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# Canadian hereditary angioedema guideline

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## Abstract

Hereditary angioedema (HAE) is a disease which is associated with random and often unpredictable attacks of painful swelling typically affecting the extremities, bowel mucosa, genitals, face and upper airway. Attacks are associated with significant functional impairment, decreased Health Related Quality of Life, and mortality in the case of laryngeal attacks. Caring for patients with HAE can be challenging due to the complexity of this disease. The care of patients with HAE in Canada is neither optimal nor uniform across the country. It lags behind other countries where there are more organized models for HAE management, and where additional therapeutic options are licensed and available for use. The objective of this guideline is to provide graded recommendations for the management of patients in Canada with HAE. This includes the treatment of attacks, short-term prophylaxis, long-term prophylaxis, and recommendations for self-administration, individualized therapy, quality of life, and comprehensive care. It is anticipated that by providing this guideline to caregivers, policy makers, patients and their advocates, that there will be an improved understanding of the current recommendations regarding management of HAE and the factors that need to be considered when choosing therapies and treatment plans for individual patients. The primary target users of this guideline are healthcare providers who are managing patients with HAE. Other healthcare providers who may use this guideline are emergency physicians, gastroenterologists, dentists and otolaryngologists, who will encounter patients with HAE and need to be aware of this condition. Hospital administrators, insurers and policy makers may also find this guideline helpful.

**Keywords:** Hereditary angioedema, Guideline, Recommendations, Acute attacks, Short-term prophylaxis, Long-term prophylaxis, Self-administration, Individualized therapy, Quality of life, Comprehensive care, GRADE

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## Introduction

### Background

Hereditary angioedema due to C1 inhibitor deficiency (C1-INH-HAE) is an autosomal dominant condition with an estimated prevalence of approximately 1:50,000 [1,2]. It results in random and often unpredictable attacks of painful swelling typically affecting the extremities, bowel mucosa, genitals, face and upper airway [3]. Attacks are associated with significant functional impairment, decreased Health Related Quality of Life (HRQoL), and mortality in the case of laryngeal attacks [4,5]. The swelling in HAE is a result of impaired regulation of bradykinin synthesis [6]. Bradykinin is a nonapeptide kinin formed from high molecular weight kininogen by the action of plasma kallikrein. Bradykinin is a very powerful vasodilator and increases capillary permeability, constricts smooth muscle and stimulates pain receptors [1].

HAE can be categorized into 3 different types depending on the level and function of C1inhibitor (C1-INH): type 1(HAE-1), type 2 (HAE-2), and HAE with normal C1-INH function (HAE-nC1INH) previously referred to as type 3 (Table 1). HAE-1 is the most prevalent, representing approximately 85% of cases and results from low antigenic and functional levels of C1-INH. HAE-2 accounts for approximately 15% of cases and is associated with a normal C1-INHprotein level but impaired C1-INH function [7,8]. C4 is reduced in 98% of cases for both HAE-1 and HAE-2, and nearly 100% of the time during an attack [7].

HAE-nC1INH (previously referred to as type 3 HAE), is much less prevalent than HAE-1 and HAE-2. The true prevalence is not known as there are no reliable assays to screen for this condition. In about 20% to 25% of identified patients, causative mutations in the gene coding for the coagulation factor XII (*F*12) have been found (HAE-nC1INH-FXII) whereas in the remaining patients no genetic cause has been identified up to now (HAE-nC1INH-unknown) [11-13]. The exact pathogenesis, however, including the mode of action of the *F*12 gene mutations and the role of estrogens is still unknown. The lack of laboratory and genetic assays (with the exception of *F*12 gene mutations) to diagnose HAE-nC1INH, has made the identification of these patients more difficult than patients with HAE-1 or HAE-2. A recent international consensus group has published criteria to make the diagnosis of HAE-nC1INH [13]. These included a history of recurrent angioedema in the absence of concomitant hives or use of medication known to cause angioedema; documented normal or near normal C4, C1-INH antigen and function; and either a *F*12gene mutation associated with the disease, or family history of angioedema and documented lack of efficacy of chronic high dose non-sedating antihistamine therapy [13].

**Table 1 Laboratory findings in hereditary angioedema**

| | C4 | C1-INHAntigen | C1INH Function |
|---|---|---|---|
| HAE - 1 | ↓ | ↓ | ↓ |
| HAE - 2 | ↓ | Normal or ↑ | ↓ |
| HAE - nC1INH | | | |
| -FXII mutation | Normal | Normal | Normal |
| -UnknownCause | Normal | Normal | Normal |

References [9,10].

Management of HAE can be divided into various approaches. The aim of treatment of acute attacks, also referred to as 'on demand therapy' is to minimize their severity, including potentially fatal upper airway edema, and associated impairment of Quality of Life (QoL). Short term prophylaxis (STP) refers to treatment meant to minimize the risk of attacks when avoidance of potential and known triggers is not possible. Long term prophylaxis (LTP) refers to ongoing treatment of HAE aimed at minimizing the overall number, frequency and/or severity of attacks. The details of specific therapies for these treatment approaches will be discussed in the sections that follow. In addition to the evidence behind the proposed recommendations, the clinical considerations for their implementation will also be discussed. The United States Preventive Services Task Force describes clinical considerations as statements that can help clinicians by offering practical information so they can tailor guideline recommendations to individual patients [14]. This Clinical Consideration section following each recommendation is intended to help place the recommendation into a clinical context.

#### *Scope and purpose*

The objective of this guideline is to provide graded recommendations for the management of patients in Canada with HAE-1, HAE-2 and HAE-nC1INH. This includes the treatment of attacks, STP, LTP, and recommendations for self-administration, individualized therapy, QoL, and comprehensive care.

The care of patients with HAE in Canada is neither optimal nor uniform across the country. It lags behind other countries where there are more organized models for HAE management, and where additional therapeutic options are licensed and available for use [15]. It is anticipated that by providing this guideline to caregivers, policy makers, patients and their advocates, that there will be an improved understanding of the current recommendations regarding management of HAE and the factors that need to be considered when choosing therapies and treatment plans for individual patients.

It is not the intent of this guideline to provide a detailed description of the pathophysiology or nomenclature of HAE which can be found elsewhere [13]. It is also not intended to be prescriptive in its recommendations, but rather to highlight issues that need to be considered when

choosing treatments options for patients with a focus on the importance of individualized care.

### *Intended audience*

The primary target users of this guideline are healthcare providers who are managing patients with HAE-1, HAE-2 and HAE-nC1INH. Other healthcare providers who may use this guideline are emergency physicians, gastroenterologists, dentists and otolaryngologists, who will encounter patients with HAE and need to be aware of this condition. Hospital administrators, insurers and policy makers may also find this guideline helpful.

## Methods

### Committee members and consensus conference participants

The Canadian Hereditary Angioedema Guideline Committee is a working committee under the umbrella of the Canadian Hereditary Angioedema Network (CHAEN)/ Réseau Canadien d'angioédème héréditaire (RCAH) http://chaen-rcah.ca/. Members on this committee included members from CHAEN/RCAH across Canada as well as the President of the Canadian HAE Patient Organization – Hereditary Angioedema (HAE) Canada/Angioédème Héréditaire (AEH) Canada. The Canadian Hereditary Angioedema Committee was responsible for defining the scope and purpose of the guideline and choosing the international participants. International participants were selected based on their contributions to the HAE literature, relating to HAE and its management, and their expertise in priority areas for this guideline including self-administration, individualized therapy, HRQoL, and comprehensive care. Those identified experts were asked to present a summary of the evidence related to these areas to all conference participants.

Conference participants included the CHAEN/RCAH Guideline Committee, international experts, all currently registered members of CHAEN who were able to attend the meeting, the President of HAE/AEH Canada and their designates, President of the international HAE patient group HAEi, Hema-Quebec, and industry representatives. An invitation was extended to representatives of the Provincial/Territorial Blood Coordinating offices.

Representatives from Industry, who manufacture products for the treatment of HAE, were also invited to provide information on their products if required during the meeting. Only medical personnel and general managers were invited but were not present during times when decisions were made. Marketing representatives were excluded.

### Funding and support

Funding for the CHAEN/RCAH Guideline Conference was done through the CHAEN/RCAH. This organization received equal support from 3 companies, who manufacture products for the treatment of hereditary angioedema (CSL Behring, Shire, and ViroPharma - Viropharma was acquired by Shire between the time of the guideline meeting and publication of the Guideline). Requests to procure funding from Provincial and National Government and Blood Agencies were not successful. Funding was used to support rental of the conference facilities, audio-taping, facilitation by an external facilitator, travel to the meeting, accommodation, and foods for all participants except for government agency representatives and patient representatives who were supported by their own agencies. No industry participants were funded by CHAEN/RCAH. No participants at the meeting were compensated for their time except for the Guideline meeting methodologist and facilitator from the Centre of Effective Practice.

The guideline meeting process was aided by a methodologist and a guideline facilitator from the Centre for Effective Practice and supported by HAE/AEH Canada.

### Conflict of interest

Details of potential conflicts of interest were elicited using the standardized International Committee of Medical Journal Editors Form for Disclosure of Potential Conflicts of Interest (Additional file 1). COI forms were distributed to attendees prior to their reviewing the manuscript, and were mandatory for all contributing authors.

### Identifying the evidence

A systematic search of Ovid MEDLINE was conducted by a librarian from the Centre for Effective Practice (KLR) on October 10, 2013, in order to identify clinical trials addressing long-and short-term prophylaxis and treatment of acute attacks in patients of any age diagnosed with HAE-1, HAE-2, or HAE-nC1INH. Outcomes of interest included frequency or severity of attacks, symptom relief and QoL measures as reported or measured by the affected subject or investigator. Studies were limited to English language publications, and there were no limits on the publication date of study other than those imposed by the database (1946-October week 1, 2013). After duplicates were removed, 416 results were found, the abstracts of which were reviewed to determine if they met the inclusion criteria. If unclear from the abstract whether the paper met these criteria, the full-text document was reviewed. One hundred and thirty two results were retrieved and reviewed in full text, and from this, 11 relevant randomized control trials and 34 lower-quality comparative studies without blinding or randomization were identified and included. No studies which met the inclusion criteria were identified for HAE-nC1INH. The full search strategy is available in Additional file 2.

### Summarizing and evaluating the evidence

Key information from the included studies such as study design, number of patients, outcome measures, side effects and funding source was extracted into evidence tables for each intervention (see Additional file 3). Evidence tables were provided to the Committee Members and were available for reference at the meeting.

Criteria for determining Levels of Evidence and Strength of Recommendation were adapted from the GRADE system, [16-18] and the process was based primarily on the Journal of Clinical Epidemiology's 2011–2013 series of articles describing the GRADE methodology. GRADE is considered "outcome centric," and traditionally recommends a single rating for each outcome across the full body of evidence. The method applied here involved evaluating the quality of each study individually, and then looking at the studies together to assign a Level of Evidence based on the collection of studies.

