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## Definition, aims, and implementation of GA 2 LEN/HAEi Angioedema Centers of Reference and Excellence

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#### SUPPORTING INFORMATION

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

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## Definition, aims, and implementation of GA<sup>2</sup>LEN/HAEi Angioedema Centers of Reference and Excellence

To the Editor,

GA<sup>2</sup>LEN, 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 GA<sup>2</sup>LEN'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). GA<sup>2</sup>LEN'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 GA<sup>2</sup>LEN/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.<sup>1</sup>

This document summarizes the aims of GA<sup>2</sup>LEN/HAEi Angioedema Centers of Reference and Excellence (ACAREs) and elaborates the requirements that ACAREs must fulfill to become

**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	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), angiotensin-converting enzyme 1 (ACE1), 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.

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(A)

**GALEN**  
Network of Excellence

**HAEi**

Audit Date: \_\_\_\_\_ Head of the Center: \_\_\_\_\_  
 Audited Center: \_\_\_\_\_  
 Auditor: \_\_\_\_\_ Deputy Auditor: \_\_\_\_\_  
 Last audit: \_\_\_\_\_

Introduction / Not up					
Requirement	Description	Subscribed	Yes/No	Yes	No
1. Professionalism or affiliation	Center needs to be a hospital or affiliated with a medical school or a center for research and/or patient care (academic or non-academic).	Center must be a hospital or affiliated with a medical school or a center for research and/or patient care (academic or non-academic).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Professional staff with relevant training and qualifications	Center needs to have a multidisciplinary team including physicians (allergists, immunologists) and other relevant staff (nurses, dietitians, etc.) with relevant training and qualifications for angioedema patients.	Center must have a multidisciplinary team including physicians (allergists, immunologists) and other relevant staff (nurses, dietitians, etc.) with relevant training and qualifications for angioedema patients.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Open to children and adolescents	Center needs to be able to provide care for angioedema patients of all ages, with a focus on children and adolescents.	Center must be able to provide care for angioedema patients of all ages, with a focus on children and adolescents.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Have multidisciplinary with specific angioedema training	Center staff needs to have specific training in the management of angioedema, including for children and adolescents.	Center staff must have specific training in the management of angioedema, including for children and adolescents.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Multidisciplinary approach	Center needs to be able to provide care for angioedema patients of all ages, with a focus on children and adolescents.	Center must be able to provide care for angioedema patients of all ages, with a focus on children and adolescents.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Accessibility and visibility	Angioedema patients need to be able to find the center via information on the web, via social media, and other relevant channels. Where applicable, center needs to have patient testimonials, where applicable.	Center must be able to find the center via information on the web, via social media, and other relevant channels. Where applicable, center needs to have patient testimonials, where applicable.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Communication skills	Center staff needs to be able to communicate effectively with angioedema patients in their own language.	Center staff must be able to communicate effectively with angioedema patients in their own language.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Quality management	Center needs to have Quality Management (QM) system in place, including a standard operating procedure (SOP).	Center must have Quality Management (QM) system in place, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Structural documentation	Center needs to have a structural documentation system in place, including a standard operating procedure (SOP).	Center must have a structural documentation system in place, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Critical incidents reporting and your management	Center needs to have a critical incidents reporting system in place, including a standard operating procedure (SOP).	Center must have a critical incidents reporting system in place, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Assessment of current practice and patient needs	Center needs to have a system in place to assess current practice and patient needs, including a standard operating procedure (SOP).	Center must have a system in place to assess current practice and patient needs, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. In-house consultation	Center needs to have a system in place to provide in-house consultation, including a standard operating procedure (SOP).	Center must have a system in place to provide in-house consultation, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Active participation of research funding and support for educational activities and education	Center needs to have a system in place to provide research funding and support for educational activities and education, including a standard operating procedure (SOP).	Center must have a system in place to provide research funding and support for educational activities and education, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

(B)

