

## **NHF-McMaster Guideline: Care Models for Hemophilia Management** Scoping Document by Menaka Pai, BSc MSc MD FRCPC, McMaster University

**This document provides background information on hemophilia, with a focus on care utilization and care models. It also outlines the purpose of the NHF's Guideline on Care Models for Hemophilia Management, and how the guideline will be developed.**

**Please read through the entire document. It will specify what contributions you need to make at this point in the process, to ensure that the guideline addresses issues that are important to patients, care providers, policy makers, and other stakeholders.**

**After you fully review this document, you will be asked (via an electronic survey) to share your thoughts on the questions that the NHF's Guideline should ask regarding care models for hemophilia management.**

### **I. Preamble**

The National Hemophilia Foundation (NHF) is dedicated to finding better treatments and cures for inherited bleeding disorders and to preventing the complications of these disorders through education, advocacy and research. Through the efforts and guidance of NHF's Medical and Scientific Advisory Council (MASAC), an internationally-renowned group of expert scientists, physicians and other treatment specialists, NHF has long been engaged in advancing the standard of clinical care and issuing treatment recommendations for all bleeding disorders.

In 2012, the NHF held a strategic summit to develop a plan for hemophilia care within the evolving US health care environment, which includes an increased emphasis on evidence-based care. The Summit report included a call for NHF to sponsor the production and maintenance of evidence-based clinical practice guidelines (CPGs). These CPGs will adhere to a rigorous methodological standard, making them eligible for inclusion in the US Department of Health and Human Services' Agency for Healthcare Research and Quality National Guidelines Clearinghouse (NGC). The goal of these CPGs will be to support patient-centered clinical decision-making and optimize hemophilia care for each patient.

For its first CPG on Care Models for Hemophilia Management, NHF has partnered with McMaster University. McMaster has an international reputation for its work in CPG development, and it will provide methodological support to define the Guideline Panel, manage conflict of interest, and conduct the key elements of guideline development - literature search, evidence profiling, and grading the evidence. Drs. Holger Schunemann and Alfonso Iorio of the Department of Clinical Epidemiology and Biostatistics at McMaster University will be serving as co-principal investigators for the project.

### **II. What is Hemophilia?**

Hemophilia is an X-linked congenital lifelong bleeding disorder caused by mutations in clotting factor genes. The genetic mutation results in deficiency of a coagulation factor: factor VIII in hemophilia A, or factor IX in hemophilia B. Hemophilia A represents 80% of the total hemophilia population. Hemophilia is considered a rare disease, with an estimated

frequency (incidence) of approximately 1 in 10 000 (hemophilia A) and 1 in 50 000 (hemophilia B) people. The incidence of hemophilia is the same globally and does not vary by race or ethnicity. However, the *reported* prevalence in the population varies significantly among countries, even among the wealthiest of nations.<sup>1,2</sup> In the United States, there are approximately 19,000 individuals living with hemophilia.

Hemophilia causes bleeding, the severity of which is generally proportional to the coagulation factor level. The settings in which bleeding occurs vary with the severity of the disease.<sup>3</sup> Bleeding occurs only in response to significant injury or surgery in patients with mild hemophilia, and in the setting of either severe or moderate injury or surgery in moderate hemophilia. Bleeding occurs spontaneously and at an early age in severe hemophilia. Female carriers of the disease have variable factor levels, and experience bleeding more often than matched controls if their factor levels are reduced by over 50%. (They are also exposed to the additional bleeding challenges of menstruation, pregnancy and childbirth.) Most hemophilia-related bleeding is internal, into the joints and muscles. However, affected individuals can have bleeding into mucus membranes (e.g., mouth, gums, nose, genitourinary tract), as well as intracranial, gastrointestinal and soft tissue bleeds.

Bleeding can be managed by replacing the deficient coagulation factor. Individuals with more severely reduced factor levels require higher doses of coagulation factors for full replacement. Factor replacement can either occur on-demand (i.e., following a bleed), or prophylactically to prevent bleeding. Prophylaxis can be considered an ongoing "maintenance" therapy that converts patients from a severe to more moderate phenotype, thus reducing the risk of spontaneous bleeding. It can take the form of primary prophylaxis (i.e., initiated before the onset of serial bleeding) or secondary prophylaxis (i.e., after the process of serial bleeds has begun).<sup>4,5</sup> There is clear evidence that prophylaxis is effective in preserving joint function in hemophilia.<sup>6</sup>

