

## C1 inhibitor deficiency: 2014 United Kingdom Consensus Document

**Short title:** 2014 UK HAE Consensus

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**Glossary of Abbreviations**

HAE	Hereditary angioedema
AAE	Acquired angioedema
UK PIN	UK Primary Immunodeficiency Network
HAE UK	Hereditary Angioedema UK
UK	United Kingdom

## Summary

C1 inhibitor deficiency is a rare disorder manifesting with recurrent attacks of disabling and potentially life-threatening angioedema. Here we present an updated 2014 United Kingdom consensus document for the management of C1 inhibitor-deficient patients, representing a joint venture between the United Kingdom Primary Immunodeficiency Network and Hereditary Angioedema UK. To develop the consensus, we assembled a multi-disciplinary steering group of clinicians, nurses and a patient representative. This steering group first met in 2012, developing a total of 48 recommendations across 11 themes. The statements were distributed to relevant clinicians and a representative group of patients to be scored for agreement on a Likert scale. All 48 statements achieved a high degree of consensus, indicating strong alignment of opinion. The recommendations have evolved significantly since the 2005 document, with particularly notable developments including an improved evidence base to guide dosing and indications for acute treatment, greater emphasis on home therapy for acute attacks and a strong focus on service organisation.

## Introduction

C1 esterase inhibitor deficiency (C1 inhibitor deficiency) is a rare disorder that may be genetic (hereditary angioedema, HAE) [1] or less commonly acquired (acquired angioedema, AAE) [2]. The disease has an estimated prevalence of 1: 50 000; any ethnic group may be affected, and many cases are undiagnosed [3-5]. C1 inhibitor deficiency manifests with episodic attacks of bradykinin-mediated localised subcutaneous and/ or submucosal swellings, with a predilection for the face, extremities, gut, genitals, oro-pharynx and upper respiratory tract [6]. Abdominal attacks are extremely painful and disruptive, whilst laryngeal swelling is life-threatening and accounts for the very significant lifetime mortality reported from historical data [6-8].

The evidence base for disease management has expanded significantly since the first United Kingdom (UK) consensus document was published in 2005 [9]. For acute therapy, extensive data are now available for two new drugs that target the bradykinin pathway [10-17], for two established plasma-derived C1 inhibitor replacement products [18-20] and for a novel recombinant C1 inhibitor concentrate product [21-23]. Further evidence supports the use of home therapy for acute attacks, an approach with clear benefits for patients and the wider health economy [24-28]. The effectiveness of regular C1 inhibitor concentrate injections for long-term prophylaxis is now more firmly established, presenting an alternative to attenuated androgens for selected patients [19, 29]. In parallel with these advances in medical management, focused research efforts have revolutionised our understanding of the impact of C1 inhibitor deficiency on the physical, emotional and economic health of patients and their families [5, 30-34], thus informing the application of this improved evidence base.

A number of documents have translated these data into evidence-based guidelines [24, 35-40], but none fully reflect the priorities and organisation of services for C1 inhibitor-deficient patients in the United Kingdom. With these considerations in mind, The United Kingdom Primary Immunodeficiency Network (UK PIN – a cross-disciplinary professional association) and the patient group Hereditary Angioedema UK (HAE UK) jointly commissioned this project to update the 2005 UK Consensus Document.

Several considerations are particularly pertinent to the context of this document. The United Kingdom National Health Service is dealing with unprecedented financial pressure, and whilst successive governments have continued to pledge commitment to a healthcare system that is free at the point of demand, traditional hospital-based models of health care are unlikely to be affordable for the UK in the long-term. Recent government initiatives have focused on community and patient-centred ‘integrated’ care, both as a means to ensure long-term affordability and to improve social and medical outcomes [41]. There has also been increased awareness of rarer diseases, with the needs of affected patients recognised in UK initiatives [42]. Finally, there is a perception that the provision of specialist services for C1 inhibitor-deficient patients varies geographically [43], with possible underlying factors including the availability of funding for high-cost drugs and the location of major centres of expertise.

In England, these considerations have contributed to radical reform of specialist services for patients with C1 inhibitor deficiency and other rare diseases: centralised funding has been devolved to NHS England, with the commissioning specification encouraging expert patient-centred care, co-ordinated by specialist centres that fulfil predefined standards [44]. The organisation of services in other UK Nations differs: in Wales, all patients access services at

the Immunodeficiency Centre in Cardiff, with centrally commissioned resources transferred from Health Boards; in Scotland, patients access local services or travel across Unitary Health Board areas where this is not possible, with high-cost medicines accessed through a Pharmacy Board structure overseen by the Scottish Medicines Committee; in Northern Ireland, services are centralised to the Regional Immunology Service in Belfast, with a local process for the approval of high-cost drugs.

