NATIONAL HEMOPHILIA FOUNDATION
for all bleeding and clotting disorders

MASAC Document #206
(Replaces #174)

MASAC RECOMMENDATIONS REGARDING RARE COAGULATION FACTOR DISORDERS

The following recommendations were approved by the Medical and Scientific Advisory Council (MASAC) on November 12, 2011, and adopted by the NHF Board of Directors on November 13, 2011.

Rare plasma protein coagulation disorders may result in a hemorrhagic or a thrombotic tendency based upon the specific coagulation factor affected and the associated level of deficiency. The treatment advances achieved for hemophilia A and B over the last two decades have not been mirrored in advances for these other disorders. Table 1 provides a listing of these very rare plasma protein deficiencies.

Due to the rarity of these disorders, the costs of research and development and of conducting clinical trials are often prohibitive when balanced against the potential market. For these reasons, individuals with rare coagulation factor disorders have limited or no options for treatment and suffer increased morbidity from their disease. Investigator-initiated Investigational New Drug protocols for use of a medication in these disorders places significant burden on the investigator and the manufacturer and therefore may preclude treatment of patients with rare deficiencies with potentially useful agents. In the US, these problems have created a dangerous lack of access to appropriate therapy for a small but important subset of the coagulation disorders community.

Regulatory pathways for product licensure have been geared towards collection of data in more prevalent conditions. Increased availability of specific safe and effective replacement products has hinged upon development of regulatory guidelines to allow submission of limited data sets for initial licensure of therapeutic products targeted towards these rare disorders with commitments to track adverse events post licensure. In addition, for each of these disorders, a national data system is required to develop the knowledge base necessary to advance care and treatment for these disorders and to allow data comparison or grouping to achieve international harmonization. Table 2 lists gaps in areas that play a pivotal role in advancing the knowledge base and care of individuals affected with these disorders.

Therefore, MASAC supports a multifaceted approach to address these identified gaps. These broad based approaches include:

Diagnosis	1. Improved diagnostic capability underpinned by accurate laboratory testing.
Education	2. Disease-specific education easily and widely accessible for all caregivers.
Collaboration	3. Collaboration with national and international agencies that interface with affected populations on all levels (CDC, ATHN, FDA, EN-RBD, NIH, NHF, WFH).
Data	4. Development of improved data sources to increase knowledge of disease-associated sequelae, treatments utilized, and associated adverse events.

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Therapy	5. Increased range of therapeutic interventions available for treatment.
Research	6. Increased research in rare disorders, both basic science and clinically orientated.
Advocacy	7. Advocacy to improve diagnosis, knowledge, treatment, care and outcomes.
Care	8. Identification and promotion of disease-specific centers of excellence for care including the Hemophilia Treatment Center network and other identified care sources.

MASAC recommends continued targeted activities to achieve improved diagnostic capabilities, education of care providers regarding these disorders, knowledge of sequelae experienced throughout the lifespan, increased therapeutic products for treatment, and research, advocacy, and international data harmonization to ultimately improve the care of all individuals affected with very rare plasma protein deficiencies. Collaboration across all agencies involved in the care and treatment of these individuals is required on an ongoing basis to achieve desired outcomes and long-term goals.

Please see the current version of the MASAC document titled, "MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders," for specifics regarding available products for treatment of these disorders.

Table 1: Hemorrhagic and Thrombotic Rare Plasma Protein Deficiencies

Hemorrhagic Disorders	**Thrombotic Disorders**
Factor VII	Antithrombin
Factor XI	Protein C
Prothrombin	Protein S
Factor V	Plasminogen
Factor X	Dysfibrinogenemia
Factor XIII	Congenital TTP
Combined Factor V & VIII	
Combined Factors II, VII, IX, X	
Platelet defects	
Alpha-2 Antiplasmin	
Plasminogen activator inhibitor 1	
Hypo- and afibrinogenemia	

Table 2: Gaps complicating rare disorders and associated potential impact on care and outcomes

IDENTIFIED GAPS	IMPACT
Insufficient knowledge of the clinical presentation	▪ Increased morbidity and potentially mortality ▪ Delayed diagnosis due to insufficient knowledge of the deficiency by the initial care providers ▪ Variety of initial care providers due to a variety of manifestations of some disorders (e.g. ligneous conjunctivitis in plasminogen deficiency) ▪ Delayed referral to a center expert in diagnosis and care
Inadequate knowledge of the range of clinical manifestations relevant to each gender across the life-span	▪ Inadequate presumptive medical counseling ▪ Attribution of symptoms to incorrect pathophysiologic processes ▪ Use of incorrect therapeutic intervention ▪ Withholding therapeutic intervention when required
Lack of universally available accurate diagnostic testing capability resulting in an inaccurate or inability to establish a diagnosis	▪ Inaccurate diagnosis ▪ Inability to establish a diagnosis ▪ Lack of an established normal range based upon age and sex
Non-specific diagnostic codes	▪ Inability to query databases to establish accurate • Number of affected population • Number of medical contacts for each patient or deficiency • Cost • Source of care, etc.
Accurate knowledge of affected population and sources of care	▪ Difficulty to provide required supportive data to encourage production of a therapeutic product ▪ Inability/difficulty to identify participants for potential clinical trials ▪ Inability to determine overall cost and burden of each disorder
Lack of availability of safe and effective replacement products	▪ Increased morbidity and potentially mortality ▪ Use of products potentially associated with increased risk or adverse events ▪ Lack of financial support/reimbursement through payers for unlicensed interventions or products
Ability to develop and conduct clinical trials to meet required endpoints for licensure of replacement products	▪ Inability to identify affected population eligible for enrollment ▪ Lack of effective therapy ▪ Limited population results in decreased ability to recoup cost of product development
Ability to track adverse events experienced by the affected population both due to the underlying disorder or related to therapeutic interventions	▪ Lack of well publicized accessible registry dedicated to track disease associated adverse events ▪ Inadequate reporting of adverse events experienced by the population due to use of a specific therapy, either licensed or unlicensed

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