Patients with hemophilia access care in the inpatient, outpatient and emergency settings. A 2007 U.S. study demonstrated that the mean annualized number of office visits for adult hemophilia patients ranged from 6.98 to 18.33 (higher in individuals with coexisting HIV and HCV infection).<sup>7</sup> Mean annualized inpatient costs ranged from \$1,104 to \$5,665 while mean annualized emergency room costs ranged from \$17 to \$367.<sup>7</sup> Hemophilia care has largely shifted towards the home infusion (home care) and outpatient setting in most countries, as patients are taught to self-administer factor replacement prophylactically, and prevent new bleeds from worsening by administering additional factor replacement early.<sup>8-12</sup> There is evidence that home care is underutilized in developing countries.<sup>8,10</sup>

Hemophilia confers a high cost to individual patients and the health care system.<sup>7,13-15</sup> In developed countries, this cost is estimated to be anywhere between \$80,000 and \$300,000 per patient year.<sup>16</sup> These costs are distributed differently between patients and payers in different countries. The bulk of the treatment cost of hemophilia is directed towards coagulation factor replacement.<sup>17</sup> Coagulation factors, particularly when given prophylactically, are costly; a 2012 economic evaluation reported that the incremental cost-effectiveness ratio for prophylaxis ranges from "cost saving and clinically beneficial" to over \$1.4 million U.S. dollars per additional quality-adjusted life year (QALY) if prophylaxis replaces on-demand treatment.<sup>4,18</sup>

### **III. Delivery of Care in Hemophilia**

The primary aim of hemophilia care is to prevent and treat bleeding, generally by replacing the deficient clotting factor. However, individuals with hemophilia have a variety of other health needs beyond the prevention and treatment of bleeding. They may require management of the complications of bleeding, including muscle bleed and debilitating joint disease. The input of musculoskeletal experts may be required. Some individuals with hemophilia have acquired viral infection(s) transmitted through blood products used to treat their hemophilia. Coagulation factors are now replaced with recombinant clotting factor concentrates and other non-plasma-derived hemostatic agents, but prior to the 1990s, factor replacement was commonly done using unpurified blood products. Many individuals with hemophilia contracted blood borne infections, including HIV and hepatitis C, from tainted blood products in the 1980s. There is evidence that these individuals access care differently, and that they may require management of viral infections and their sequelae (including opportunistic infections, malignancies and liver disease).<sup>7</sup> They may require care from infectious disease specialists (whose manage viral infections), hepatologists or gastroenterologists (who manage liver disease associated with hepatitis). Mostly as a result of treatment availability, the life expectancy of hemophilia patients has significantly improved; consequently, there is a need to manage diseases typical of aging (e.g., coronary artery disease). These often require preventative medical treatment or interventional procedures that must be adapted to the needs of patients with hemophilia. The experience of living with a chronic, lifelong genetic disease must also be addressed. Individuals with hemophilia may experience limitations on their activity, resulting in social stigma, vocational challenges and decreased quality of life. These may change over the life span. Attention to psychosocial health is thus important as well, for individuals with hemophilia *and* their families. Finally, hemophilia is a rare disease with costly treatment. This has obvious implications on the modality for care provision and reimbursement.

There are a variety of models used worldwide to deliver care to individuals with hemophilia:<sup>19</sup>

#### **a) No care**

This term refers to the complete absence of care. This is the *de facto* model of care in individuals with hemophilia who do not have access to care, due to resource constraints.<sup>20</sup> There is also evidence that, particularly in the developing world, many patients with hemophilia are not even diagnosed.<sup>21</sup>

#### **b) Non-disease specific care**

This term refers to care delivery that does not include replacement of deficient coagulation factors. For example, joint bleeds may be managed with RICE (rest-ice-compression-elevation) only.

#### **c) Disease specific care delivered in non-specialized centers by non-specialized providers**

This term refers to care delivery that does include replacement of deficient coagulation factors, but is delivered in generalized settings by providers who are not specialized hemophilia treaters. For example, joint bleeds may be managed in an emergency room or primary care setting with factor replacement, prescribed by a general practitioner. Other specialists may be accessed in an ad hoc fashion.

***d) Disease specific care delivered in non-specialized centers by specialized providers***

This term refers to care delivery that does include replacement of deficient coagulation factors, and is delivered in generalized settings. However, care is provided by an individual with specialized training in hemophilia. For example, joint bleeds may be managed in an emergency room or primary care setting with factor replacement, prescribed by a hematologist. This hematologist may see the hemophilia patient in an ongoing fashion. Other specialists may be accessed in an ad hoc fashion.