Each identified randomized control trial was assessed by two reviewers (KL-R, VP) for quality using the Cochrane Risk of Bias Tool [19]. Any disagreements were resolved by a third reviewer (SB). Randomized trials were initially rated as High quality levels of evidence, with quality being downgraded for evidence of bias on the Cochrane tool and if there was evidence of inconsistency (Additional file 3: Table S1). Non-randomized, non-blinded trials were considered to be Low quality evidence.

Multiple factors were considered when assigning the Strength of Recommendation, including quality of evidence, balance between desirable and undesirable effects, values and preferences, and costs (Additional file 3: Table S2).

Additional file 3 describes additional detail how quality was assessed and the criteria used to determine the Strength of Recommendation. The quality ratings were presented at the meeting during the discussion of draft recommendations. Additional files 4 and 5 list the HAE RCT evidence tables and the lower quality comparison study evidence respectively.

### Recommendation development and approval

The Chair (SB) developed draft recommendations based on the identified literature, and presented them to the Committee Members who approved them in draft. Invited Committee Members were assigned specific topic areas and were asked to review the evidence relevant to their topic and present the body of evidence for consideration at the Guideline meeting. After the summary was presented, the Consensus Conference Participants were provided an opportunity to discuss the literature. Following this discussion, the draft recommendation was presented and the group discussed the specific wording of the recommendation before voting anonymously via electronic voting to agree or disagree with the recommendation, or abstain. If 80% consensus was not reached, there was additional group discussion, the recommendation was rephrased, and a new vote conducted. This process was conducted a maximum of 3 times. If 80% consensus was not reached, it was considered that the committee was unable to reach consensus.

Once the phrasing of a recommendation was approved by the group, the proposed Level of Evidence was presented by the methodologist guideline facilitator (High, Moderate, Low, Very Low, or Consensus). The Level of Evidence was then discussed, revised if necessary, and similarly voted on as outlined above.

The suggested Strength of Recommendation (Strong or Weak) was then presented to the group. The methodologist guideline facilitator proposed a Strength of Recommendation based on the Level of Evidence, the balance between desirable and undesirable effects, values and preferences. These factors were discussed amongst the group before voting to accept the proposed Strength of Recommendation. All votes were recorded and presented in real time with the recommendations. Table 2 is a summary of all the recommendations, the level of evidence supporting each recommendation, and the strength of each recommendation.

For each topic area, group discussions were captured on audiotape, and used to inform the clinical considerations for each recommendation.

To mitigate any real or perceived bias that may have influenced the outcomes, industry representatives at the meeting were asked to leave the room after the scientific presentations and were not present during any discussion either of the data, wording of the recommendations, levels of evidence, strength of recommendations, or the voting process.

Prior to the in-person meeting, the Committee Members determined that open discussion amongst conference participants regarding an approach to individualized therapy would be beneficial. For this topic, small round table discussions were facilitated prior to recommendation review and voting, and additional clinical considerations were.

## Guideline recommendations

### Treatment of acute attacks of HAE types 1 and 2

#### *Background*

Acute attacks of HAE may be spontaneous or precipitated by an external stimulus and range from mild to life-threatening. The decision to treat an attack depends on many variables and the severity of an attack cannot always be predicted by its earliest manifestations. The aim of treating acute attacks is to reduce the duration and severity of an attack, to minimize the impact of an attack on the functional ability of the patient, and reduce morbidity and potential mortality.

Despite the increase in available beneficial therapies, some therapies which have not been shown to be effective in trials continue to be used in acute attacks due to either historical precedent or lack of awareness.

**Table 2 Summary of recommendations**

| Recommendation | Level of Evidence and Strength of Recommendation |
|---|---|
| **Treatment of Acute Angioedema Attacks** | |
| 1. Effective therapy should be used to treat acute attacks of angioedema to reduce duration and severity of attacks. | High, Strong |
| 2. pdC1-INH is an effective therapy for the treatment of acute attacks. | High, Strong |
| 3. Icatibant is an effective therapy for the treatment of acute attacks. | High, Strong |
| 4. Ecallantide is an effective therapy for the treatment of acute attacks. | High, Strong |
| 5. rhC1-INH is an effective therapy for the treatment of acute attacks. | High, Strong |
| 6. Attenuated androgens should not be used to treat acute attacks. | Low, Strong |
| 7. Tranexamic acid should not be used to treat acute attacks. | Low, Strong |
| 8. Frozen plasma could be used for treatment of acute attacks if other recommended therapies are not available. | Low, Strong |
| 9. We recommend early treatment of attacks to reduce morbidity (Level of Evidence: Moderate) and mortality (Level of Evidence: Expert Opinion). | Moderate, Strong/Expert Opinion, Strong |
| 10. All attacks of angioedema involving the upper airway are medical emergencies and must be treated immediately. (Level of Evidence: Low) In addition, we recommend emergency department assessment. (Level of Evidence: Expert Opinion). | Low/Expert Opinion, Strong |
| **Acute Treatment of HAE with Normal C1-INH** | |
| 11. There is insufficient evidence to make a recommendation for or against the use of HAE-specific therapies in the treatment of acute attacks in patients with HAE with normal C1-INH. | Very Low / Insufficient Evidence |
| **Short-Term Prophylaxis** | |
| 12. Short-term prophylaxis should be considered prior to known patient-specific triggers and for any medical, surgical or dental procedures. | Low, Strong |
| 13. HAE-specific acute treatment should be available during and after any procedure. | Low, Strong |
| **Long-Term Prophylaxis In HAE 1 & 2** | |
| 14. Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration and severity of attacks. | High, Strong |
| 15. Attenuated androgens are effective for long-term prophylaxis in some patients. | Moderate, Strong |
| 16. Plasma-derived C1-INH is effective for long-term prophylaxis in some patients. | High, Strong |
| 17. Anti-fibrinolytics are effective for long-term prophylaxis in some patients. | Moderate, Strong |
| 18. It is not necessary to fail other long-term prophylaxis therapies before use of C1-INH for long-term prophylaxis is considered. | Expert Opinion, Strong |
| 19. There is insufficient evidence to make a recommendation for or against long-term prophylaxis for patients with HAE with normal C1-INH. | Very Low/Insufficient Evidence |
| **Self-Administration** | |
| 20. All patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies. | Low, Strong |
| **Approach to Individualized Therapy** | |
| 21. The decision to start or stop long-term prophylaxis depends on multiple factors and should be made by the patient and an HAE specialist. | Expert Opinion, Strong |
| **Quality of Life** | |
| 22. Health care providers should specifically address factors known to affect quality of life with HAE patients. Management of HAE should aim to improve patients' quality of life. | Low, Strong |
| **Comprehensive Care** | |
| 23. Comprehensive care should be available for all patients with HAE. | Low, Strong |

Nine randomized trials were identified which demonstrated improvement in duration and severity of acute attacks of HAE types 1 and 2 [20-29]. The therapies studied were plasma derived C1-INH (pdC1-INH), recombinant human C1-INH (rhC1-INH), icatibant and ecallantide. Table 3 lists the specific agents, their

**Table 3 Therapies for HAE supported by high level of evidence**

| HAE specific treatment | Product name and company | Mechanism of Action | Approved Indications In Canada | Dose | Adverse Events |
|---|---|---|---|---|---|
| C1-INH – Plasma | Berinert® (CSL) | Replaces CI-INH | Acute treatment | 20 IU/Kg intravenous | Anaphylaxis/Thrombosis (rare);Transmission of infectious agents (theoretical) |
| | Cinryze® (Shire) | Replaces CI-INH | Long term Prophylaxis | 1000 IU q3-4 days intravenous | Anaphylaxis/Thrombosis (rare);Transmission of infectious agents (theoretical) |
| – Recombinant | Rhucin® (Pharming) | Replaces CI-INH | Not licensed | 50 U/Kg Intravenous | Anaphylaxis (rare) |
| Ecallantide | Kalbitor® (Dyax) | Inhibits plasma kallikrein | Not licensed | 30 mg subcutaneous injection | Anaphylaxis (uncommon) |
| Icatibant | Firazyr® (Shire) | Blocks bradykinin 2 receptor | Acute treatment | 30 mg subcutaneous injection | Pain, swelling, pruritis at injection site (common) |
| | | | | | Exacerbation of coronary artery disease (theoretical) |

mechanism of action, their licensed indications in Canada, the recommended dosages, and important potential adverse reactions. The quality of individual studies is described under the drug-specific recommendations which follow. Based on the rating of each study using the Cochrane Risk of Bias Tool (see Additional file 4), as well as the overall consistent effect of therapy on the relevant outcomes (reduction of duration and severity of acute attacks), and effect size, this body of evidence determined by the conference participants to be of High quality.

Based on the Level of Evidence, the potential severity of the outcomes and the low risk of adverse effects, the panel voted for a Strong Recommendation in favour of the use of effective therapies in the treatment of acute attacks.

***Recommendation 1***

**Effective therapy should be used to treat acute attacks of angioedema to reduce duration and severity of attacks.**

**Level of Evidence: High** (96% Agree, 4% Disagree)
**Strength of Recommendation: Strong** (100% Agree)

*Clinical considerations*

The panel emphasized the importance of changing practice towards the use of effective therapies based on evidence based data, and specifically not using therapies which were not supported by evidence, such as antihistamines, corticosteroids and epinephrine which are directed at treating histamine mediated angioedema.

***Recommendation 2***

**pdC1-INH is an effective therapy for the treatment of acute attacks.**

**Level of Evidence: High** (100% Agree)
**Strength of Recommendation: Strong** (100% Agree)

*Clinical considerations*

The pdC1-INH is a human blood product. Treatment with pdC1-INHreplaces the deficient protein in patients with HAE-1 and HAE-2.Berinert® (CSL Canada) is the only licensed product in Canada for the treatment of acute attacks of HAE-1 and HAE-2. It has been licensed since 2010, and is available throughout Canada, through Canadian Blood Services or Hema-Quebec. It can be used to treat all attacks of HAE-1 and HAE-2 in adults and children. The recommended dosage is 20 U/kg administered intravenously either by healthcare professionals or by patients and their caregivers who have been trained in its administration. It has been shown to effectively treat acute attacks in pediatric and adult patients with HAE-1 and HAE-2 [22].

Although not currently licensed in Canada for the treatment of acute attacks, Cinryze® (Shire) is licensed in Europe for treatment of acute attacks in adolescent and adult patients with HAE-1 and HAE-2at a dose of 1000 units intravenously initially and another 1000 units if no response. It has been shown to reduce the median time to onset of unequivocal relief of symptoms compared to placebo group [29].

The dose derived for treatment of acute attacks comes from clinical trials. There have been no head to head trials comparing products so it cannot be concluded that different doses of different products were equally effective. There is some evidence that efficacy is dose dependant, but this has not been confirmed with rigorous dose finding trials [30]. The pdC1-INH products are safe and well tolerated when used as indicated with no documented transmission of infectious agents.