It was not felt appropriate to replicate the excellent work that has produced a plethora of recent evidence-based guidelines in the field of C1 inhibitor deficiency [24, 35-40]. Instead, we sought to produce a UK-specific document that is complementary to existing guidelines.

To achieve this aim, the guidelines have been produced using the Delphi method, a structured process that aims to produce consensus amongst a group of experts. We report here the consensus process and statements that were ultimately approved. This document, together with standards for specialist services issued by UK-PIN [45], provides a framework for the management of C1 inhibitor-deficient patients in the United Kingdom.

## Methods

The research design for the consensus was based on the Delphi method: respondents are presented with a series of statements, each of which is scored for agreement using a 4-point Likert scale as follows: strongly agree, tend to agree, tend to disagree, strongly disagree. Following the first round of responses, any statements considered contentious (typically less than 66% of respondents agree) may be reviewed, with the final list of statements representing the consensus.

The questionnaire was developed by The HAE Consensus Steering Group, which included a patient representative, eight physicians with a specialist interest in the disease and three specialist nurses. Through a day of discussion on 26 September 2012, the Steering Group agreed a total of 48 consensus statements across 11 themes. When developing these statements, the Steering Group considered developments in the evidence base, published guidelines for specialist services (44, 45) and personal experiences. The statements were incorporated into a consensus questionnaire, with a slightly modified plain language version generated for patient use. Questionnaires were sent to all UK-based physicians and specialist nurses known to be involved in the management of C1 inhibitor-deficient patients, and additionally to the membership of key professional organisations (**Table 1**). Patients were invited to express their opinion by HAE UK. Two subsequent opportunities to complete the questionnaire were provided by electronic mail, and additional paper copies were distributed at professional and academic meetings.

The process was facilitated by Triducive Ltd, who collated the anonymised data for consideration by the panel. A second meeting was held in on 18 November 2013 to discuss the findings and approve the consensus statements.

Accepted Article



## Results

91 health care workers (51 consultant immunologists and/ or allergists, 10 specialist registrars training in clinical immunology or allergy, 14 immunology specialist nurses, 16 other or unknown designations) responded, representing the majority of health care professionals who actively care for this patient group. A total of 36 patients with C1 inhibitor deficiency responded. All four nations within the United Kingdom were represented amongst respondents.

The consensus statements are listed in **Table 2**. A high degree of consensus was obtained during the first round, with over 90% of respondents indicating 'strongly agree' or 'tend to agree' to all of the statements and few abstentions (**supplementary Table S1**). As all statements achieved consensus in excess of 90%, no iterative amendment was required.

Consensus was highest amongst patient respondents, with over 97% agreement to all statements. Amongst healthcare workers, agreement of >90% was achieved in response to 47 of 48 questions; statement 20 - concerning use of antifibrinolytics in prophylaxis - achieved 88.8% agreement. In general, most statements elicited 'strong agreement', with 'tend to disagree' and 'strongly disagree' rarely observed. Consensus remained extremely high when analysed by occupation or specialty, although small numbers limit the interpretation of subgroup analysis. Alignment of these statements to accreditation standards for specialist centres published by UK-PIN is described in **supplementary Table S2**.

A facility for freetext comments was utilised by a minority of respondents to comment on the statements and study process: one respondent criticised the document for being too 'centralist' and another suggested that the definition of 'specialist centre' should be kept

flexible enough to allow for different models of care. Some questions (for example concerning children, or new medications) were indicated as inappropriate for those without specific expertise. We note that some respondents did not comment on all statements, presumably denoting lack of expertise or opinion as regards a particular statement (see **supplementary Table S1**).

## Discussion

We present here an updated UK consensus for the management of patients with C1 inhibitor deficiency. The consensus was developed using the Delphi method, an established process for the collation of opinion from a group of experts. According to this process, respondents indicate agreement with statements in rounds; after each round, facilitators collate and anonymised the responses to guide amendment of the statements for future rounds. The process is completed when pre-defined levels of consensus are reached. This method was pursued in order to produce guidelines that are complementary to recent publications [24, 35-40] and with an emphasis on UK services.