***e) Integrated Care Model***

Also known as the "Comprehensive Care" model or the "Hemophilia Treatment Center" model, this term refers to the continuous supervision of all medical and psychological aspects affecting the hemophilia patient and their family.<sup>19,22,23</sup> It generally demands that all modalities of care - access to care providers, as well as diagnostic and therapeutic facilities - are delivered in a single specialized centre, by a team of health care providers. This team includes a medical director (generally a pediatric and/or adult hematologist), a nurse coordinator, a musculoskeletal expert (physiotherapist, occupational therapist, physiatrist, orthopedist, rheumatologist), a psychosocial expert (generally a social worker or psychologist), and a specialized laboratory service. Integrated Care Models may also include or have access to pain specialists, dentists, geneticists, gastroenterologists, infectious disease specialists, immunologists, gynecologists/obstetricians, and vocational counsellors. Integrated Care Centres provide access to emergency care at all times. Hemophilia Treatment Centres in the U.S. that deliver integrated care for hemophilia are organized into regional and national networks that coordinate care, secure and administer funding, provide technical assistance, organize professional education and training, and engage in data collection and analysis.

Different models of care delivery have different implications for reimbursement and funding.<sup>18,24</sup> They may be more or less feasible to implement in a given setting, depending on local health care resources, culture, values and preferences. These different models may also have a differential impact on health outcomes in hemophilia.<sup>25-27</sup>

**IV. Rationale for NHF Guidance on Care Models for Hemophilia Management**

A number of guidance documents, including the 2013 *World Federation of Hemophilia Guidelines for the Management of Hemophilia*, the 2008 *European Principles of Haemophilia Care* and a 1995 statement from the Association of Hemophilia Clinic Directors of Canada, have advocated for integrated care as the optimal model of care in individuals with hemophilia.<sup>19,28-30</sup>

However, there is still limited evidence on the impact of different models of care on objective health outcomes in hemophilia. There are no randomized controlled trials in this area, as is typical in the area of assessment of complex public health interventions. A few observational studies have been conducted that demonstrate integrated care models have a significant effect on reducing mortality and hospitalization in patients with hemophilia.<sup>25-27</sup> However, their effect on other health outcomes has not been assessed in full detail, and

questions about the ideal composition of services and providers for optimal hemophilia care remain unanswered.

The NHF-McMaster CPG on Care Models for Hemophilia Management will explore the effect of different models of care in hemophilia, based on a systemic and thorough search of available evidence, and drawing from evidence of care models for other chronic illnesses as necessary. This CPG has the potential to:

- Identify best practices in hemophilia care delivery
- Specify the set of diagnostic, therapeutic, and supplemental services that are most important for hemophilia patients across the U.S.
- Identify the range of clinical and non-clinical care providers that are most important for hemophilia patients across the U.S.

## **V. The First Step - Asking Good Questions**

The recommendations that the NHF develops and provides to patients, clinicians, policy makers and others should answer their questions about what model(s) of care are optimal for hemophilia management. Developing good recommendations starts with asking good questions. A good question should address "real life" issues that these stakeholders face every day.

To ensure that we ask good questions, we will use the PICO ("population, intervention, comparison, outcomes") framework. PICO is a widely used approach that allows for structured development of a guideline. An example of a PICO question taken from a guideline on contact investigation in tuberculosis is as follows:

*"In people living in low and middle income countries who have contact with new or recurrent cases of TB, does contact investigation compared to no contact investigation, affect overall mortality, the consequences of TB infection, adverse effects of treatment, and resource use?"*

This question clearly defines the population ("people living in low and middle income countries who have contact with new or recurrent cases of TB "), the intervention ("contact investigation"), the comparator ("no contact investigation") and the outcomes ("overall mortality, consequences of TB infection, adverse effects of treatment, resource use"). This question also lends itself to modification and development of sub-questions. For example, the population could be further separated into various risk groups. Adults and children could be reviewed separately, as could patients with different disease severities. Contact investigations could be compared to other treatment strategies, instead of to no strategy. Different outcomes that patients and providers consider important could be considered as well.

The first step in creating the NHF-McMaster Guideline is brainstorming a list of questions that it will address. Each question must be refined and framed in the "PICO" format. Prior to the first Guideline Panel meeting in June 2014, several potential issues the guideline could address were identified:

- What is the optimal model for delivery of care in hemophilia?