***Recommendation 3***

**Icatibant is an effective therapy for the treatment of acute attacks.**

**Level of Evidence: High** (97% Agree, 3% Disagree)
**Strength of Recommendation: Strong** (96% Agree/ 4% Disagree)

#### Clinical considerations

Bradykinin is a key mediator in inducing angioedema through activation of the bradykinin B2 receptor [6]. Icatibant is a synthetic 10-amino acid peptide and acts as a selective bradykinin B2 receptor antagonist. It is administered as a single 30 mg subcutaneous injection. It has been shown to effectively treat acute attacks in adult patients with HAE-1 and HAE-2 [20,25]. Icatibant is licensed in Europe and the USA for self-administration for the treatment of HAE attacks. (Addendum: Icatibant was licensed by Health Canada July 16, 2014). It is generally well-tolerated, although 90% of patients experience transient local pain, swelling, and erythema at the injection site.

***Recommendation 4***

**Ecallantide is an effective therapy for the treatment of acute attacks.**

**Level of Evidence: High** (94% Agree, 6% Disagree)
**Strength of Recommendation: Strong** (94% Agree, 6% Disagree)

#### Clinical considerations

Plasma kallikrein generates bradykinin through cleavage of high-molecular-weight kininogen [6,31,32]. Ecallantide is a 60-amino acid recombinant protein that acts as an inhibitor of kallikrein. It is administered as three 10 mg subcutaneous injections for a total dose of 30 mg. It has been shown to effectively treat acute attacks in adolescent and adult patients with HAE-1 and HAE-2 [26]. Martinez-Saguer et al. [33] ecallantide (is not currently licensed in Canada but access can be requested through) the Special Access Program of Health Canada. Hypersensitivity and sometimes anaphylactic-type reactions have been described with this agent in 5% or administrations, of which approximately 50% were possible anaphylactic reactions. Subcutaneous administration is associated with fewer of these episodes (1.6%), but is still a concern [32]. In the USA, ecallantide is approved for treatment of acute attacks, but must only be administered by healthcare professionals who are trained and are prepared to treat adverse reactions.

***Recommendation 5***

**rhC1-INH is an effective therapy for the treatment of acute attacks.**

**Level of Evidence: High** (100% Agree)
**Strength of Recommendation: Strong** (97% Agree, 3% Abstain)

#### Clinical considerations

The rhC1-INH (conestat-alpha) is generated in the mammary glands of transgenic rabbits and is identical to pdC1-INH except for the degree of protein glycosylation [34]. This difference in glycosylation results in shorter plasma mean half-life of the recombinant product [33,35], however the effect this has on physiologic activity is not known [30]. It has been shown to effectively treat acute attacks in adult patients with HAE-1 and HAE-2 [28]. It is administered intravenously at a dose of 50 U/kg in people up to 84 Kg and at a dose of 4200 U for people above 84 Kg. Because of an isolated anaphylactic reaction after administration of rhC1-INH to a rabbit allergic person, those with anti-rabbit IgE should be excluded before prescribing. It is not currently licensed in Canada but access can be requested through the Special Access Program of Health Canada.

***Recommendation 6***

**Attenuated androgens should not be used to treat acute attacks.**

**Level of Evidence: Low** (97% Agree, 3% Abstain)
**Strength of Recommendation: Strong** (100% Agree)

***Recommendation 7***

**Tranexamic acid should not be used to treat acute attacks.**

**Level of Evidence: Low** (93% Agree, 7% Disagree)
**Strength of Recommendation: Strong** (83% Agree, 10% Disagree, 7% Abstain)

#### Clinical considerations

Attenuated androgens such as the 17 α-alkylated anabolic androgen danazol and anti-fibrinolytic drugs such as tranexamic acid have not been shown to be efficacious in the treatment of acute attacks of HAE-1 and HAE-2. Given the lack of evidence for these agents in the acute treatment of HAE, the Committee strongly agreed that they should not be used for the treatment of acute HAE attacks as other agents with documented efficacy are available in Canada.

***Recommendation 8***

**Frozen plasma could be used for treatment of acute attacks if other recommended therapies are not available.**

**Level of Evidence: Low** (96% Agree, 4% Abstain)
**Strength of Recommendation: Strong** (100% Agree)

#### Clinical considerations

Frozen plasma (FP) is a blood product which contains C1-INH in association with other plasma proteins. Frozen plasma (FP) is not as safe as solvent detergent plasma (SDP) with respect to pathogen inactivation, and the level of evidence that frozen plasma is effective in the treatment of acute attacks of HAE −1 and HAE-2 is low. It also contains potential substrates for the generation of additional bradykinin and in theory could worsen attacks of angioedema. Also, not all blood banks in Canada stock FP and

there are special requirements to enable access to SDP. Hence, there may be a significant delay in getting FP and/or SDP in a timely manner - in some cases up to 24 hours. Therefore, it was strongly felt by the Committee that frozen plasma products, although potentially beneficial, should only be used if other recommended therapies are not available and that every effort should be made to ensure timely and appropriate therapy for acute attacks [36,37].

***Recommendation 9***

**We recommend early treatment of attacks to reduce morbidity (Level of Evidence: Moderate) and mortality (Level of Evidence: Expert Opinion).**

**Level of Evidence: Moderate** (92% Agree, 8% Disagree)
**Strength of Recommendation: Expert Opinion/ Strong** (92% Agree, 4% Disagree, 4% Abstain)

#### *Clinical considerations*

Early treatment likely leads to more rapid symptom resolution. Observational studies have suggested that early treatment can be efficacious in reducing the duration of an attacking some patients [38-42]. Therefore, despite the absence of a high level of evidence, expert opinion was strong endorsing early treatment in an attempt to reduce morbidity and likely mortality. Because of the potential barriers in accessing therapy in a timely manner, patients should be trained on how to self-administer therapies appropriate for the treatment of acute attacks of HAE. If patients are not able to self-administer their own therapy, efforts should be made to ensure that this therapy is made available to them without a significant delay (see Recommendation #21).

***Recommendation 10***

**All attacks of angioedema involving the upper airway are medical emergencies and must be treated immediately. (Level of Evidence: Low) In addition, we recommend emergency department assessment. (Level of Evidence: Expert Opinion).**

**Level of Evidence: Low** (96% Agree, 4% Disagree)
**Strength of Recommendation: Expert Opinion/ Strong** (100% Agree)

#### *Clinical considerations*

Attacks of HAE are unpredictable and potentially life-threatening. Mortality due to laryngeal angioedema is well recognized [3]. All attacks of laryngeal angioedema should be considered medical emergencies, and therapies that have been shown to be effective in the treatment of HAE should be readily available and given immediately. It is also recommended that all patients with laryngeal edema, even following self-therapy, be assessed in the emergency department in the event that the angioedema does not respond to therapy, and expertise in airway management is required [43].

### Treatment of acute attacks of HAE with normal C1 INH function

#### *Background*

HAE-nC1INH is a rare disease that can be a challenge to diagnose with certainty as was discussed above. It has been suggested, without confirmatory evidence that bradykinin may play a role in the pathogenesis of this disease which has led to speculation that therapies used for HAE-1 and HAE-2 may be beneficial [13]. There is also indirect evidence that anti-histamine therapy is not effective in this patient group [44]. Owing to the difficulty in identifying this subset of patients with HAE, and that there have been neither significant case series nor controlled clinical trials with respect to therapeutic intervention for acute attacks, we cannot recommend specific therapeutic interventions as this time.

***Recommendation 11***

**There is insufficient evidence to make a recommendation for or against the use of HAE-specific therapies in the treatment of acute attacks in patients with HAE with normal C1-INH.**

**Level of Evidence: Very Low** (96% Agree, 4% Disagree)
**Strength of Recommendation: Insufficient Evidence** (N/A)

#### *Clinical considerations*

The committee felt that there was insufficient evidence to make a specific recommendation regarding the use of therapies that have been shown to be efficacious for the acute treatment of HAE-1 and HAE-2 in patients with HAE-nC1INH.

However, in spite of this, if patients meet the clinical profile of HAE-nC1INH, a trial of HAE specific therapy could still be considered with the understanding that there is a very low level of evidence to support this and some reports demonstrate lack of efficacy for use of either pdC1INH or icatibant [45-48]. This may not be surprising given that there are neither abnormalities in C1-INH level or function, nor any confirmatory evidence if a role for bradykinin.

### Short-term prophylaxis

#### *Background*

STP refers to the practice of treating patients to reduce the risk of associated and consequent morbidity and mortality during a period of time when there may be an increased risk of having an attack of angioedema.

It is well recognized that physical trauma, as can occur during medical and dental procedures, can induce episodes of angioedema [49,50]. Upper airway manipulation, including during dental surgery and intubation, is at particularly high risk due to its association with upper airway swelling. However, even minor procedures can precipitate angioedema and the ability to predict when

this may occur cannot be made with certainty. Attacks can occur anywhere from hours to several days after a procedure [49].

It is also suspected that other causes, such as emotional stressors can precipitate attacks. Individual patients may also be aware of specific triggers that have been known to trigger their attacks.

Despite these observations, there is a lack of controlled clinical trials in this area, and most data come from retrospective reviews and surveys [49,51-53].

***Recommendation 12***

**Short-term prophylaxis should be considered prior to known patient-specific triggers and for any medical, surgical or dental procedures.**

**Level of Evidence: Low**(96% Agree, 4% Disagree)

**Strength of Recommendation: Strong** (93% Agree, 7% Disagree)

***Recommendation 13***

**HAE-specific acute treatment should be available during and after any procedure.**

**Level of Evidence: Low**(92% Agree, 4% Disagree, 4% Abstain)

**Strength of Recommendation: Strong** (100% Agree)

#### *Clinical considerations*

There was extensive discussion as to when STP should be used and consideration was given to the development of a list of high and low risk procedures in this context. However, there is lack of data regarding the specific risk associated with each of a wide range of medical and dental procedures; it was felt that STP should be considered for all medical, surgical and dental procedures. One study assessed the risk of angioedema following surgery without prior pre-procedural prophylaxis as 5 – 30%, irrespective of type and extent of surgery [53]. Based on this, and our inability to link the risk of an attack to a specific procedure [49,53]; it was felt that STP should at least be considered for all procedures as well as known patient-specific triggers. This recommendation was intended to remain broad in its scope as the risk of appropriate STP would likely be minimal compared to any real or perceived risk of not using STP when felt necessary. If the decision is made not to administer STP, all patients should have two acute treatment doses of appropriate therapy immediately available as per Recommendation 13. What is not known from the current data is how many patients have been denied, or have chosen not to pursue necessary procedures due to perceived risks, or not being offered STP. Ensuring access to STP may help mitigate the risk associated with procedures and enable patients to seek and receive the care they need [54].

In the absence of rigorous data on specific dosing, pre-procedural prophylaxis with pdC1-INHconcentrate is recommended however there have not been controlled dose finding studies. Response however does appear to be dose related. In one study patients had about a 30% risk with no prophylaxis, 15% risk with 500 units of pdC1-INH which was reduced to about 5% risk at 1000 units [49]. Furthermore, given that breakthrough attacks have occurred even with prophylactic pdC1-INH concentrates at 1,000 units, at least one additional treatment for acute attacks should be available. In Canada, pdC1-INHBerinert®is approved by Health Canada for acute treatment and pdC1-INH Cinryze is approved by Health Canada for long-term prophylaxis. In Europe, Cinryze is licensed to be given 1000 units within 24 hours of the procedure, or Berinert1000 units within 6 hours of an anticipated procedure.