The consensus has evolved significantly since the previous 2005 UK document. A particularly important development is an improved evidence base to guide the management of acute attacks. The dosing of C1 inhibitor concentrate (statement 17) was particularly emphasised given the availability of guidance from robust trial data [18-21]. However, clinical experience suggests that individualised dosing is appropriate, including higher doses where treatment is delayed and lower doses when treatment is immediately available (statement 18). In keeping with other recent guidelines [24, 35-40], the document supports the wider use of acute treatment for disabling attacks (statement 3) rather than limiting treatment to severe episodes. Statement 3 (treatment of HAE should follow international guidance and standards, whilst considering the resources available in the UK) and statement 12 (patients should take medication according to clinical need rather than financial considerations) could perhaps be considered to conflict. We would emphasise however that as currently worded, the consensus for statements 2 and 3 does not mandate treatment for all attacks - rather, less serious attacks are considered to be *potentially* treatable. Consideration

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of treatment costs will form part of the decision process when weighing up whether symptoms are sufficiently disabling to warrant therapy within the parameters of statement 12. Regarding long-term prophylaxis, the value of closely-monitored androgens with appropriate monitoring is endorsed (statements 19-25). A greater emphasis is placed on long-term prophylaxis with C1 inhibitor concentrate (statement 27), reflecting an improved evidence base [19, 29] and increased experience amongst clinicians and patients. Long-term prophylaxis with tranexamic acid continues to be supported in the paediatric setting where options are limited (statement 46). A more guarded statement was supported (with 88.9% consensus amongst healthcare workers) for the general use of this agent for long-term prophylaxis (statement 20); this was the only statement to achieve consensus below 90%, reflecting a weak evidence base and mixed practice.

Saule and colleagues published an observational series including 16 women with hereditary angioedema, describing modest benefit from progestagens in long-term prophylaxis [46]. The authors recommended either desogestrel 75mg daily ('Cerazette'), medroxyprogesterone acetate (Depo-Provera) or norethisterone 10mg daily. The latter two options provide a higher dose and possibly a higher response rate. A statement about the role of progestagens as long-term prophylaxis was not included in this document because the relevant paper was not published at the time of the steering group meeting.

The results also indicate strong consensus on aspects of service organisation and delivery, showing overwhelming support for specialist services (statements 5-9), patient self-management and home therapy (statement 4). We welcome the principle of patient-centred, community-based care, supported by easily accessible specialist expertise and, where appropriate, local centres. The haemophilia model of self-administration of intravenous

medications by patients and their families demonstrates that this model is feasible and cost-effective. The net financial effects of such an approach as applied to C1 inhibitor deficiency in the UK have not been defined, but data from Denmark demonstrates the benefits of the approach in reducing hospital attendance and the burden of disease [47]. The results of the consensus clearly indicate that both patients and healthcare workers endorse this model for C1 inhibitor deficiency, in order to ensure that patients can achieve their full potential by early education and training in the prevention and management of acute attacks.

Some important performance characteristics of the Delphi method should be considered.

The consensus involves scientific evidence, but does not involve rigorous review of scientific evidence in order to produce guidance. This has produced a document that is complementary to existing guidelines from other bodies. It does not seek to replicate or replace their work, but rather adds another form of expert opinion evidence to the literature. Compared to the generation of evidence-based guidelines by small panels of experts, the Delphi method is more inclusive and gathers opinion from a larger number of professionals. The anonymity of respondents may temper domination of the process by opinion leaders and encourages free expression. However, the issue is not completely resolved as the question set is determined by a steering group.

Another key difficulty is selection of the panel members: a very inclusive process may produce an invalid consensus by including responses from respondents who lack expertise in the field, whereas an overly exclusive process may not reflect a true consensus. We attempted to engage with a wide variety of stakeholders outside the Clinical Immunology and Allergy Community by collaborating with relevant professional bodies, distributing paper copies at professional meetings and permitting peer-to-peer distribution of questionnaires.

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A significant number of responses were obtained from outside the Immunology & Allergy Community, which in addition to 51 responses from Clinical Immunologists and/ or Allergists is felt to capture the large majority of healthcare workers directly involved in the management of this disease. As these respondents work independently in specialist centres throughout the UK, we can be confident that the remarkably high consensus does not reflect training or service led by small number of opinion leaders. However, it must be acknowledged that the UK Allergy & Immunology Community constitutes a small group with a longstanding tradition of cooperation through organisations such as UK-PIN. In addition, the methodology does not permit the calculation of a defined response rate. Compared to the healthcare worker dataset, results from patient respondents are less robust due to relatively small numbers (n=36) and the risk of ascertainment bias.

