interaction with other ACAREs	Letter of intent to serve as a GA²LEN/HAEi ACARE auditor and to contribute to ACARE network activities, projects, and meetings	☐ ☐ _____	A
15.	"Never give up" attitude	Staff needs to exhibit high motivation to help angioedema patients and show understanding that they may be the last resort of patients. Staff needs to convey to patients, that they are in good care and that the center will help them, however hard this may be	Evidence of "never give up" attitude by staff interview	☐ ☐ _____	B
Management					
16.	Knowledge of and adherence to international guidelines[2] and consensus documents[3] for angioedema	All center staff members need to know the current versions of these international guidelines and their corresponding national guidelines, if available. Center approach to angioedema needs to be based on guideline recommendations.	International guidelines and consensus documents for angioedema are present (paper / electronic version [4]) Center staff can answer questions on guideline recommendations Center physicians can show, by use of a patient file, that the management decisions are based on guideline recommendations	☐ ☐ _____ ☐ ☐ _____ ☐ ☐ _____	A
17.	Knowledge and use of current nomenclature and classification of angioedema	Center staff needs to know and use the current angioedema classification and nomenclature	Evidence that staff uses current angioedema nomenclature and classification[5] e.g. by interview and/or patient file review	☐ ☐ _____	A
18.	Knowledge and use of guided history taking/awareness	Structured history taking by center physicians is essential and a checklist can facilitate this.	Checklist for history taking needs to be present and used as evidenced by interview or angioedema patient file review	☐ ☐ _____	A
19.	Knowledge and use of differential diagnostic algorithm	Center physicians need to be aware of the differential diagnoses of angioedema and know how not to miss them.	Differential diagnostic algorithm[6] needs to be present and used as evidenced by interview or angioedema patient file review	☐ ☐ _____	A
20.	Standardized assessments and monitoring of disease activity, impact and control of disease	The use of instruments for assessing disease activity, impact and control allows for standardized measurements and monitoring of patients can help to optimize angioedema management.	AAE², AE-QoL[7], AECT[8] or other validated tools for the assessment of angioedema disease activity, impact and control need to be present and used At least one of them needs to be used in 80% of recurrent angioedema patients	☐ ☐ _____ ☐ ☐ _____	A
21.	Identification of comorbidities and underlying causes	Center needs to have access to and use measures to identify comorbidities and causes of chronic recurrent angioedema, for example C1 inhibitor testing and genetic testing	Evidence that diagnostic measures for angioedema comorbidities and underlying causes are used, e.g. C4 and C1 inhibitor tests, genetic testing	☐ ☐ _____	A
22.	Family screening and pedigree charting	In patients with hereditary angioedema, all first-degree family members need to be screened and a pedigree (a family tree) needs to be prepared. SOPs are needed as is the use of appropriate instruments for pedigree charting and updating.	Standardized documentation of family screening and pedigree charting Instrument / techniques are available and used as evidenced by patient file review	☐ ☐ _____ ☐ ☐ _____	A
23.	Knowledge and use of therapeutic algorithm	Center physicians need to know and apply therapeutic guideline algorithms.	Evidence that staff uses current therapeutic algorithms for the treatment of patients with angioedema, e.g. by interview and/or patient file review	☐ ☐ _____	A
24.	Counseling	Counseling of patients and their families, for example on triggers of exacerbation, on emergency medication/measures, daily life issues can help to optimize angioedema management	Evidence that angioedema patients receive counseling, e.g. by interview and/or patient file review	☐ ☐ _____	A
Research					
25.	Scientific orientation	Center staff needs to be up-to-date with the literature on angioedema, especially on pathogenesis, for example by participation in journal club, attending annual meetings of scientific societies, membership in scientific societies	Evidence of knowledge of the current angioedema literature, e.g. by interview	☐ ☐ _____	A
26.	Scientific activity	Angioedema research activities in basic science, clinical science, translational science, epidemiology, and/or public health	Evidence of scientific activities and projects on angioedema	☐ ☐ _____	A
27.	Scientific productivity	Center needs to show that its research activities result in publications and other scientific output	≥1.5 peer-reviewed publication on angioedema per year per center physician	☐ ☐ _____	A
28.	Clinical trials	Center needs to participation in clinical trials, pharma and/or investigator-initiated, diagnostic and/or therapeutic trials on angioedema	≥1.5 trials in angioedema per year per center physician	☐ ☐ _____	A
29.	Participation in registry	Registries can help to better understand angioedema. Center needs to participate in international, national, and/or regional registry activities, e.g. CURE[9]	Evidence that center enters data on angioedema patients in a registry	☐ ☐ _____	A
Education					
30.	Educational activities	Center needs to contribute to the education of physicians who see patients with angioedema, e.g. dermatologists, allergists, ER physicians, pediatricians, general practitioners and family physicians, and of medical students, residents, patients, and the general public	Evidence of 1 educational activity on angioedema per year for physicians and 1 per year for patients	☐ ☐ _____	A
Advocacy					
31.	Increase awareness of angioedema	Center needs to increase awareness and knowledge of angioedema, for example by contributing to HAE day[10], UrticariaDay[11], support of the ACARE Network	Evidence of 1 advocacy /awareness activity on angioedema per year	☐ ☐ _____	A
32.	Interaction with and support of patient organizations	Patient organizations can help to improve the management of angioedema and angioedema patients	Evidence of interaction with angioedema patient organization	☐ ☐ _____	A