Attenuated androgens may be considered for STP when surgery-related risk is considered low and other HAE-specific acute treatments are not immediately available. If androgens are chosen for STP, Danazol can be considered starting 5 days before the anticipated procedure or trigger and continuing 2–3 days after the anticipated trigger (Danazol 2.5 to 10 mg/kg/day, maximum 600 mg/day) [9]. Disadvantages with androgen therapy include perceived inferior efficacy to pdC1-INH concentrate and side effects such as emotional irritation and lability, menstrual disturbance, and vaginal dryness which can occur with short term use. Attenuated androgens areal so not suitable in pregnancy nor during breast feeding, and a pregnancy test should be considered before initiation of therapy with androgens. Recurrent short-term uses may be associated with similar effects seen with long-term androgen use as discussed below.

Anti-fibrinolytic agents such as tranexamic acid have been used for STP with suggested dosages of 25 mg/kg 2–3 times daily to a maximum of 3–6 g per day, 5 days before and 2–5 days after the procedure or anticipated trigger. The efficacy for prevention of attacks, however, is unknown and this agent should only be used if other therapies are not available.

### Long-term prophylaxis in HAE types 1 and 2

#### *Background*

LTP refers to the use of ongoing regular treatment to prevent attacks of HAE when on demand treatment does not sufficiently meet patient treatment requirements as discussed below in the Approach to Individualized Therapy section. Prophylactic therapy may be considered for patients with recurrent episodes of angioedema to reduce the frequency, duration and severity of attacks. The specifics of when to consider and when to initiate LTP are discussed below.

***Recommendation 14***

**Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration and severity of attacks.**

**Level of Evidence: High** (100% Agree)

**Strength of Recommendation: Strong** (100%)

#### *Clinical considerations*

The aim of LTP is to reduce the frequency and/or severity of attacks of HAE and minimize the impact of HAE on their QoL so as to enable patients to live normal lives. Some patients may be candidates for long-term therapy and the benefits and risks associated with such treatments should be explored to optimize patient care. It is important to remember that no prophylactic regimen has been associated with the complete elimination of angioedema. Therefore, despite being on prophylaxis, all patients should be equipped to treat acute attacks in a manner consistent with Recommendation #1 and an acute treatment plan should be agreed between patient and physician.

***Recommendation 15***

**Attenuated androgens are effective for long-term prophylaxis in some patients.**

**Level of Evidence: Moderate** (92% Agree, 4% Disagree, 4% Abstain)

**Strength of Recommendation: Strong** (90% Agree, 6% Disagree, 4% Abstain)

#### *Clinical considerations*

Controlled trials and observational studies have demonstrated that treatment with 17-alpha-alkylated anabolic androgens, such as danazol, reduces the frequency and severity of HAE attacks [55-60]. Although one of the trials was a randomized controlled trial the level of evidence for the trial was not considered High as there were insufficient details on funding, sequence generation, and outcome reporting [55]. Historically, many patients have been controlled with androgen therapy and their use in some patients may be acceptable provided that the lowest effective dose is used to achieve efficacy and minimize adverse effects. Expert opinion suggests the optimal dose for danazol, to minimize adverse effects, is ≤200 mg/day [9].

Androgens can affect serum lipid levels, can be hepatotoxic resulting in hepatitis and have been associated with hepatocellular adenoma and, in very rare cases, carcinoma [58,61,62]. It is recommended that all patients on androgen therapy be monitored for hypertension and have a complete blood count, liver enzymes, urinalysis, serum alpha-fetoprotein, creatine phosphokinase and lipid profile performed every 6 months, and an annual liver ultrasound [15].

Virilising effects of androgen therapy can occur and include menstrual irregularities, masculinization, irreversible voice alteration, and hirsutism. Psychological side effects include emotional irritability and lability, aggressive behaviour and depression. Androgens are associated with interactions with several medications. They are contraindicated in pregnancy and during lactation, before puberty, and in patients with androgen-dependent malignancy and hepatitis [61,62].

Patients need to be made aware of these side effects when considering and while on androgen therapy and physicians should carefully consider the risks and benefits for the particular patient.

***Recommendation 16***

**Plasma-derived C1-INH is effective for long-term prophylaxis in some patients.**

**Level of Evidence: High** (100% Agree)

**Strength of Recommendation: Strong** (100% Agree)

#### *Clinical considerations*

Controlled clinical trials have demonstrated that pdC1-INH used for prophylaxis in HAE-1 and HAE-2 reduces the number, duration and severity of attacks of angioedema [27,29]. Currently, Cinryze® (Shire) is the only approved pdC1INH product for HAE prophylaxis in Canada. However, this product has not yet been distributed in Canada. The dose of pdC1INH studied was 1000 U once or twice weekly (usually every 3–4 days). No dose finding studies have been done and at 1000 units twice a week the attacks are reduced by only 50%.

Side effects reported in trials with pdC1-INH are minimal. In the trial of Cinryze® for LTP, 21 of 24 subjects (88%) had one or more adverse events, however only three adverse events (pruritus and rash, light-headedness, and fever) were classified as possibly related to the study drug. Two patients in that study demonstrated an increase in the number of attacks of HAE. A paper based on the FDA registry of drug related adverse events, reported 10 cases of severe thrombosis related to the use of Cinryze® in three years between 2008 and 2011 [63]. The reason for these thrombotic events has not been further elucidated. It has been assumed to be related to the use of central lines. However, the use of these should also be avoided due to the associated risk of serious infection [63,64].

On-going monitoring of a patients response to therapy is recommended. In addition, as intravenous therapy requires ongoing venous access follow-up should ensure proper technique is used to maximize the health of the veins.

***Recommendation 17***

**Anti-fibrinolytics are effective for long-term prophylaxis in some patients.**

**Level of Evidence: Moderate** (96% Agree, 4% Disagree)

**Strength of Recommendation: Strong** (86% Agree, 14% Disagree)

#### Clinical considerations

The benefit of the anti-fibrinolytic agent tranexamic acid was demonstrated in a randomized placebo controlled trial with 18 subjects aged 12 years and overtaking 1 g of tranexamic acid three times a day [65], and a double-blind crossover study of epsilon aminocaproic acid in 9 patients aged 7 to 40 years resulting in these agents being given a moderate level of evidence [66]. These data suggested that anti-fibrinolytic agents could be useful for LTP for HAE-1 and HAE-2. However, their role in current LTP was felt to be justified only in some patient groups due to the lack of efficacy and the potential side effects at the dosage studied. Although not specifically studied in paediatric patients, it was felt, due to the concern of using attenuated androgens in this patient demographic, that anti-fibrinolytic agents could be considered. The recommended dosage for tranexamic acid is 30–50 mg/kg daily divided in 2 or 3 doses to a maximum of 6 g per day.

***Recommendation 18***

**It is not necessary to fail other long-term prophylaxis therapies before use of pdC1-INH for long-term prophylaxis is considered.**

**Level of Evidence: Expert Opinion** (100% Agree)
**Strength of Recommendation: Strong** (100% Agree)

#### Clinical considerations

The elements to consider when deciding to start prophylaxis are discussed below, in the approach to individualized therapy section. However, there is no recommended order or hierarchy for which therapies should be chosen for LTP. This should be based on the efficacy of the therapy, its side effects and safety, and the patient's preference. The participants were unanimous in their recommendation that should a patient require long-term prophylaxis they can be started on prophylactic pdC1-INH without need to be tried on other prophylactic therapies first.

### Long-term prophylaxis in HAE with normal C1-INH function

#### Background

Patients with HAE-nC1INH share similar clinical characteristics with HAE-1 and HAE-2 patients, including the risk of random unpredictable attacks of debilitating and potentially life threatening angioedema [44]. These similarities have led to speculation that treatments used for LTP for HAE-1 and HAE-2 may be beneficial for patients with HAE-nC1-INH; however, due to the lack of data a recommendation for this intervention could not be made.

***Recommendation 19***

**There is insufficient evidence to make a recommendation for or against long-term prophylaxis for patients with HAE with normal C1-INH.**

**Level of Evidence: Very Low** (100% Agree)
**Strength of Recommendation: Insufficient Evidence** (N/A)

#### Clinical considerations

The absence of good evidence in the LTP of HAE with nC1-INHpatients makes it difficult to make specific recommendations regarding treatment. Patients should avoid known triggers of angioedema such as exogenous estrogen and angiotensin converting enzyme (ACE) inhibitors. There is some evidence that progesterone, anti-fibrinolytics and attenuated androgens may be efficacious in patients with HAE-nC1INH [12]. However, the data were of low quality and uniform recommendations could not be made regarding their use. The committee felt strongly that more data are needed in this area and appropriate trials should be done to help guide future treatment recommendations.

### Self-administration

#### Background

Self-administration refers to the treatment of patients outside of a health care facility either by the patient's themselves or by a trained caregiver. The recognition and support of self-administration as treatment for HAE go back to the first international consensus document on HAE in 2003 and has been repeatedly recommended in subsequent consensus statements and guidelines [9,15,67]. It has been shown to be a safe and convenient option for patients, allows for early treatment, and may reduce the overall treatment costs of this group when compared to hospital-based therapy [68]. However, despite the demonstrated benefits of self-administration in terms of efficacy and improved QoL, an online survey done in the USA revealed that only 8.1% of treating physicians had patients who self-treated and only 3.5% received home healthcare assisted administration [69,70]. Although specific data in Canada is lacking, there is little reason to think it would differ much from these findings. Self-administration of blood products for rare blood disorders is not without precedent and has been the cornerstone of effective therapy for hemophilia for more than three decades in Canada [71].

Treatment is more efficacious when attacks are treated early [72]. Evidence has shown that the earlier an attack is treated the sooner it resolves [26,42,73,74]. The ability to treat an attack early depends on reducing the number of steps required between recognition of an attack that requires treatment and implementation of effective treatment. Obligating patients to travel to a health care

facility to receive a therapy which has been shown to be effective when administered at home, or outside of a healthcare facility, adds to the delay in receiving treatment, may result in many attacks not being treated. Patients may also face difficulties in accessing treatment if local healthcare facilities are unfamiliar with this condition. The World Allergy Organization's global guideline emphasizes that all therapies should be available to all HAE patients worldwide and that home- and self-administration are preferred because they reduce morbidity, absenteeism, cost, disease burden and potentially mortality, as well as improveQoL [15,75].

Carrying a personal supply of pdC1-INH by patients has been shown to reduce the time spent waiting for treatment [5]. Additionally, patients who self-administered or had on-demand therapy have been shown to have reduced severity and duration of attacks, and an improved QoL.