The assumption that all participants are equal in terms of knowledge and experience represents another weakness of the methodology. This probably accounts for a relatively high number of abstentions amongst respondents for several more technical statements, notably 24, 25, 45 and 46. Finally, where successive rounds are utilised, the risk is that the process may mould opinion rather than simply collate opinion; this was not a concern in this project as consensus was reached within a single round. Despite the shortcomings, the very high level of consensus amongst healthcare workers and a small sample of patients do indicate strong alignment of opinion.

This project has not explicitly addressed hereditary bradykinin-mediated angioedema that is not related to C1 inhibitor deficiency [48], but many of the statements would be applicable to this group, whose specific needs are also addressed in a separate consensus document [49].

Although the document is UK-centric, the themes of quality improvement, patient-centred

care and increasing healthcare costs are a focus and challenge for most higher-income nations at the current time.

Whilst responses are confidential and not individually available to the steering committee, those responding have been invited to publically support this paper. 64 of 91 health care professionals indicated their publicly declared support and are listed (**Table 3**) as the UK 2014 C1 Inhibitor Deficiency Consensus Group.

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All authors contributed to the consensus process as members of the Steering Committee. The manuscript was written by Dr Longhurst and Dr Tarzi and critiqued by all authors.

### **Conflicts of Interest**

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Dr Longhurst is a medical advisor to HAE UK. She has received funding to attend conferences and other educational events, acted as medical advisor or speaker, has received donations to her departmental funds and has received financial and other assistance with patient care projects from the following companies: Biocryst, CSL Behring, SOBI Biovitrum, Shire, Dyax and Viropharma. Dr Tarzi has received travel grants from Shire and Viropharma, has provided remunerated in-house training to staff at CSL-Behring and has attended advisory boards hosted by Shire, Viropharma and Swedish Orphan Biovitrum. John Dempster has received travel grants from Shire, Viropharma and CSL-Behring. He has provided remunerated in-house training to staff at CSL-Behring and has attended advisory boards hosted by Shire, Viropharma and CSL-Behring. Fran Ashworth has received travel grants from Shire and attended advisory panels hosted by Shire and CSL-Behring. Dr Claire Bethune has received travel grants to attend scientific meetings and attended advisory boards hosted by Shire, Viropharma and CSL-Behring. Christine Symons has received travel grants from Shire, CSL Behring, and Viropharma. She has attended advisory boards for Shire and Viropharma and contributed to the construction of CSL-Behring HAE website. She is a Nurse advisor to HAE UK. David Edgar has received travel grants from Shire and CSL Behring and attended an advisory board for CSL-Behring. Dr Mark Gompels has been a member of advisory panels for Shire, CSL-Behring and Viropharma. Dr Suranjith Seneviratne has received travel grants to attend scientific meetings and attended advisory boards hosted by Shire, SOBI Biovitrum and Viropharma.



<b>Professional Organisation</b>
Association of Clinical Pathologists
British Association of Dermatologists
British Dental Association
British Society for Allergy and Clinical Immunology
British Society for Immunology
College of Emergency Medicine
Institute of Biomedical Science
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of Pathologists

