Topic Nomination Form for New ASH Clinical Practice Guidelines

Author Information

1. **Date proposal submitted:** August 14, 2016

2. **Your name:** Nathan Connell, MD, MPH

3. **Coauthor names, if applicable:** Paula James MD, FRCPC and William Nichols, MD

4. **Sponsoring ASH committee, if applicable:** Not applicable

5. **Your ASH member number:** 1066773

6. **Your email:** NTConnell@partners.org

7. **If ASH undertakes development of a guideline on this topic, would you be interested in serving on the guideline panel? (Yes/No):**
    a. Connell: YES
    b. James: YES
    c. Nichols: YES

8. **I understand that if this proposal moves forward, ASH leadership must approve all individuals to serve on the guideline panel. In accordance with ASH policy, a majority of the panel including the chair and the vice-chair must have no current material interests in companies with products that could be affected by the guidelines. (Yes/No)**
    a. Connell: YES
    b. James: YES
    c. Nichols: YES

9. **I understand that if this proposal moves forward, ASH staff and leadership will determine an appropriate schedule and budget to which all involved must adhere. (Yes/No)**
    a. Connell: YES
    b. James: YES
    c. Nichols: YES

Title and Abstract

10. **Title of your proposed topic:** The diagnosis and management of von Willebrand disease

11. **Describe your proposed topic in <250 words, including the primary clinical question(s) to be addressed by guidelines. You may find it useful to complete the remainder of this form first:**

    Von Willebrand disease (VWD) is a common inherited bleeding disorder with a wide variety of clinical presentations and degree of severity. This purpose of this clinical practice guideline would be to outline the key diagnostic features of the various subtypes of VWD along with the specific management of this disease. This guideline would be an update to the 2007 NHLBI report and we propose to address the following questions:

    1. Diagnosis and Evaluation:
        a. What are the key clinical features of VWD?
        b. Which laboratory tests should be used to make an initial diagnosis of VWD?
        c. What are the laboratory findings in each of the various subtypes of VWD?
        d. What are the key clinical and laboratory features of acquired von Willebrand syndrome (AVWS)?
    2. Management:
        a. What is the ideal management for type 1 VWD?
        b. What is the ideal management for the various subtypes of type 2 VWD?
        c. What is the ideal management for type 3 VWD?
        d. What considerations are made in the management of VWD during pregnancy?
        e. How should patients with an unclear diagnosis of VWD be managed, including those with low VWF (i.e. VWF levels between 0.30 – 0.5 IU/mL)?
        f. What is the ideal management for AVWS?
    3. Support Structure:
        a. What types of VWD should be managed in a specialized treatment center?
        b. What is the ideal way to manage the psychosocial aspects of VWD?
        c. What are the cost implications of various VWD treatment strategies from a societal, payer, and patient perspective?

Scope

12. **Describe the disease or condition to be addressed by guidelines. Consider if the scope could be limited to subtypes of the disease or risk groups:**

    Von Willebrand disease (VWD) is an inherited bleeding disorder due to decreased production, absence of, or abnormal function of von Willebrand factor. It is one of the most common bleeding disorders, and therefore a common consult that hematologists receive. There is a great deal of heterogeneity in the clinical presentation of these patients and therefore firm diagnosis and ideal management can be difficult.

    Type 1 VWD is due to a partial quantitative deficiency of VWF, is autosomal dominant, and represents approximately 75% of patients with the disease. Type 2 VWD is due to a qualitative

defect, is usually inherited in an autosomal dominant pattern, and has multiple subtypes. Type 3 is the least common type of VWD due to its autosomal recessive inheritance and is due to a virtually complete deficiency of VWF. [i]

The proposed clinical practice guideline would provide a clear outline for the diagnosis of VWD including its various and less common subtypes and attempt to standardize the treatment.

We propose that in addition to the steps taken by the 2007 NHLBI guidelines, the ASH clinical practice guideline should examine the evidence for:

- Defining the diagnostic criteria for each subtype of VWD
- The thresholds for initiating therapy
- Treatment goals

In addition, these guidelines could also attempt to address:

- Standardized diagnostic tools for VWD
- Psychosocial issues of patients with VWD
- Access to care
- Considerations of cost and resource utilization

If ASH feels the topic is too large to pursue at this time, then the scope could be limited to the diagnosis and management of mild, Type 1 VWD or just focus the practice guideline on the management aspects of VWD rather than the diagnostic evaluation.