***Recommendation 20***

**All patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies.**

**Level of Evidence: Low** (100% Agree)
**Strength of Recommendation: Strong** (100%)

#### *Clinical considerations*

Although the level of evidence was low for the recommendation that all patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates, it was considered a strong recommendation unanimously. This is consistent with prior consensus statements and guidelines [9,15,76]. The importance of early therapy should not be underestimated, and barriers that affect its implementation should be removed. Currently in Canada, pdC1INH is licensed for on demand therapy (Berinert®) and for routine prophylaxis (Cinryze®). Because pdC1INH is a blood product and dispensed by blood banks in Canada, blood banks should adapt uniform operating procedures to enable access to pdC1INH by all suitable candidates and ensure uniform care for all patients regardless of location. The *Canada Health Act* is intended to guarantee equal access to health services and health care. Geographic disparities in care are known to exist. Self-administration of therapy in HAE will remove these disparities. Although, pdC1INH is an intravenous product and requires special considerations including product tracking and patient training, the use of intravenous blood products for self-administration is not unique. Hemophilia self-administration programs, which are similar, have been widely implemented across Canada and have been shown to be effective [71,77].

Treatments that do not require intravenous access for either acute treatment or prophylaxis would simplify self-administered treatment. Ecallantide and icatibant are efficacious subcutaneous therapies which are administered for the treatment of acute attacks as discussed above. Ecallantide is not licensed in Canada but may be accessed through the special access program. Ecallantide should usually be administered only by a healthcare practitioner with experience and facilities to treat anaphylactic reactions which occur in 3-8% of patients. Clinical trials are also being conducted evaluating the use of subcutaneous C1INH for LTP therapy [78,79].

Although not all patients will be suitable candidates for self-administered therapy, the option should be considered in the overall care plan of HAE patients. If patients are considered appropriate, and willing to learn self-administered therapy, they should agree to specific criteria as outlined in previously published international home-therapy guidelines [80,81]. With self-administered therapy, patients need to be regularly monitored to ensure appropriate control of their symptoms, compliance and competency. This is discussed further in the section on Individualized therapy.

### Approach to individualized therapy

#### *Background*

HAE is a dynamic chronic disease and attacks of angioedema can vary in frequency and severity over the patient's lifetime. This variability makes it important for patients to be evaluated regularly to ensure that therapy is appropriate and is being used correctly, and that side effects of therapies are being minimized. A recently published document outlines an approach to monitoring attack frequency and severity [76].

Perhaps one of the most challenging areas in patient treatment is deciding when to start or stop LTP therapy. Although guidelines exist on which agents to use when starting LTP, there is no evidence comparing the use of LTP to acute on-demand therapy regarding benefit and risk. In the absence of such evidence, given the clinical importance of this therapeutic approach, the committee attempted to determine which variables should be considered when trying to decide when to start or stop LTP.

***Recommendation 21***

**The decision to start or stop long-term prophylaxis depends on multiple factors and should be made by the patient and an HAE specialist.**

**Level of Evidence: Expert Opinion** (100% Agree)
**Strength of Recommendation: Strong** (97% Agree, 3% Disagree)

#### *Clinical considerations*

LTP should be considered when on-demand therapy does not allow HAE patients to lead healthy and

productive. There was considerable discussion regarding factors that should be considered when deciding to start LTP. It was generally agreed that the key considerations in making the decision included the efficacy of on-demand therapy to control the severity and frequency of attacks. Although in the past some consensus documents have tried to define the number and severity of attacks as a reference point to consider when to start LTP [10], there was significant concern about the arbitrary nature by which this would be defined. This approach might lead to denying LTP to patients whose QoL is impacted, yet not meeting a specifically defined frequency of attacks. It was felt that, although the frequency of attacks is important, it is only one among many factors including severity of previous attacks, how readily patients can access emergency treatment, and their ability to administer on demand therapy, which should also be considered.

Although the aim of LTP is to reduce the number and severity of attacks, it does not eliminate the risk completely. Patients must be aware that starting LTP does not mean that they will no longer have attacks and that those attacks can still be fatal. All patients must have a plan to treat attacks on demand despite being on LTP therapy. All patients must be monitored to ensure that LTP is efficacious and that side effects are being recorded [76].

When starting LTP it is important to understand and emphasize that LTP is not necessarily a lifelong therapy and that treatment needs ongoing re-evaluation. It may be helpful to try to define what the expectations are as objectively as possible when starting LTP. Part of the monitoring process should be to examine these goals and ensure they are being met.

The decision to stop LTP also generated significant discussion. All participants felt LTP with androgens should be stopped immediately if a patient became pregnant, was breast feeding or if the patient was less than Tanner stage 5 development. Other factors that may lead to the consideration of stopping LTP is ongoing stable control with LTP therapy with no evidence of breakthrough attacks of angioedema. If the decision to stop LTP is made, all patients must ensure that they have access to the administration of appropriate on-demand therapy of acute attacks as is consistent with Recommendation #20. All members of the patients comprehensive care team should be aware of the plan to stop LTP in case complications arise.

When stopping LTP with attenuated androgens or anti-fibrinolytics, the majority of participants agreed that a gradual taper is recommended, if the patient is not pregnant, while monitoring the frequency of and the impact on the patient's QoL. When stopping LTP with pdC1-INH it was felt it could either be stopped abruptly or the frequency of administration decreased, while monitoring the patient's response.

The committee was unanimous that the decision to start or stop LTP should be made jointly by the patient and an HAE specialist. The patient needs to be informed of the risks and benefits of all therapies, as discussed in the relevant sections above, to enable making an informed decision. Particular attention is needed when attenuated androgens are being considered for LTP in special populations such as women of childbearing age and children. Additionally, long-term effects on vein health need to be considered when considering repeated IV infusions.

## Quality of life

### *Background*

The Constitution of the World Health Organization (WHO) defines health as "A state of complete physical, mental, and social well-being not merely the absence of disease." It follows that the measurement of health and the effects of health care must include not only changes in the frequency and severity of diseases but also an estimation of wellbeing and HRQoL. The impact of HAE on a person's HRQoL can be considerable. A survey done in the USA in 2004 revealed that 85% of patients were afraid of sudden closure of their airway, 75% experienced intolerable pain and 53% were concerned about transmitting HAE to their offspring [82]. A recent study of 457 HAE patients from the USA reported significantly poorer health-related QoL versus population norms, based on the SF-12 Physical Component Summary and Mental Component Summary [83]. Productivity was also markedly impaired in all Work Productivity and Activity Impairment-General Health categories, including 34% overall work impairment. Because of their most recent HAE attack, workers lost a mean of 3.3 days; students lost a mean of 1.9 days. In a Swedish registry of HAE patients missed days from work and school were documented [84]. In a multicenter European Study absenteeism from work and school as well as marked loss in productivity with the most recent attack and in between attacks were recognized [85].

The Burden of Illness Study in Europe (Denmark, Germany, Spain) have shown that HAE had a high impact on daily activities during attacks and that HAE also impacted patients' daily activities between attacks [73,85,86]. In this study patients also reported substantial anxiety about future attacks, traveling, and passing HAE to their children [82]. Based on Hospital Anxiety and Depression Scale scores, 38 and 14% had clinically meaningful anxiety and depression, respectively [73]. Moreover, 51% (n = 84) indicated that HAE had hindered their career/educational advancement [85].

In Sweden and France, attack frequency was shown to have a negative effect on HRQoL as measured by EQ5D today [84] or SF-36 [87]. Attack severity was shown to be related with absenteeism [84,85].

HAE has a significant impact on QoL both during and between attacks and on absenteeism during attacks [73,84,85]. In aSpanish study assessing the development of a disease-specific QoL questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency, the factors cited most often by both experts and patients as affecting their QoL included potentially life-threatening attacks; the adverse side effects of medication (in several cases associated with chronic treatment); the unavailability of acute specific treatment at several health care centres; hereditary transmission; the lack of a known trigger which could be avoided; and the fact that it is a rare disease about which health care professionals know very little. The authors particularly noted that patients and experts may not agree on what are the most relevant aspects of HAE [88]. Aesthetics was mentioned more often by patients than by experts. On the other hand, experts were more likely to mention the adverse side effects of treatment. This finding supports the general opinion that the clinician's view of disease severity does not necessarily match with the patient's perception.

***Recommendation 22***

**Health care providers should specifically address factors known to affect quality of life with HAE patients. Management of HAE should aim to improve patients' quality of life.**

**Level of Evidence: Low** (100% Agree)

**Strength of Recommendation: Strong** (100% Agree)

### *Clinical considerations*

Assessment of HAE control as it relates to the frequency, duration and severity of attacks is not the only thing to consider when monitoring patients. Data suggests that factors which relate to a patients qualify of life are important when following patients with HAE. An international specific HRQoL questionnaire for adult patients with HAE due to C1-inhibitor deficiency has been developed [89] and is available for its use in clinical practice. The factors that impact a patient's QoL may be different than those anticipated by the healthcare providers. Modifications should be made to improve a patient's QoL wherever possible. A small study demonstrated that self-administration of pdC1-INH improved QOL on both physical and psychological parameters. Patients were able to resume a normal life without restriction [75]. Implementation of self-administered therapy may lead to an improved QoL by reducing the suffering caused by treating attacks too late or leaving them untreated altogether. It was reinforced at the meeting by the patient representatives that there are still significant barriers to getting timely and appropriate therapy at centres across Canada, likely from the lack of awareness of HAE and the appropriate therapies available for treatment. On-going research is required to determine additional factors that may have impact HAE patients' QoL.

## Comprehensive care

### *Background*

Comprehensive care of patientsis based on integration of the organization, delivery, and management of services related to diagnosis, treatment, care, rehabilitation and health promotion. The comprehensive care model has been adopted by many rare disease groups and there is evidence in other rare diseases that this model results in better patient outcomes and reduced costs [71]. Haemophilia has used this model for decades. HAE is similar to other rare blood disorders, including haemophilia, because it is a chronic condition that is potentially life threatening and requires a highly specialized, multidisciplinary team to manage. However, although HAE is similar to other conditions, it is also different enough to require its own framework to meet the specific needs of these patients. The recommendation to provide comprehensive care for

**Table 4 Requirements for comprehensive care in the management of hereditary angioedema patients**

| |
|---|
| **Best Clinical Treatment outcomes including:** |
| a. A comprehensive care team made up of nurse coordinator, clinician, social worker, data manager, pain management specialist, genetic counsellor, and administrative support; |
| b. Access to specialized diagnostic testing; |
| c. Access to home treatment; |
| d. A networked Patient Information System to facilitate product recalls - collect data on therapy outcome measures and safety, and facilitate participation in clinical trials |
| e. Access to clinical advances as they become available; |
| f. Access to 24 hour support; |
| g. Access to up-to-date standards of care, including standardized wallet cards; |
| h. Tracking and intermittent audit of quality outcomes including beneficial and adverse outcomes through secure, comprehensive and networked data management. |
| **Education of patients and staff regarding:** |
| a. Responsible Self/Family Care (home care model) with home and self-infusion/administration instruction and support; |
| b. Developments in the cause, diagnosis, treatment, outcomes, and prognosis of HAE |
| c. Changes in the administrative management of the clinic |
| **An environment conducive to research including:** |
| a. Access to and support for clinical trials of new treatments; |
| b. Access to and support for translational research in diagnosis and prognosis; |
| c. Access to and support for psychosocial research such as quality of life studies. |
| **An advisory or oversight board with patient group representation for each clinic** |

Reference [9].

patients with HAE is not new and exists in previously published guidelines. The specific elements of comprehensive care for HAE in Canada were published previously and are listed in Table 4.