**Table 1: Professional Societies invited to participate in the consensus process**

**Table 2: Consensus statements**

Uploaded separately

Accepted Article

Ms Karen Abrams, Specialist Nursing Practitioner in Immunology, Oxford University Hospitals NHS Trust  
Dr Hana Alachkar, Consultant Immunologist, Salford Royal NHS Foundation Trust  
Dr Peter Arkwright, Senior Lecturer&Honorary Consultant Paediatric Immunologist, University of Manchester  
Dr.Gururaj Arumugakani, Specialist Registrar in Immunology, Leeds Teaching Hospitals NHS Trust  
Mrs Fran Ashworth, Clinical Nurse Specialist in Immunology, Sheffield Teaching Hospitals NHS Trust  
Dr Amolak S Bansal, Consultant in Immunology and Allergy, Epsom and St Helier University Hospitals NHS Trust  
Dr Claire Bethune, Consultant Immunologist, Plymouth Hospitals NHS Trust  
Dr. Malini Bhole, Consultant Immunologist, The Dudley Group NHS Foundation Trust  
Dr Matthew Buckland, Consultant Immunologist, Barts Health NHS Trust, London  
Dr Catherine Cale, Consultant Paediatric Immunologist, Great Ormond Street Hospital NHS Foundation Trust  
Dr Anita Chandra, Clinical Immunologist, Cambridge University Hospitals NHS Foundation trust  
Dr Ignatius Chua, Specialist Registrar in Immunology, Barts Health NHS Trust  
Dr Sheila Clark, Consultant Dermatologist, Mid Yorkshire and Leeds Teaching Hospitals NHS Trusts  
Professor Christopher Corrigan, Professor of Allergy, Asthma & Respiratory Science, Kings College London  
Mr John Dempster, Immunology Nurse Specialist, Barts Health NHS Trust  
Dr Tina A Dixon, Consultant Allergist, Royal Liverpool and Broadgreen University Hospital NHS Trust  
Dr Philip Dore, Consultant Immunologist, Hull & East Yorkshire Hospitals NHS Trust  
Dr Michael Duddridge, Consultant Clinical Immunologist, University Hospitals of Leicester NHS Trust  
Dr David Edgar, Consultant Immunologist, The Royal Hospitals, Belfast  
Dr Efreem Eren, Consultant Immunologist, University Hospital Southampton NHS Foundation Trust  
Mrs Alex Farragher, Immunology Specialist Nurse,Central Manchester University Hospitals NHS Foundation Trust  
Dr TJ Flood, Consultant in Paediatric Immunology, The Newcastle upon Tyne Hospitals NHS Trust  
Dr Tomaz Pereira Garcez, Consultant Immunologist, Central Manchester University Hospitals NHS Foundation Trust  
Dr Mark Gompels, Consultant Immunologist, North Bristol NHS Trust  
Dr Clive Grattan, Consultant Dermatologist, Norfolk and Norwich Hospitals NHS Trust  
Dr Elizabeth Griffiths, SpR in Allergy, Guys and St Thomas's NHS Trust, London  
Dr Sofia Grigoriadou, Consultant Immunologist, Barts Health NHS Trust  
Professor Tim Harris, Professor of Emergency Medicine, Barts Health NHS Trust  
Dr Grant Hayman, Consultant Clinical Immunologist, Epsom & St Helier University Hospitals NHS Trust  
Dr Richard Herriot, Consultant Immunologist, Aberdeen Royal Infirmary  
Dr Archana Herwadkar, Consultant Immunologist, Salford Royal NHS Foundation Trust  
Dr Aarnood Huissoon, Consultant Immunologist, Heart of England NHS Foundation Trust  
Dr Rashmi Jain, Consultant Immunologist, Oxford University Hospitals NHS Trust

Dr Stephen Jolles, Consultant Immunologist, University Hospital of Wales  
 Dr M Yousuf Karim, Consultant Immunologist, Frimley Park Hospitals NHS Foundation Trust&The Royal Surrey County Hospital NHS Foundation Trust  
 Dr DS Kumararatne Consultant Immunologist, Cambridge University Hospitals NHS Trust  
 Dr Hilary Longhurst, Consultant Immunologist, Barts Health NHS Trust  
 Ms Lorena Lorenzo, Immunology Specialist Nurse, Barts Health NHS Trust  
 Dr Joanna, Lukawska, Locum Consultant Allergist, Royal National Throat Nose and Ear Hospital  
 Dr John Maher, Senior Lecturer in Immunology&Honorary Consultant Immunologist, King's College London  
 Miss Clare Malcolmson, Clinical Nurse Specialist in Immunology, Great Ormond Street Hospital NHS Foundation Trust  
 Dr Ania Manson, SpR in Clinical Immunology, Barts Health NHS Trust  
 Ms Gail Menzies, Immunology Nurse Specialist, Ninewells Hospital Dundee  
 Dr Joanne Miller, Specialist Registrar in Clinical Immunology, Oxford University Hospitals NHS Trust  
 Dr Vasantha Nagendran, Consultant Immunologist, Epsom and St Helier University Hospitals NHS Trust  
 Dr Iman Nasr, SpR in Immunology, Barts Health NHS Trust  
 Dr Sadia Noorani, Consultant Immunologist, Sandwell and West Birmingham NHS Trust  
 Dr D G Paige, Consultant Dermatologist, Barts Health NHS Trust, London  
 Dr Andrew Riordan, Consultant in Paediatric Infectious Diseases and Immunology, Alder Hey Children's NHS Foundation Trust  
 Ms Carol Ross, Specialist Nursing Practitioner in Clinical Immunology, Oxford University Hospitals NHS Trust  
 Dr Sinisa Savic, Consultant Clinical Immunologist, Leeds Teaching Hospitals NHS Trust  
 Dr Suranjith Seneviratne, Consultant Immunologist, Royal Free London NHS Foundation Trust  
 Dr Ravishankar Sargur, Consultant Immunologist, Sheffield Teaching Hospitals NHS Foundation Trust  
 Dr Anna Shrimpton, Consultant Immunologist, Sheffield Teaching Hospitals NHS Foundation Trust  
 Mr Craig Simon, Immunology Nurse Specialist, Royal Liverpool & Broadgreen University Hospitals NHS Trust  
 Dr Catherine Stroud, Consultant Immunologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust  
 Mrs Christine Symons, Nurse Consultant in Immunology, Plymouth Hospitals NHS Trust  
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 Dr Moira J Thomas, Consultant Immunologist, Gartnavel General Hospital Glasgow  
 Dr Andrew P Volans, Consultant in Emergency Medicine, York Teaching Hospital NHS Foundation Trust  
 Ms Ruth Weldon, Clinical Nurse Specialist Immunology & Allergy, Nottingham University Hospitals NHS Trust  
 Dr Paul Williams, Consultant Clinical Immunologist, University Hospital of Wales  
 Dr Philip Wood, Consultant Immunologist, Leeds Teaching Hospitals NHS Trust  
 Dr Patrick FK Yong, Consultant Clinical Immunologist, Frimley Health NHS Foundation Trust