Audit result: ☐ All requirements fulfilled, no areas with a need for further improvement, center should be certified
☐ All requirements fulfilled, some areas require further improvement, center should be certified
Areas with a need for further improvement:
_____
_____
_____

☐ Most requirements fulfilled, center should be certified after
☐ providing documentation that the following requirements are fulfilled
_____
_____
_____
☐ re-audit in _____ months

Comments: _____
_____
_____

Categories (Cat.): Requirements of the category A are specific for ACARELs, whereas requirements of the category B are part of the GA²LEN Centers of Reference and Excellence (CORE) Quality Management and Certification program. Category B requirements do, therefore, not need to be audited, if the angioedema center's institution is a member of or audited and certified GA²LEN CORE, for example the UCARE network.
References: 1 = For example, the international WAO/EAACI guideline on HAE (Maurer et al., Allergy & WAO Journal 2018), the EAACI/GA²LEN/EDF/WAO guideline for urticaria (Zuberbier et al. Allergy 2018), and the International/canadian hereditary angioedema guideline (Betschel et al., Allergy Asthma Clin Immunol 2019); 2 = For example, the international consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency (Farkas et al., Allergy 2017) and the international consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency (Caballero et al., J Allergy Clin Immunol 2012); 3 = Maurer et al., Practical algorithms for diagnosing patients with recurrent wheals or angioedema. Allergy 2013); 4 = Weller et al., Development, validation and initial results of the angioedema activity score (AAS). Allergy 2013), the AAS is available at www.more-aas.de; 5 = Weller et al., Development and construct validation of the angioedema Quality of Life Questionnaire (AE-QoL). Allergy 2012, the AE-QoL is available at www.more-aeqol.de; 6 = Weller et al., The angioedema quality of life questionnaire (AE-QoL) – assessment of sensitivity to change and minimal clinically important difference. Allergy 2016; 7 = Weller et al., Development of the angioedema control test (AECT) – a patient-reported outcome measure that assesses disease control in patients with recurrent angioedema. Allergy 2019), the AECT is available at www.mean-control.de; 8 = Critical incidents are mistakes, for example in the diagnostic work-up, the treatment, or the management of patients; 9 = www.urticaria-registry.com/; 10 = www.haeday.org; 11 = www.urticariaday.org
Abbreviations: AAS = Angioedema activity score; AE-QoL = Angioedema quality of live questionnaire; AECT = Angioedema control tool; CAT = categories; CINDU = Chronic inducible angioedema; CME = Continued medical education; CURE = Chronic angioedema registry; ER = Emergency room; GA²LEN = Global Allergy and asthma European Network; QM = Quality management, SOP = standard operating procedures; UCARE = Urticaria Center of Reference and Excellence.