***Recommendation 23***
**Comprehensive care should be available for all patients with HAE.**
**Level of Evidence: Low** (100% Agree)
**Strength of Recommendation: Strong** (100% Agree)

### *Clinical Considerations*

Although the importance of the comprehensive care model in HAE was recognized by the committee unanimously, and specific recommendations have existed with respect to its requirements, this care model is not available to all patients with HAE in Canada. The provincial and territorial model of health care funding makes implementation of nationally uniform HAE comprehensive care clinics challenging. Despite this, the fundamentals of comprehensive care should be uniform across the country and equally accessible across all geographic locations. Support should be provided by provincial and territorial governments to ensure that proper standards of care are being met. Treatments for HAE can be expensive; however inappropriate treatment of HAE may be even more costly. It was recognised by the committee that on-going monitoring of comprehensive care programs is essential to measure their impact on patients' outcomes such as disease control, QoL and economic effects.

## Special populations

The committee recognized that management of HAE in certain populations were not specifically addressed in this guideline. These include paediatric HAE patients and HAE patients during lactation and menstruation. The recently published WAO document specifically addressed recommendations for the management of HAE-1 and −2 in children [15]. An international consensus and practice guidelines on the gynaecologic and obstetrical management of female patients with hereditary angioedema caused by C1 inhibitor deficiency was recently published by Caballero et al. [90] and readers are referred to those publications with the understanding that they are not specific to Canadians.

## Additional files

**Additional file 1: Conflict of Interest Form.**

**Additional file 2: Search Strategy.**

**Additional file 3: Levels of Evidence and Strength of Recommendation.**

**Additional file 4: HAE RCT Evidence Tables.** Includes data extraction, quality assessments, and study reference codes and citations for randomized control trials.

**Additional file 5: HAE Lower Quality Comparison Study Evidence Tables.** Includes data extraction, quality assessments, and study reference codes and citations for lower quality comparison studies.

### Abbreviations

HAE: Hereditary Angioedema; C1-INH: C1 inhibitor; C1-INH-HAE: Hereditary Angioedema due to C1Inhibitor Deficiency; HRQoL: Health Related Quality of Life; HAE-1: Hereditary Angioedema Type 1; HAE-2: Hereditary Angioedema Type 2; HAE-nC1INH: Hereditary Angioedema with Normal C1 Inhibitor; *F*12: Factor 12; HAE-nC1INH-FXII: Hereditary Angioedema due to Factor XII mutations; HAE-nC1INH-unknown: Hereditary Angioedema due to unknown cause; QoL: Quality of Life; STP: Short-term Prophylaxis; LTP: Long-term Prophylaxis; CHAEN: Canadian Hereditary Angioedema Network; RCAH: Réseau Canadien d'angioédème héréditaire; pdC1-INH: Plasma Derived C1-inhibitor; rhC1-INH: recombinant C1-inhibitor.

### Competing interests

Dr. Betschel reports personal fees from CSL, Shire, ViroPharma, Baxter, Novartis, and Canadian Blood Services unrelated to the submitted work.
Ms. Badiou has no reported conflict.
Dr. Binkley reports consultation fees from Advisory Boards with Dyax, Shire, ViroPharma, and CSL Behring unrelated to the submitted work.
Dr. Hébert reports Advisory Board a consulting fee and clinical research from Shire and CSL Behring unrelated to the submitted work.
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SB prepared the manuscript. KLR developed the search strategy and prepared the evidence tables. All authors were involved in wording of the recommendations and reviewing and determining the level of evidence for each recommendation. All authors have read, revised and approved the manuscript.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Instructions

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## 1. Identifying information.

## 2. The work under consideration for publication.

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## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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**Non-Financial Support:** Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.

**Other:** Anything not covered under the previous three boxes
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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Stephen
2. Surname (Last Name): Betschel
3. Date: 09-August-2014
4. Are you the corresponding author? ☑ Yes ☐ No
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL | ✓ | ✓ | | | |
| Shire | | ✓ | | | |
| Viropharma | | ✓ | | | |
| Baxter | | ✓ | | | |
| Novartis | | ✓ | | | |
| Canadian Blood Services | | ✓ | | | |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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## Section 6. Disclosure Statement

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Dr. Betschel reports grants and personal fees from CSL, personal fees from Shire, personal fees from Viropharma, personal fees from Baxter, personal fees from Novartis, personal fees from Canadian Blood Services, outside the submitted work; .

## Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Jacquie
2. Surname (Last Name): L.-Badiou
3. Date: 15-August-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr. Stephen Betchels

5. Manuscript Title: CHAEN Guideline
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name) Karen
2. Surname (Last Name) Binkley
3. Date Dec 16/2013
4. Are you the corresponding author? ☐ Yes ☑ No
5. Manuscript Title
Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

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## Section 4. Intellectual Property – Patents & Copyrights

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## Section 4 Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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## Section 6 Disclosure Statement

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Section 2 - The meeting where the guidelines were developed was sponsored equally by Shire, CSL Behring & ViroPharma but they had no input + were absent during voting

Section 3 I have been a consultant and/or have served on advisory boards to Dyax, Shire, ViroPharma & CSL Behring

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Jacques
2. Surname (Last Name): Hebert
3. Date: 03-July-2014

4. Are you the corresponding author? ☐ Yes ☑ No  Corresponding Author's Name

5. Manuscript Title: Canadian HAE Guidelines

6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| Shire and CSL Behring | ☐ | ☐ | ☐ | ☑ | Ad Board member, Consultant and involed in clinical research |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Hebert reports other from Shire and CSL Behring, outside the submitted work; .

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Amin
2. Surname (Last Name): Kanani
3. Date: 14-January-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr. Stephen Betschel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| Viropharma | ☐ | ☐ | ☐ | ☑ | Advisory Board |
| CSL Behring | ☐ | ☐ | ☐ | ☑ | Speaker's Honorarium and CME sponsorship |

## Section 4. Intellectual Property -- Patents & Copyrights

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**The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.**

## 1. Identifying information.

## 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

## 3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

## 5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

### Definitions.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Paul
2. Surname (Last Name): Keith
3. Date: 31-January-2014
4. Are you the corresponding author? ☐ Yes ☑ No — Corresponding Author's Name
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL Behring | ✓ | ✓ | | | |
| Viropharma | | ✓ | | | |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Keith reports grants and personal fees from CSL Behring, personal fees from Viropharma, outside the submitted work; .

## Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name) Gina
2. Surname (Last Name) Lacuesta
3. Date 12-December-2013
4. Are you the corresponding author? ☑ Yes ☐ No
5. Manuscript Title Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

| Name of Institution/Company | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments | |
|---|---|---|---|---|---|---|
| CSL Behring | ☑ | ☐ | ☐ | ☐ | | |
| viropharma | ☑ | ☐ | ☐ | ☐ | | |
| shire | ☑ | ☐ | ☐ | ☐ | | |

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

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| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments | |
|---|---|---|---|---|---|---|
| CSl Behring | ☐ | ☑ | ☐ | ☐ | Advisory board | |

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| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| viropharma | ☐ | ☑ | ☐ | ☐ | advisory board |
| shire | ☐ | ☑ | ☐ | ☐ | advisory board |
| shire | ☐ | ☐ | ☐ | ☑ | travel sponsorship to attend International meeting on HAE |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

## Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Dr. Lacuesta reports grants from CSL Behring, grants from viropharma, grants from shire, during the conduct of the study; personal fees from CSl Behring, personal fees from viropharma, personal fees from shire, other from shire, outside the submitted work; .

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): William
2. Surname (Last Name): Yang
3. Date: 04-July-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Dr. Stephen Betchel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL Behring | ☑ | ☐ | ☐ | ☑ | research grant in HAE, national advisory board, unrestricted educational grants; lectures, including, transportation/lodging and meals with respect to appropriate activities listed above |
| Shire/Viropharma | ☑ | ☐ | ☐ | ☑ | global/national advisory board, unrestricted educational grants; lectures including, transportation/ lodging and meals with respect to appropriate activities listed above |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Emel
2. Surname (Last Name): Aygören-Pürsün
3. Date: 06-July-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Betschel, Stephen

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL Behring | ✓ | ✓ | | | |
| Shire/Viropharma | ✓ | ✓ | | | |
| Sobi | | ✓ | | | |
| Biocryst | ✓ | | | | |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Aygören-Pürsün reports grants and personal fees from CSL Behring, grants and personal fees from Shire/Viropharma, personal fees from Sobi, grants from Biocryst, outside the submitted work; .

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Jonathan A.
2. Surname (Last Name): Bernstein
3. Date: 12-December-2013
4. Are you the corresponding author? ☐ Yes ☑ No — Corresponding Author's Name:
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

| Name of Institution/Company | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL Behring | ✓ | ✓ | | | I am a consultant, speaker and PI on studies |
| ViroPharma | ✓ | ✓ | | | I am a consultant, speaker and PI on studies |
| Shire | ✓ | ✓ | | | I am a consultant, speaker and PI on studies |
| Dyax | ✓ | ✓ | | | I am a consultant, speaker and PI on studies |
| Pharming/Santaurus | ✓ | ✓ | | | I am a consultant and PI on studies |
| Journal of Angioedema | | | | | I am on the editorial board; no support |
| HAEA | | | | | I am on the medical advisory board; no support |
| Joint Task Force Practice Parameter | | | | | I am an author for the Angioedema Practice Parameter; no support |

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

## 5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

### Definitions.

**Entity:** government agency, foundation, commercial sponsor, academic institution, etc.
**Grant:** A grant from an entity, generally [but not always] paid to your organization
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**Non-Financial Support:** Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.

**Other:** Anything not covered under the previous three boxes
**Pending:** The patent has been filed but not issued
**Issued:** The patent has been issued by the agency
**Licensed:** The patent has been licensed to an entity, whether earning royalties or not
**Royalties:** Funds are coming in to you or your institution due to your patent

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Konrad
2. Surname (Last Name): Bork
3. Date: 30-December-2013
4. Are you the corresponding author? ☐ Yes ☑ No — Corresponding Author's Name
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL Behring | ☐ | ☑ | ☐ | ☐ | |
| Shire | ☐ | ☑ | ☐ | ☐ | |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Bork reports personal fees from CSL Behring, personal fees from Shire, outside the submitted work; .

## Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

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## 1. Identifying information.