**Table 3: Respondents who publicly declare their support for the document**

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Table 2: 2014 C1 inhibitor deficiency consensus statements (page 1 of 2)

<b>A: TREATMENT OBJECTIVES</b>
1. Each C1 inhibitor-deficient patient should be able to manage his or her symptoms proactively in such a way that they maintain personal safety and minimal disruption in living a healthy and productive life
2. Treatment of HAE should follow international guidance and standards, whilst considering the resources available in the UK
3. All disabling attacks irrespective of location are eligible for treatment as soon as they are clearly recognized
4. Patient self-treatment is the ideal service model in line with government policy
<b>B: ACCESS TO EXPERTISE</b>
5. Every patient should be under the supervision of a specialist hub centre for HAE, either directly or via a spoke centre
6. A specialist centre has appropriate resources and a sufficient cohort of patients to maintain appropriate expertise in the treatment of HAE
7. Informative educational literature and support should be made available to every HAE patient
8. People with suspected HAE need to have access to a specialist centre expert
9. Every patient (including children) should be offered the option of home administration with appropriate monitoring, training and governance
<b>C: ACCESS TO MEDICATION</b>
10. Every patient should hold a safe quantity (minimum of one) of acute treatment doses at home dependent on individual needs
11. It is important that arrangements are in place to facilitate speedy replacement of acute attack medication after use so that the patient may proactively manage their symptoms safely with minimum disruption to living a healthy and productive life
12. Patient should take their medication according to clinical need rather than financial considerations
<b>D: ACUTE TREATMENT</b>
13. Plasma derived C1 inhibitors (Berinert, Cinryze), recombinant C1 inhibitor (Ruconest) and Icatibant (Firazyr) are all acceptable options for acute treatment
14. Icatibant may be particularly useful in enabling self administration as intravenous access is not necessary
15. Regular prophylactic treatment with C1 Inhibitor may be appropriate for patients requiring treatment for two or more attacks per week
16. Plasma-derived C1 Inhibitor is the treatment of choice for acute attacks of HAE for children, pregnant and breast-feeding women, and those trying to conceive
<b>E: DOSING OF C1 INHIBITOR</b>
17. We recommend that patients use the licensed dose of C1 inhibitor. In certain circumstances; the dose may need adjustment according to clinical response
18. A higher dose may be required if treatment is delayed. For early treatment via self administration, lower doses may be appropriate
19. If a second dose is needed, then the full dose will be required. It may therefore be a false economy to dose inappropriately low in the first instance
<b>F: LONG-TERM PROPHYLAXIS</b>
20. Evidence for the efficacy of antifibrinolytics is poor, however a minority of patients may find them helpful
21. Attenuated androgens are effective in long term prophylaxis for most people
22. The lowest effective dose of attenuated androgen should be used to minimize side effects
23. High doses of androgens may provoke severe side effects without added benefits