(B)

GA²LEN ACARE A GA²LEN | HAEi NETWORK HAEi

The GA²LEN ACARE office hereby certifies that the

Department and Center Name
and/or Name of Head of Center, City, Country

has been externally audited and fulfills the GA²LEN | HAEi quality criteria as a

GA²LEN | HAEi Angioedema Center of Reference and Excellence (GA²LEN | HAEi ACARE).

Date: xx.yy.2019 Valid until: xx.yy.2021

Professor Marcus Maurer — Anthony Cavallo

FIGURE 1 A and B, Audit checklist for GA²LEN/HAEi Angioedema Center of Reference and Excellence (ACARE) certification (A) and certificate awarded to GA²LEN/HAEi ACAREs upon a successful audit (B). A, The list shows and explains the requirements for becoming a GA²LEN/HAEi ACARE and the deliverables that are reviewed during the audit process. B, The certificate is awarded for 2 y and requires successful re-audit to be extended

What are the requirements for GA²LEN/HAEi ACAREs? ACAREs are required to demonstrate excellence in the management of angioedema, research activities, efforts in education, and advocacy activity. ACAREs need to fulfill 32 requirements, which are explained in the audit checklist (Figure 1A). This checklist includes specific deliverables for each requirement. For example, the requirement to know and follow international guidelines and consensus documents for angioedema (Requirement #16) entails that physicians and other ACARE healthcare professionals have read and understood the current versions of these guidelines and consensus documents and that their recommendations are implemented in their center.

These guidelines and consensus documents include, for example, the international WAO/EAACI guideline for HAE, the EAACI/GA²LEN/EDF/WAO guideline for urticaria, the International/Canadian hereditary angioedema guideline,[2-5] the international consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency, the international consensus on the use of genetics in the management of HAE,[6] and the international consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency.[7] The deliverables for this requirement are that (a) current guideline and consensus document versions are present (paper or electronic version) at the center, (b) ACARE staff can answer questions on the recommendations these documents provide, and (c) ACARE physicians can show, upon request, by use of a patient file, that patient management decisions are based on guideline recommendations (Figure 1B).

This publication marks our intent to start the implementation of the GA²LEN/HAEi ACARE initiative. Specialty centers for angioedema have started to apply to become ACAREs, and audits and certifications are ongoing (Figure 1B). We expect that most GA²LEN UCARE centers and many angioedema specialty centers will become ACAREs in the near future. We predict and hope that by 2022, GA²LEN/HAEi ACAREs will be established in every continent. This will result in a strong global network of angioedema specialists, promote angioedema research, and harmonize and improve angioedema management worldwide. GA²LEN and HAEi will measure the impact of ACAREs over time and document and report the benefits of this initiative. ACARE network activities and a current list of ACAREs are posted on the network's website (www.acare-network.com).

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CONFLICT OF INTEREST

Dr Maurer reports grants and personal fees from Allakos, personal fees from Aralaz, grants and personal fees from AstraZeneca, grants and personal fees from BioCryst, grants from Blueprint, grants and personal fees from CSL Behring, grants and personal fees from FAES, grants and personal fees from Genentech, grants from Kalvista, grants from Lilly, grants from Menarini, grants and personal fees from Novartis, grants from Leo Pharma, grants from Moxie, grants from Pharming, personal fees from Pharvaris, grants and personal fees from Roche, from Sanofi, grants and personal fees from Shire/Takeda, grants and personal fees from UCB, grants and personal fees from Uriach, outside the submitted work. Dr Aberer reports other from Takeda, other from CSL Behring, outside the submitted work. Dr Ansotegui reports personal fees from Mundipharma, personal fees from Roxall, personal fees from Sanofi, personal fees from MSD, personal fees from Faes Farma, personal fees from Hikma, personal fees from Astra Zeneca, personal fees from Stallergens, outside the submitted work. Dr Aygören-Pürsün reports personal fees from Adverum, grants and personal fees from BioCryst, grants and personal fees from CSL Behring, grants and personal fees from Kalvista, personal fees from Pharming, grants and personal fees from Shire/Takeda, during the conduct of the study. Dr Banerji reports grants from Takeda, BioCryst, personal fees from Takeda, BioCryst, CSL, Pharming, Pharvaris, Kalvista, outside the submitted work. Dr Aberer reports other from Takeda, other from CSL Behring, outside the submitted work. 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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.