13. Which age group would be addressed? (Check all that apply.)

- Children and adolescents
- Adults
- Elderly adults

14. If applicable, describe other special populations or subgroups to be addressed, e.g., pregnant women, patients with co-occurring conditions:

A special population to be addressed by these guidelines is the management of VWD in pregnancy. Pregnant women have a number of physiologic changes in the coagulation system during pregnancy and hematologists are often asked to provide recommendations for management during labor and delivery as well as the postpartum period. Additionally, the guidelines could also address the management of women with VWD outside pregnancy (i.e. gynecologic management).

15. If applicable, describe populations that should be excluded from the scope and explain why:

Not applicable

16. Are the described populations with this disease or condition commonly seen or treated by hematologists? Consider both U.S. and international settings. If possible, provide references.

Epidemiologic data indicate that VWD is the most common bleeding disorder in the United States and affects approximately 1 in every 100 individuals, approximately 3.2 million people.[ii] While many patients have VWD, the symptomatic prevalence is approximately 1 in 1000.[iii,iv,v] Worldwide, it is estimated that as many as 74,000,000 individuals have VWD and as most are undiagnosed. [vi]

17. **Which aspect of clinical care is to be addressed by guidelines? (Check all that apply.)**
    - ✓ Screening
    - ✓ Prophylaxis
    - ✓ Diagnosis
    - ✓ Treatment
    - ✓ Maintenance or management

Rationale for Guidelines

18. **Will guidelines on this topic address uncertainty in clinical practice? If possible, provide references, evidence, or observations to describe the uncertainty.**

In 2004, the National Heart Lung Blood Institute (NHLBI) started work on clinical practice guidelines for VWD. They convened an expert panel to evaluate the current science in VWD and "come to consensus regarding clinical recommendations for the diagnosis, treatment, and management of this common inherited bleeding disorder." The initial date restriction for the literature search was 1990-2004 and subsequently expanded to include landmark papers prior to 1990 as well as additional references through October 2006. The guidelines underwent internal and external review, and were published by the NHLBI in December 2007. [vii]

The National Hemophilia Foundation published a report in 2015 as a summary of a strategic summit on VWD.[viii] Key stakeholders were invited to participate in address several issues related to VWD. This included a section on clinical challenges, including the clinical processes by which the diagnosis is confirmed as well as discussion about clinical practice guidelines.

The participants concluded that development of an updated clinical practice guideline was needed in order to standardize and improve care. They stated that the guidelines published by NHLBI in 2008 "represented important progress toward a comprehensive guideline. " They also stated "however, although much of the guideline is still relevant, it scope concurrent see her insufficient more than 6 years after its publication and more than 8 years after the time span of its literature review. " They also noted that the National Guideline Clearinghouse considered "the guideline out of date and it has been archived."

19. **Will guidelines on this topic address practice variations? If possible, provide references, evidence, or observations to describe variations.**

The NHF report notes significant variation in practice and lack of alignment with best practices due to limited awareness by clinicians.

20. Will guidelines on this topic reduce or justify the use of interventions associated with high costs or resource use? If possible, provide references, evidence, or observations to describe the magnitude and impact of the costs or resource use.

The treatment of VWD often involves the use of intravenous medications or even coagulation factor replacement therapy. Major costs associated with these products are in both the acquisition of the factor replacement product and in the administration costs, sometimes accounting for 90% of the cost associated with the disease.[ix] Evaluation of the literature about cost considerations can be included in the scope of the panel. If there is insufficient evidence for the panel to reach a conclusion, then the panel can consider outlining high priority areas for future research.

21. List guidelines currently included in the National Guideline Clearinghouse (www.guideline.gov) that address this topic. Include title, year of publication, and sponsoring organization. If possible, also conduct a web search for guidelines from organizations with pertinence to the topic (e.g., the British Committee for Standards in Haematology, other U.S. medical specialty societies, disease-specific societies), including organizations not included in the Clearinghouse (e.g., the National Comprehensive Cancer Network).

National Guideline Clearinghouse: A search of the NGC database for "von Willebrand disease" returns 19 results. Of these, only six (6) meet the updated 2013 NGC criteria. Five (5) of these are for patients with sickle cell disease and one (1) report addresses reduction of venous thromboembolism in hospitalized adults.