Table 2: 2014 C1 inhibitor deficiency consensus statements (page 1 of 2)

24. Doses of danazol above 200mg daily should be exceptional
25. Doses of stanozolol above 4mg daily should be exceptional
26. Treatment registries should be completed to allow better understanding of new products
27. Exceptionally, C1 inhibitor prophylaxis may be required when control of acute attacks is not possible by other means (including for children). This should be reviewed at regular intervals
<b>G: TREATMENT PLANS</b>
28. All patients should have a treatment plan for acute and elective surgery, including dentistry
29. All patients should have an additional treatment plan in place to ensure their safety when away from home or abroad
30. Treatment plans should be developed according to individual need and updated regularly
<b>H: ROLE OF THE SPECIALIST NURSE</b>
31. The specialist immunology nurse is pivotal in patient care
32. All patients should have timely access to a specialist immunology nurse
33. The specialist immunology nurse has a key role in supporting the patient and their family in the practicalities of living with HAE to achieve the best quality of life
<b>I: PATIENT SUPPORT</b>
34. Because HAE is a rare condition, patient information should be comprehensive and consistent
35. HAE patients benefit from direct contact with others with the same condition
36. Advocacy is important in ensuring equality of access and benefit
37. Patients may have inappropriately low expectations of QoL with HAE, which may limit their life options. This should be addressed
38. Patient information should be provided in an easily accessible and up to date format including electronic media
39. Specialist HAE patient support groups such as HAEUK have an important role in disseminating best practice in partnership with health care professionals
<b>J: COMMISSIONING</b>
40. Central funding of HAE treatments will allow equality of access
41. Central funding of HAE treatments will allow affordability through a shared financial risk
42. A national approach to commissioning of HAE services enables accurate estimation of likely costs, based on mean resource utilisation
43. Commissioning of home therapy will reduce utilisation of hospital services
<b>K: CHILDREN AND ADOLESCENTS</b>
44. Children require exceptional treatment plans, which need to be developed according to individual need and updated regularly
45. The use of attenuated androgens should be avoided in pre-adolescent children
46. Tranexamic acid is the drug of choice for prophylaxis in children
47. Treatment registries should be completed to allow better understanding of unlicensed products
48. Treatment plans for children and adolescents should address planning for issues such as school trips and examinations

Statement	Degree of Consensus by respondent group		
	Healthcare	Patients	Abstentions
1	98.9	100	0
2	98.9	97.2	0
3	97.8	100	0
4	95.6	100	0
5	98.9	100	0
6	100	100	0
7	98.9	100	0
8	97.8	100	0
9	97.2	97.2	0
10	95.6	100	1
11	100	100	1
12	97.8	100	1
13	95.3	100	5
14	94.1	100	6
15	95.2	100	8
16	96.4	100	9
17	95.3	100	5
18	91.7	97.1	7
19	93.8	97.1	10
20	88.6	100	13
21	91.1	97.1	13
22	96.3	97.1	11
23	97.4	97.1	14
24	97.3	100	19
25	94.4	97	21
26	97.5	100	12
27	98.8	100	7
28	98.9	100	3
29	97.7	100	5
30	98.9	100	4
31	96.6	97.1	4
32	97.7	97.1	4
33	98.9	97.1	4
34	100	100	3
35	94.1	97.1	6
36	97.1	100	4
37	98.8	100	6
38	97.7	100	3
39	96.5	100	5
40	97.6	100	9
41	95	100	11
42	95	100	11
43	96.3	100	9
44	97.5	100	9
45	97.4	100	15
46	98.3	97.1	16
47	98.8	100	11
48	98.8	100	10

Supplementary table S1: Consensus statistics

**Supplementary table S2: Alignment of UK C1inhibitor consensus statements with UK Primary Immunodeficiency Network (UKPIN) accreditation standards**