Management					
Requirement	Description	Subscribed	Yes/No	Yes	No
14. Support of the ACARE network	Center needs to be a member of the ACARE network and participate in its activities.	Center must be a member of the ACARE network and participate in its activities.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Research and innovation	Center needs to have a system in place to support research and innovation, including a standard operating procedure (SOP).	Center must have a system in place to support research and innovation, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Knowledge and use of current evidence	Center needs to have a system in place to ensure that staff are up-to-date on current evidence, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on current evidence, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Knowledge and use of differential diagnosis algorithm	Center needs to have a system in place to ensure that staff are up-to-date on differential diagnosis algorithms, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on differential diagnosis algorithms, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Individualized assessment and treatment of disease severity, impact and control of disease	Center needs to have a system in place to ensure that staff are up-to-date on individualized assessment and treatment of disease severity, impact and control of disease, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on individualized assessment and treatment of disease severity, impact and control of disease, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Identification of comorbidities and underlying causes	Center needs to have a system in place to ensure that staff are up-to-date on identification of comorbidities and underlying causes, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on identification of comorbidities and underlying causes, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Family counseling and patient therapy	Center needs to have a system in place to ensure that staff are up-to-date on family counseling and patient therapy, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on family counseling and patient therapy, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Knowledge and use of therapeutic algorithms	Center needs to have a system in place to ensure that staff are up-to-date on therapeutic algorithms, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on therapeutic algorithms, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Counseling	Center needs to have a system in place to ensure that staff are up-to-date on counseling, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on counseling, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Research					
Requirement	Description	Subscribed	Yes/No	Yes	No
23. Research excellence	Center needs to have a system in place to ensure that staff are up-to-date on research excellence, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on research excellence, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Scientific activity	Center needs to have a system in place to ensure that staff are up-to-date on scientific activity, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on scientific activity, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Scientific productivity	Center needs to have a system in place to ensure that staff are up-to-date on scientific productivity, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on scientific productivity, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Clinical trials	Center needs to have a system in place to ensure that staff are up-to-date on clinical trials, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on clinical trials, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Participation in registries	Center needs to have a system in place to ensure that staff are up-to-date on participation in registries, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on participation in registries, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Education					
Requirement	Description	Subscribed	Yes/No	Yes	No
28. Educational activities	Center needs to have a system in place to ensure that staff are up-to-date on educational activities, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on educational activities, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Activity					
Requirement	Description	Subscribed	Yes/No	Yes	No
29. Increase awareness of angioedema	Center needs to have a system in place to ensure that staff are up-to-date on increasing awareness of angioedema, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on increasing awareness of angioedema, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. Interaction with and support of patient organizations	Center needs to have a system in place to ensure that staff are up-to-date on interaction with and support of patient organizations, including a standard operating procedure (SOP).	Center must have a system in place to ensure that staff are up-to-date on interaction with and support of patient organizations, including a standard operating procedure (SOP).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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 Area with a need for further improvement: \_\_\_\_\_  
 Most requirements fulfilled, center should be certified after providing documentation that the following requirements are fulfilled: \_\_\_\_\_  
 no audit in \_\_\_\_\_ months

Comments: \_\_\_\_\_

**GALEN** EAACI  
The GALEN 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 GALEN HAEi quality criteria as a GALEN HAEi Angioedema Center of Reference and Excellence (GALEN HAEi ACARE).  
 Date: 06/20/2019 Valid until: 06/20/2021

FIGURE 1 A and B, Audit checklist for GA<sup>2</sup>LEN/HAEi Angioedema Center of Reference and Excellence (ACARE) certification (A) and certificate awarded to GA<sup>2</sup>LEN/HAEi ACAREs upon a successful audit (B). A, The list shows and explains the requirements for becoming a G<sup>A2</sup>LEN/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

certified. It also provides (see Appendix S1) background information on GA<sup>2</sup>LEN 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 GA<sup>2</sup>LEN 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 GA<sup>2</sup>LEN UCARE network and (b) input from angioedema patients, general practitioners, and angioedema specialists.

What are the aims of GA<sup>2</sup>LEN/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.

What are the requirements for GA<sup>2</sup>LEN/HAEi ACAREs? ACAREs are required to demonstrate excellence in their center 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/GA<sup>2</sup>LEN/EDF/WAO guideline for urticaria, the International/Canadian hereditary angioedema guideline,<sup>2-5</sup> 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,<sup>6</sup> and the international consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency.<sup>7</sup> 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 GA<sup>2</sup>LEN/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 GA<sup>2</sup>LEN UCARE centers and many angioedema specialty centers will become ACAREs in the near future. We predict and hope that by 2022, GA<sup>2</sup>LEN/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. GA<sup>2</sup>LEN 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](http://www.acare-network.com)).

#### ACKNOWLEDGMENTS

The GA<sup>2</sup>LEN/HAEi ACARE is supported by its twin network, the GA<sup>2</sup>LEN UCARE network ([www.ga2len-ucare.com](http://www.ga2len-ucare.com)). We thank Beate Schinzel for expert help with formatting and revising the manuscript as well as its submission.

#### 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. Dr Bernstein reports grants and personal fees from Shire/Takeda, grants and personal fees from CSL Behring, grants and personal fees from BioCryst, grants and personal fees from Kalvista, grants from IONIS, grants and personal fees from Novartis/Genentech, grants and personal fees from Astra Zeneca, grants and personal fees from Sanofi Regeneron, from HAEA MAB, during the














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#### SUPPORTING INFORMATION

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