- For individuals with hemophilia, what components (i.e., care providers, facilities, services) of an integrated care model are demonstrated to improve patient outcomes? Has the relevance and role of different components changed over time?
- What is the impact of an integrated care model on process outcomes and patient-relevant outcomes (e.g., reduced hospitalizations, lower frequency of bleeding episodes, risk of long-term joint damage, days lost to work) for:
  - all individuals with hemophilia?
  - specific subgroups of patients with hemophilia (defined, e.g., by age, disease severity, complications and comorbidities)?
- What is the impact of a network of hemophilia treatment centers on health outcomes for individuals with hemophila?
- What are the pros and cons of mixed models (i.e., coexistence of different models of hemophilia care delivery)

These issues propose possible populations, interventions and comparators, however they must be refined to take the format of PICO questions.

A list of potential outcomes has also been generated. There are abundant outcomes available in the field of hemophilia, many of them patient reported. However, not all outcome measures can be objectively measured. Some examples of the individual outcome measures to consider in the development of this guideline are:

- Need for additional hemostatic treatment
- Need for analgesics
- Pain
- Functional status
- Mobility of the joint
- Re-bleeding
- Breakthrough bleeds
- Pharmacoeconomic endpoints (e.g., cost, QALY)
- MRI and other radiographic assessments
- Absenteeism
- Life expectancy
- Hospitalization
- Bleeding episodes
- Number of target joints
- Access to care
- Inpatient visits
- Outpatient visits (to different care providers)
- Emergency room visits

Note that these are listed in random order, and will be ranked as part of the guideline development process. Combined measurements and scoring systems may also be useful. Some of these are listed here:

*[www.wfh.org/en/resources/functional-and-physical-examination-tools?](http://www.wfh.org/en/resources/functional-and-physical-examination-tools?)*

Patient-reported outcome measures may also be included in this guideline. Patient-reported assessment of quality of life has been explored in hemophilia, with studies done on generic measures (i.e., SF-36 Health Survey, Sickness Impact Profile, PedsQL, KINDL Questionnaire), as well as hemophilia-specific measures (e.g., HAEMO-QOL-A, Haemo-QoL, CHO-KLAT).<sup>16,31</sup> Tools for treatment satisfaction, patient preference, and levels of function have also been developed.<sup>32</sup>

**Based on the background material in this document, and your own experience and expertise, please think about the following:**

- a) What other questions regarding models of care in hemophilia management come to mind?**
- b) Can you identify other important populations, models of care, care processes and outcomes that this guideline needs to address?**

**You do not need to respond to this scoping document with your thoughts right now. However, we will soon be sending you an electronic survey, to get your feedback.**

**Your guidance will ensure that the systematic reviews conducted by the McMaster team addresses the right areas; only the PICO items identified at this stage will be explicitly considered during the subsequent search for evidence.**

## **VI. The Next Steps - Developing the Guideline**

In line with NGC, Institute of Medicine (IOM) and GRADE standards for guideline development, the NHF-McMaster Guideline will be built on a systematic review of the literature, and transparent processes for assessing the quality of evidence and developing recommendations.

An initial Guideline Panel meeting will be convened on June 21, 2014 to finalize the PICO questions, decide on the relative importance of identified outcomes, and agree on the outcomes to be assessed. The PICO questions and priority outcomes will be the basis for the systematic review.

A systematic review protocol will then be developed to address the chosen PICO questions. This protocol will clearly lay out the search terms, search strategy (methodology, inclusion and exclusion criteria) and techniques to identify relevant published and unpublished articles, manuscripts, abstracts and presentations. The systematic review will also identify key research gaps. Quality of evidence assessment will be based on the GRADE (Grading of recommendations, assessment, development and evaluation) methodology. GRADE tables will be prepared, to summarize the evidence in a clear and accessible format.

A second Guideline Panel meeting will be convened in May 2015 to assess the evidence (including an appraisal of its quality, conducted by the McMaster team), review the GRADE tables, and formulate the recommendations. During the meeting, facilitated decision-making will ensure that recommendations are made in a consensus based and transparent manner. The Guideline Panel will be asked to consider the quality of evidence, the balance of benefits and harms, the values and preferences that inform the recommendation, and resource use. Based on these factors, the Guideline Panel will decide on whether to make strong or weak recommendations for or against given interventions.

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