Topic:	Ref:	Statement	UK PIN standard
<b>Treatment Objectives</b>	1	Each C <sub>1</sub> inhibitor deficient patient should be able to manage his or her symptoms proactively in such a way that they maintain personal safety and minimal disruption in living a healthy and productive life	
	2	Treatment of HAE should follow international guidance and standards, whilst considering the resources available in the UK	B1
	3	All disabling attacks irrespective of location are eligible for treatment as soon as they are clearly recognised	
	4	Patient self-treatment is the ideal service model in line with government policy	A4, B2
<b>Access to Expertise</b>	5	Every patient should be under the supervision of a specialist hub centre for HAE, either directly or via a spoke centre	
	6	A specialist centre has appropriate resources and a sufficient cohort of patients to maintain appropriate expertise in the treatment of HAE	A2, A4, B1-4, C1-5 D1-4, D7-9, E1-7
	7	Informative educational literature and support should be made available to every HAE patient	D2, C6
	8	People with suspected HAE need to have access to a specialist centre expert	B1, B2

<b>Access to Medication</b>	9	Every patient (including children) should be offered the option of home administration with appropriate monitoring, training and governance	B3, B4, C4, C5, D7-9, E1-7
	10	Every patient should hold a safe quantity (minimum of one) of acute treatment doses at home dependent on individual needs	A4,B3,D7-8
	11	It is important that arrangements are in place to facilitate speedy replacement of acute attack medication after use so that the patient may proactively manage their symptoms safely with minimum disruption to living a healthy and productive life	B3, C4-5
	12	Patient should take their medication according to clinical need rather than financial considerations	A3, A4
<b>Acute Treatment</b>	13	Plasma derived C1 inhibitors (Berinert, Cinryze), recombinant C1 inhibitor (Ruconest) and Icatibant (Firazyr) are all acceptable options for acute treatment	A4, C4, D8
	14	Icatibant may be particularly useful in enabling self administration as intravenous access is not necessary	C4, E1-6
	15	Regular prophylactic treatment with C1 Inhibitor may be appropriate for patients requiring treatment for two or more attacks per week	A4,C4, D8
	16	Plasma C1 Inhibitor is the treatment of choice for acute attacks of HAE for children, pregnant and breast-feeding women, and those trying to conceive	
<b>Dosing of C<sub>1</sub> Inhibitor Medication</b>	17	We recommend that patients use the licensed dose of C1 inhibitor. In certain circumstances; the dose may need adjustment according to clinical response	A2, B1-2
	18	A higher dose may be required if treatment is delayed. For early treatment via self administration, lower doses may be appropriate	A2, B1-2
	19	If a second dose is needed, then the full dose will be required. It may therefore be a false economy to dose inappropriately low in the first instance	A2, B1-2

<b>Long Term Prophylaxis</b>	20	Evidence for the efficacy of antifibrinolytics is poor, however a minority of patients may find them helpful	A2, B1-2
	21	Attenuated androgens are effective in long term prophylaxis for most people	A2, B1-2, D3
	22	The lowest effective dose of attenuated androgen should be used to minimize side effects	A2, B1-2, D3, D8, F1
	23	High doses of androgens may provoke severe side effects without added benefits	A2, B1-2, D3, D8, F1
	24	Doses of Danazol above 200mg daily should be exceptional	A2, B1-2, D3, D8, F1
	25	Doses of stanozolol above 4mg daily should be exceptional	A2, B1-2, D3, D8, F1
	26	Treatment registries should be completed to allow better understanding of new products	D3, F1, F7
	27	Exceptionally, C1 inhibitor prophylaxis may be required when control of acute attacks is not possible by other means (including for children). This should be reviewed at regular intervals	A4, B3, D3, D7-8
<b>Treatment Plans</b>	28	All patients should have a treatment plan for acute and elective surgery including dentistry	D2, D8
	29	All patients should have an additional treatment plan in place to ensure their safety when away from home or abroad	D2, D8
	30	Treatment plans should be developed according to individual need and updated regularly	D8
<b>Role of the Specialist Nurse</b>	31	The specialist immunology nurse is pivotal in patient care	B2
	32	All patients should have timely access to a specialist immunology nurse	B2, B3
	33	The specialist immunology nurse has a key role in supporting the patient and their family in the practicalities of living with HAE to achieve the best quality of life	B2, A2



<b>Accepted Article</b> <b>Patient Support</b>	34	Because HAE is a rare condition, patient information should be comprehensive and consistent	B2, B3, C6, D2,D5
	35	HAE patients benefit from direct contact with others with the same condition	
	36	Advocacy is important in ensuring equality of access and benefit	
	37	Patients may have inappropriately low expectations of QoL with HAE, which may limit their life options. This should be addressed	
	38	Patient information should be provided in an easily accessible and up to date format including electronic media	D5
	39	Specialist HAE patient support groups such as HAEUK have an important role in disseminating best practice in partnership with health care professionals	