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**Other:** Anything not covered under the previous three boxes
**Pending:** The patent has been filed but not issued
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**Licensed:** The patent has been licensed to an entity, whether earning royalties or not
**Royalties:** Funds are coming in to you or your institution due to your patent

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Teresa
2. Surname (Last Name): Caballero
3. Date: 28-December-2013
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betschel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

| Name of Institution/Company | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments | |
|---|---|---|---|---|---|---|
| CHAEN | ☐ | ☐ | ☐ | ☑ | Payment for travel requirements for attending consensus meeting | |

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments | |
|---|---|---|---|---|---|---|
| Viropharma | ☐ | ☑ | ☐ | ☐ | Advisory Board | |
| Shire HGT | ☐ | ☑ | ☐ | ☐ | Advisory Board | |
| CSL-Behring | ☐ | ☑ | ☐ | ☐ | Advisory Board | |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| Sobi | ☐ | ✓ | ☐ | ☐ | Advisory Board |
| Viropharma | ☐ | ✓ | ☐ | ☐ | Speaker bureau |
| Shire HGT | ☐ | ✓ | ☐ | ☐ | Speaker bureau |
| Novartis | ☐ | ✓ | ☐ | ☐ | Advisory Board |
| MSD | ☐ | ✓ | ☐ | ☐ | Speaker bureau |
| Shire HGT | ☐ | ☐ | ☐ | ✓ | Clinical trial fee paid to IdiPaz |
| Shire HGT | ☐ | ☐ | ☐ | ✓ | Member of IOS Executive Committee |
| Shire HGT | ☐ | ☐ | ☐ | ✓ | Writing assistance for IOS manuscripts |
| Dyax | ☐ | ☐ | ☐ | ✓ | Writing assistance for a manuscript |
| Shire HGT | ☐ | ☐ | ☐ | ✓ | Writing assistance for a manuscript |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ✓ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

| Patent? | Pending? | Issued? | Licensed? | Royalties? | Licensee? | Comments |
|---|---|---|---|---|---|---|
| HAE-QoL | ✓ | ☐ | ☐ | ☐ | IdiPaz (Hospital La Paz Institute for Health Research) | Specific Health Related Quality of Life questionnaire for patients with HAE-C1-INH |

## Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

✓ No other relationships/conditions/circumstances that present a potential conflict of interest

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Caballero reports other from CHAEN, during the conduct of the study; personal fees from Viropharma, personal fees from Shire HGT, personal fees from CSL-Behring, personal fees from Sobi, personal fees from Viropharma, personal fees from Shire HGT, personal fees from Novartis, personal fees from MSD, other from Shire HGT, other from Shire HGT, other from Shire HGT, other from Dyax, other from Shire HGT, outside the submitted work; In addition, Dr. Caballero has a patent HAE-QoL pending to IdiPaz (Hospital La Paz Institute for Health Research).

## Evaluation and Feedback

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**Royalties:** Funds are coming in to you or your institution due to your patent

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Marco
2. Surname (Last Name): Cicardi
3. Date: 05-May-2014
4. Are you the corresponding author? ☐ Yes ☑ No — Corresponding Author's Name
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL Behring | ☐ | ☑ | ☐ | ☐ | |
| ViroPharma | ☑ | ☑ | ☐ | ☐ | |
| Shire | ☑ | ☑ | ☐ | ☐ | |
| Dyax | ☑ | ☑ | ☐ | ☐ | |
| SOBI | ☐ | ☑ | ☐ | ☐ | |
| Pharming | ☐ | ☑ | ☐ | ☐ | |
| BioCryst | ☐ | ☑ | ☐ | ☐ | |
| SigmaTau | ☐ | ☑ | ☐ | ☐ | |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

## Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

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## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Cicardi reports personal fees from CSL Behring, grants and personal fees from ViroPharma, grants and personal fees from Shire, grants and personal fees from Dyax, personal fees from SOBI, personal fees from Pharming, personal fees from BioCryst, personal fees from SigmaTau, outside the submitted work; .

## Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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## 1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

## 2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". The complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

## 3. Relevant financial activities outside the submitted work.

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## 4. Other relationships.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Timothy
2. Surname (Last Name): Craig
3. Effective Date (07-August-2008): 18-April-2013
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Peters

5. Manuscript Title: Predictors of Response to Tiotropium Versus Salmeterol in Adults with Asthma
6. Manuscript Identifying Number (if you know it): JACI-D-13-00097

## Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc…)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 1. Grant | ☐ | ☐ | ☑ | ACRN, NHLBI | ACRN was finded by NHLBI | × |
| | | | | | | ADD |
| 2. Consulting fee or honorarium | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 3. Support for travel to meetings for the study or other purposes | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 5. Payment for writing or reviewing the manuscript | ☑ | ☐ | ☐ | | | × |
| | | | | | | ADD |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

**The Work Under Consideration for Publication**

| Type | No | Money Paid to You | Money to Your Institution* | Name of Entity | Comments** | |
|---|---|---|---|---|---|---|
| 6. Provision of writing assistance, medicines, equipment, or administrative support | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 7. Other | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 1. Board membership | ✓ | ☐ | ☐ | AAAAI | Interest Section Leader | × |
| 1. Board membership | ✓ | ☐ | ☐ | ACAAI | Board Member | × |
| 1. Board membership | ✓ | ☐ | ☐ | ALA- PA | Board Member | × |
| 1. Board membership | ✓ | ☐ | ☐ | JCAAI | Board Member | × |
| | | | | | | ADD |
| 2. Consultancy | ☐ | ✓ | ☐ | CSL Behring | under 20,000 | × |
| 2. Consultancy | ☐ | ✓ | ☐ | Dyax | under 10,000 | × |
| 2. Consultancy | ☐ | ✓ | ☐ | Viropharma | under 10,000 | × |
| 2. Consultancy | ☐ | ✓ | ☐ | Shire | under 10,000 | × |
| 2. Consultancy | ☐ | ✓ | ☐ | Merck | under 10,000 | × |
| | | | | | | ADD |

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

**Relevant financial activities outside the submitted work**

| Type of Relationship (in alphabetical order) | No | Money Paid to You | Money to Your Institution* | Entity | Comments | |
|---|---|---|---|---|---|---|
| 3. Employment | ✓ | | | | | ✕ |
| | | | | | | ADD |
| 4. Expert testimony | | ✓ | | support doctor in case of anaphylaxis | defense work for doctor. under 10,000 | ✕ |
| | | | | | | ADD |
| 5. Grants/grants pending | | | ✓ | Viropharma | research over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | CSL Behring | research over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Shire | research 10,000 to 25,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Dyax | research over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Pharming | research 10,000 to 25,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Forrest | over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Genentech | over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Biota | over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | GSK | over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Grifols | 10,000-25,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Novartis | over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Sanofi Aventis | over 50,000 | ✕ |
| 5. Grants/grants pending | | | ✓ | Boehringer Ingelheim | over 50,000 | ✕ |
| | | | | | | ADD |
| 6. Payment for lectures including service on speakers bureaus | | ✓ | | Viropharma | speaker under 20,000 | ✕ |
| 6. Payment for lectures including service on speakers bureaus | | ✓ | | CSL Behring | speaker under 20,000 | ✕ |
| 6. Payment for lectures including service on speakers bureaus | | ✓ | | Dyax | speaker under 20,000 | ✕ |
| 6. Payment for lectures including service on speakers bureaus | | ✓ | | Merck | speaker under 10,000 | ✕ |
| 6. Payment for lectures including service on speakers bureaus | | ✓ | | Norvartis | speaker under 10,000 | ✕ |
| 6. Payment for lectures including service on speakers bureaus | | ✓ | | Genentech | speaker under 10,000 | ✕ |

# ICMJE Form for Disclosure of Potential Conflicts of Interest

| | | | | | | |
|---|---|---|---|---|---|---|
| 6. Payment for lectures including service on speakers bureaus | ☐ | ✓ | ☐ | TEVA | speaker under 20,000 | × |
| | | | | | | ADD |
| 7. Payment for manuscript preparation | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 8. Patents (planned, pending or issued) | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 9. Royalties | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 10. Payment for development of educational presentations | ☐ | ☐ | ✓ | Vietnam Education Foundation | Salary support | × |
| | | | | | | ADD |
| 11. Stock/stock options | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 12. Travel/accommodations/ meeting expenses unrelated to activities listed** | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |
| 13. Other (err on the side of full disclosure) | ✓ | ☐ | ☐ | | | × |
| | | | | | | ADD |

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

## Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Hide All Table Rows Checked 'No'  SAVE

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## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

## 5. Relationships not covered above.

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**Royalties:** Funds are coming in to you or your institution due to your patent

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Henriette
2. Surname (Last Name): Farkas
3. Date: 14-December-2013
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen D. Betschel, HBSc, MD, FRCPC

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| Shire | ☐ | ☑ | ☐ | ☐ | fees for consulting , lectures |
| Sobi | ☐ | ☑ | ☐ | ☐ | fees for consulting , lectures |
| Viropharma | ☐ | ☑ | ☐ | ☐ | fees for consulting |
| CSL Behring | ☐ | ☑ | ☐ | ☐ | fees for consulting |

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## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

## Section 5. Relationships not covered above

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## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Farkas reports personal fees from Shire, personal fees from Sobi, personal fees from Viropharma, personal fees from CSL Behring, outside the submitted work; .

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Hilary
2. Surname (Last Name): Longhurst
3. Date: 30-January-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betschel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSLBehring | ✓ | ✓ | | ✓ | Educational support |
| Biocryst | | ✓ | | ✓ | research collaboration |
| Shire | ✓ | ✓ | | ✓ | Educational support |
| SOBI Biovitrum | | ✓ | | ✓ | research collaboration |
| ViroPharma | | ✓ | | ✓ | research collaboration |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

## Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Longhurst reports grants, personal fees and other from CSLBehring, personal fees and other from Biocryst, grants, personal fees and other from Shire, personal fees and other from SOBI Biovitrum, personal fees and other from ViroPharma, outside the submitted work; .

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Bruce
2. Surname (Last Name): Zuraw
3. Date: 02-July-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betschel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| Shire | ☐ | ☑ | ☐ | ☐ | |
| CSL Behring | ☐ | ☑ | ☐ | ☐ | |
| Dyax | ☐ | ☑ | ☐ | ☐ | |
| BioCryst | ☐ | ☑ | ☐ | ☐ | |
| Isis | ☐ | ☑ | ☐ | ☐ | |
| RMEI | ☐ | ☑ | ☐ | ☐ | |
| WebMD | ☐ | ☑ | ☐ | ☐ | |

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Zuraw reports personal fees from Shire, personal fees from CSL Behring, personal fees from Dyax, personal fees from BioCryst, personal fees from Isis, personal fees from RMEI, personal fees from WebMD, outside the submitted work; .