British Committee for Standards in Haematology: A search of the BCSH notes a guideline in 2014. The article, "The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology" is an update to their previous (2004) guideline.[x]

22. How will new guidelines by ASH complement existing guidelines? Consider the clinical utility of existing guidelines (setting, scope, format), their quality (rigor of methodology, transparency, currency), and the credibility of the authors and sponsoring organization. Note: the Guideline Oversight Subcommittee and the Committee on Quality may determine that it is in ASH's best interests to endorse an existing guideline.

The currently available NHLBI guidelines date from December 2007. The National Guideline Clearinghouse considers them to out of date. The ASH guidelines would update the existing NHLBI guideline effort and complement the British Guidelines. An expert consensus panel produced the NHLBI guidelines. The British Guidelines used GRADE methodology. While the British Guidelines are well written, the guidelines from ASH would have the benefit of including data about recombinant VWF (VONVENDI®). Additionally, information about the value of different VWF functional assays has been published since 2014.[xi,xii] Finally, the British guidelines

are viewed as country-specific and an ASH guideline on VWD could help standardize practice as a comprehensive document.

23. Share any knowledge you have of plans by other organizations to maintain any existing guidelines or develop new guidelines on this topic:

a. *International Society for Thrombosis and Haemostasis (ISTH)*: Dr. James has been in contact with members of ISTH. They have expressed an interest in developing guidelines on this topic and are interested in partnering with ASH.
b. *National Hemophilia Foundation (NHF)*: Dr. James has been in contact with members of NHF. They have expressed an interested in partnership, should ASH decide to proceed with guideline development.
c. *World Federation of Hemophilia (WFH):* WFH has expressed interest in a joint venture for VWD guidelines and would likely welcome an opportunity to partner with both ASH and ISTH.

References:

[i] Ng C, Motto DF, Di Paola J. Diagnostic approach to von Willebrand disease. Blood. 2015;125(13):2029-37.

[ii] Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987 Feb;69(2):454-9.

[iii] Castaman G, Eikenboom JC, Bertina RM, Rodegheiro F. Inconsistency of association between type 1 von Willebrand disease phenotype and genotype in families identified in an epidemiological investigation. Thromb Haemost 1999; 3:1065-70.

[iv] M. Bowman, W.M. Hopman, D. Rapson, D. Lillicrap and P. James. The Prevalence of Symptomatic VWD in Primary Care Practice. J Thromb Haemost 2010; 8:213-216.

[v] M. Bowman, W.M. Hopman, D. Rapson, D. Lillicrap, M. Silva, and P. James. A Prospective Evaluation of the Prevalence of Symptomatic von Willebrand Disease (VWD) in a Pediatric Primary Care Population. Pediatric Blood & Cancer 2010; 55:171-173.

[vi] Srivastava A, Rodeghiero F. Epidemiology of von Willebrand disease in developing countries. Semin Thromb Hemost. 2005 Nov;31(5):569-76.

[vii] U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. The Diagnosis, Evaluation and Management of von Willebrand Disease NIH Publication 08-5832. 2007. Retrieved from: http://www.nhlbi.nih.gov/health-pro/guidelines/current/von-willebrand-guidelines on July 7, 2016

[viii] National Hemophilia Foundation. Strategic Summit on von Willebrand Disease. 2015. Retrieved from: https://www.hemophilia.org/sites/default/files/article/documents/NHF-Strategic-Summit-Report-on-von-Willebrand-disease_1.pdf on April 15, 2016

[ix] Duncan N, Roberson C, Lail A, et al. A haemophilia disease management programme targeting cost and utilization of specialty pharmaceuticals. Haemophilia. 2014 Jul;20(4):519-26.

[x] Laffan MA, Lester W, O'Donnell JS, et al.The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. Br J Haematol. 2014 Nov;167(4):453-65.

[xi] Roberts JC, Morateck PA, Christopherson PA, Yan K, Hoffman RG, Gill JC, Montgomery RR, Zimmerman Program Investigators. Rapid discrimination of the phenotypic variants of von Willebrand disease. Blood 2016; 20:2472-80.

[xii] Favalaro EJ, Mohammed S. Towards improved diagnosis of von Willebrand disease: comparative evaluations of several automated von Willebrand factor antigen and activity assays. Thromb Res 2014; 6:1292-300.