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Henrik Balle
2. Surname (Last Name): Boysen
3. Date: 26-August-2014
4. Are you the corresponding author? ☐ Yes ☑ No — Corresponding Author's Name
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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|---|---|---|---|---|---|
| ViroPharma | ✓ | | | | Unrestricted grant |
| Shire | ✓ | | | | Unrestricted grant |
| Dyax | ✓ | | | | Unrestricted grant |
| CSL Behring | ✓ | | | | Unrestricted grant |

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## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

## 5. Relationships not covered above.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Rozita
2. Surname (Last Name): Borici-Mazi
3. Date: 12-November-2013
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betchel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL Behring | ✓ | | | | Summer Students Research Grant 2012 |
| Viropharma | | ✓ | | | Advisory Board |
| CSl Behring | | ✓ | | | Advisory Board |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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## Section 5. Relationships not covered above

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☑ No other relationships/conditions/circumstances that present a potential conflict of interest

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## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

CSL Behring has supported Summer Research students in conducting a Case Review study on Angioedema in Emergency Department. This was not a drug trial.
I have participated at Advisory Board meetings for CSL Behring and Viropharma

## Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Tom
2. Surname (Last Name): Bowen
3. Date: 05-June-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betschel

5. Manuscript Title: Canadian Hereditary Angioedema Guideline
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| CSL-Behring | ☐ | ☐ | ☐ | ☑ | Advisory board |
| Shire | ☐ | ☐ | ☐ | ☑ | Advisory Board, Travel Grant |
| Viropharma | ☐ | ☐ | ☐ | ☑ | Advisory Board, Travel Grant |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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## Section 6. Disclosure Statement

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Dr. Bowen reports other from CSL-Behring, other from Shire, other from Viropharma, outside the submitted work; .

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## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name)
Karen

2. Surname (Last Name)
Dallas

3. Date
03-July-2014

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name
?

5. Manuscript Title
Canadian HAE Guidelines

6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- [x] Yes, the following relationships/conditions/circumstances are present (explain below):
- [ ] No other relationships/conditions/circumstances that present a potential conflict of interest

only participation on Advisory Boards.

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## Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Dallas reports only participation on Advisory Boards.

## Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name) JOHN
2. Surname (Last Name) DEAN
3. Date 14/5/14

4. Are you the corresponding author? ☐ Yes ☒ No

5. Manuscript Title
Canadian HAE Guidelines

6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☒ No

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Are there any relevant conflicts of interest? ☐ Yes ☒ No

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☒ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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## Section 5. Relationships not covered above

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Kelly
2. Surname (Last Name): Lang-Robertson
3. Date: 12-August-2014
4. Are you the corresponding author? ☐ Yes ☑ No — Corresponding Author's Name
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Ms. Lang-Robertson has nothing to disclose.

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## 4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name) BENOIT
2. Surname (Last Name) LABAMÉE
3. Date 2014/01/23
4. Are you the corresponding author? ☐ Yes ☑ No
5. Manuscript Title
Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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## Section 6. Disclosure Statement

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## Evaluation and Feedback

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name)
ERIC

2. Surname (Last Name)
LEITH

3. Date
15-December-1949

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title
Canadian HAE Guidelines

6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

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nothing to disclose

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name)
Sean

2. Surname (Last Name)
Mace

3. Date
14-January-2014

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name

5. Manuscript Title
Canadian HAE Guidelines

6. Manuscript Identifying Number (If you know it)

## Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

## Section 4. Intellectual Property -- Patents & Copyrights

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16 Jan 2014 3:00PM HP LASERJET FAX p.2

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Dr. Mace has nothing to disclose.

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Christine
2. Surname (Last Name): McCusker
3. Date: 14-May-2005
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: S Betschel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

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Dr. McCusker has nothing to disclose.

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): David William
2. Surname (Last Name): Moote
3. Date: 17-January-2014
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betschel

5. Manuscript Title: not sure
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Consulting for CSL Behring, ViroPharma and Grifols

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Dr. Moote reports consulting for CSL Behring, ViroPharma and Grifols.

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# ICMJE Form for Disclosure of Potential Conflicts of Interest

## Section 1. Identifying Information

1. Given Name (First Name): Man-Chiu
2. Surname (Last Name): Poon
3. Date: 11-December-2013
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betschel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| Viropharma | ☐ | ☑ | ☐ | ☐ | participation in Advisory Board |
| CSL-Behring | ☐ | ☑ | ☐ | ☐ | participation in Advisory Board |
| Shire | ☐ | ☐ | ☐ | ☑ | attendance of Shire sponsored meeting |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Poon reports personal fees from Viropharma, personal fees from CSL-Behring, other from Shire, outside the submitted work; .

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1. Given Name (First Name): Bruce
2. Surname (Last Name): Ritchie
3. Date: 21-June-2014
4. Are you the corresponding author? ☐ Yes ☑ No — Corresponding Author's Name
5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

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1. Given Name (First Name)
DONALD

2. Surname (Last Name)
STARK

3. Date
29-August-2014

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name
Dr Stephen Bet

5. Manuscript Title
Canadian HAE Guidelines

6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

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## Section 1. Identifying Information

1. Given Name (First Name) Gordon
2. Surname (Last Name) Sussman
3. Date 11-August-2014

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title
Canadian HAE Guidelines

6. Manuscript Identifying Number (if you know it)

## Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

| Name of Entity | Grant? | Personal Fees? | Non-Financial Support? | Other? | Comments |
|---|---|---|---|---|---|
| Shire | ☐ | ☐ | ☐ | ☐ | Consultant |
| CSL Behring | ☐ | ☐ | ☐ | ☐ | Consultant |

## Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Sussman has nothing to disclose.

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## Section 1. Identifying Information

1. Given Name (First Name): Susan
2. Surname (Last Name): Waserman
3. Date: 12-December-2013
4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Stephen Betschel

5. Manuscript Title: Canadian HAE Guidelines
6. Manuscript Identifying Number (if you know it):

## Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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| Shira | ☐ | ☑ | ☐ | ☐ | |
| Virapharma | ☐ | ☑ | ☐ | ☐ | |

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Dr. Waserman reports personal fees from CSL Behring, personal fees from Shira, personal fees from Virapharma, outside the submitted work; .

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## *Appendix 2: Search Strategy*

### SEARCH STRATEGY

Database: Ovid MEDLINE(R) <1946 to October Week 1 2013>
Search conducted on October 10, 2013 by Kelly Lang-Robertson, MLIS

1 angioedemas, hereditary/ or hereditary angioedema type iii/ or "hereditary angioedema types i and ii"/ (473)
2 ("hereditary angio$" or "inherited angio$" or "familial angio$").mp. (1621)
3 hereditary C1-INH deficiency.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (17)
4 or/1-3 (1682)
5 ("clinical trial" or random$ or placebo).mp.ortu.xs. (4184453)
6 4 and 5 (815)
7 limit 4 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial) (126)
8 6 or 7 (850)
9 limit 8 to (english language and humans) (692)
10 limit 9 to (case reports or comment or editorial or letter or news) (256)
11 9 not 10 (436)

*(Note: 20 of the results from the final set were identified in the abstract review stage as duplicates)*

## PICO

**Population:**

- Patients diagnosed with type I or type II hereditary angioedema
- Patients diagnosed with type III hereditary angioedema (HAE with Normal C1-INH Function

**Intervention:**

**Acute Treatment**

- C1-INH
- rhC1-INH (Ruconest)
- Kallikrein inhibitors (Ecallantide)

- Bradykinin receptor antagonists (Icatibant)
- Antifibrinolytic drugs (tranexamic acid)
- Solvent/detergent-treated plasma (SDP)
- Fresh frozen plasma (FFP)

**Long-Term Prophylaxis**

- C1-INH
- Attenuated androgens (Danazol)
- Antifibrinolytics (tranexamic acid)
- rhC1-INH (Ruconest)
- Synthetic steroids (Tibolone)
- E-aminocaproic acid (EACA)

**Short-Term Prophylaxis**

- C1-INH-NF (Cinryze)
- Attenuated androgens (Danazol)
- Antifibrinolytics (tranexamic acid)
- Anabolic steroids
- Fresh frozen plasma (FFP)

**Comparison:**

- Any, including:
    - Placebo
    - Regular treatment
    - No intervention

**Outcome:**

- Frequency or severity of attacks, or symptom relief including:
    - Time to symptom relief (onset or complete resolution)
    - Mean symptom complex severity score (MSCS score)
    - Treatment outcome score (TOS)

- Attack duration
- Time to treatment
- Rebound/relapse
- Number of attacks (eg. median per year or per month)
- Overall QoL

## *Appendix 3: Levels of Evidence and Strength of Recommendation*

Note: Levels of Evidence and Strength of Recommendation were adapted from GRADE [1,2,3]

### TABLE 1: LEVELS OF EVIDENCE

| Quality Level | Definition |
|---|---|
| High | We are very confident that the true effect lies close to that of the estimate of the effect |
| Moderate | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect |
| Very Low | We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect |
| Note: If no published evidence was identified in an area, but the Committee and Conference Participants determined that it was important to make a recommendation this was labeled as Expert Opinion. | |

### DETERMINING LEVELS OF EVIDENCE

All non-randomized, non-blinded trials were considered to be Low Level of Evidence.

All randomized control trials were considered a High Level of Evidence, and were downgraded based on the following parameters:

| Parameters | Examples of Limitations | Effect on Level of Evidence * |
|---|---|---|
| Limitations of Design / Risk of Bias<br><br>(Cochrane Risk of Bias tool) | • Lack of allocation concealment<br>• Lack of adequate sequence generation<br>• Lack of blinding<br>• Incomplete data<br>• Selective reporting<br>• Other limitations such as stopping early | Majority of items not satisfied or not reported = downgraded by 1 level |
| Inconsistency | • Large variation in effect<br>• Poor heterogeneity of results | Downgraded by 1 level |
| Imprecision of Results | • Small sample size<br>• Wide confidence intervals around the estimate of the effect<br>• Study is underpowered | Noted but not downgraded |
| Publication Bias | • Bias introduced due to significant industry funding | Noted but not downgraded (majority of studies were industry funded) |
| Indirectness / Generalizability | • Study population or setting differs significantly from population of interest | Not applicable |

*If it was determined that the limitation was significant, the Level of Evidence was downgraded by 2 levels.

## TABLE 2: STRENGTH OF RECOMMENDATION

**Recommendations can be either STRONG or WEAK**

**Strength of Recommendation is Determined By:**

1. Quality of Evidence
   - The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
2. Balance Between Desirable and Undesirable Effects
   - The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted.
3. Values and Preferences
   - The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
4. Costs (Resource Allocation)
   - The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

## FACTORS CONSIDERED WHEN DECIDING ON A STRONG OR WEAK RECOMMENDATION

- Uncertainty in the estimates of likely benefit, and likely risk, inconvenience, and costs
- Importance of the outcome that treatment prevents
- Magnitude of treatment effect
- Precision of estimate of treatment effect
- Risks associated with therapy
- Burdens of therapy
- Risk of target event
- Costs
- Varying values

## THE IMPLICATIONS OF A STRONG RECOMMENDATION ARE

- Clinicians: Most patients should receive the recommended course of action
- Patients: Most people would want the recommended course of action and only a small proportion would not
- Policy makers: The recommendation can be adopted as a policy in most situations

## THE IMPLICATIONS OF A WEAK RECOMMENDATION ARE

- Clinicians: Different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences
- Patients: Most would want the recommended course of action, but many would not
- Policy makers: Policy making will require substantial debate and involvement of many stakeholders