

White Paper: Hemostasis Committee Hemophilia and Thrombosis Research Society

1) Introduction

The scope of bleeding disorders is broad; encompassing both inherited abnormalities as well as acquired abnormalities that are often associated with major systemic illnesses (such as advanced liver disease or DIC). Because of the complexities of hemostasis, bleeding disorders are often perplexing to both patients and physicians. The presence of a bleeding disorder may be readily detected due to symptomatic bleeding and abnormal screening laboratory tests, while the actual diagnosis remains elusive to many physicians and health care workers. Although significant advances have been made regarding basic genetic and physiological aspects of hemostasis there is much that remains unknown.

The paucity of well-designed clinical trials in the field of bleeding disorders makes evidence-based clinical practice difficult to attain. Reasons for this deficiency in independent clinical research can be found in the need for large number of participants, lack of adequate controls and increased cost. The HTRS can provide a suitable environment for the completion of meaningful clinical trials based on its large membership, the expertise of many of its members and the possibility of recruiting large number of patients. Moreover the society has a strong commitment for the promotion of research projects by young investigators.

Recognizing the need for more research in disorders of hemostasis, the HTRS is attempting to develop priorities to implement the foremost purpose of the society, which is the promotion of research that would improve the care of persons with disorders of hemostasis. The aim of this document is to identify and characterize some of the areas of greatest need. It is important to mention that this document intends to be a guideline for research. However the society remains open to new ideas and projects that investigators might have and are not included in this white paper.

2) Research Priorities

Specifically, the Hemostasis Committee recognizes two major areas where research sponsored by the society should focus:

- 1) Improved laboratory testing to assist in diagnosis and monitoring of patients.
- 2) Well-design clinical studies for better treatment strategies.

The general topics that were identified as the ones that should deserve priority are:

- Congenital Hemophilia
- Von Willebrand Disease
- Acquired Hemophilia

Rare Coagulation Factor Deficiencies
Platelet Disorders and Thrombocytopenia
Menorrhagia

1) Congenital Hemophilia

Although major advances have been made in the last decades in the care of persons with hemophilia, a paucity of adequate trials in many aspects of the care is recognized. This makes clinical practice mostly based on anecdotal information and personal experiences. Simple and fundamental questions such as rate of inhibitors with recombinant and plasma derived products or effective factor doses for different bleeds have not been answered yet.

Therefore the Committee identified the following areas as important for the development of new research projects due to the lack of current information:

- a) Efficient/cost effective utilization of factor during prophylaxis
(ie. PK based factor dosing, explore lower “dose intensity” regimens for prophylaxis)
- b) Duration of primary prophylaxis
Continued prophylaxis decision analysis for late teens/ early adults
- c) Role of adjuvant therapies, (ie antifibrinolytics) in treatment of bleeding episodes in hemophiliacs
- d) Studies of novel methods of tolerization and/or prevention of inhibitors – especially in high risk populations such as African-Americans or those with a strong family or genetic predisposition to inhibitor formation

2) VWD

Several issues make the diagnosis and treatment of patients with VWD exceedingly difficult. Particularly for those patients with type 1 disease where decisions about diagnosis and treatment may have a significant impact on their life style. Therefore there is paucity of information on how to define type 1 VWD and what are the risk factors that may affect its presentation.

Topics in VWD that will be prioritized are:

- a) Better diagnostic methodologies – how to determine those with clinically relevant disease
- b) Correlation of clinical symptoms with laboratory/genetic measures to establish risk factors for bleeding

- c) Treatment of VWD type 1 patients with DDAVP during surgery

3) Acquired hemophilia

Acquired hemophilia is a rare but potentially devastating disorder that has been “orphan” of adequate treatment for long. The data accumulated over years regarding treatment are based mainly on small series of patients. The potential of a big sample size from HTRS centers as well as the emergence of promising new agents for the treatment of autoimmune processes makes this topic especially attractive.

The aspects of this disorder that would be prioritize for research are:

- a) Completion of randomized clinical trials that explore the most successful treatments up to date
- b) ????

4) Rare coagulation factor deficiencies

Although uncommon in nature, the rare factor deficiencies have been identified as one of the topics of interest. This particular topic will benefit from true multinstitutional trials that can set up the basis for adequate treatment.

The areas identified are:

- a) Surgical management of patients with FVII or FXI deficiency
(Exploring agents, doses, duration of treatment etc.)
- b) ???????

5) Platelet disorders and thrombocytopenia

The prevalence of mild to moderate platelet disorders in the general population is unknown. The current methods to diagnose mild platelet abnormalities such as platelet aggregation are somewhat obsolete and reflect a limited aspect of platelet physiology. Also, most of the previous studies in the field suffer from lack of adequate controls. Therefore the committee feels imperative to place focus on research designed to better diagnose these syndromes and to find new alternative treatments.

Areas of interest are:

- a) Mild platelet function abnormalities diagnosis
(True prevalence, adequate controls)
- b) New treatment strategies
(Recombinant factor VIIa, DDAVP, ancillary therapy)

6) Menorrhagia

The issue of menorrhagia has gained increased recognition over the last years. However the design of clinical studies of prevalence of bleeding disorders in this population has not been ideal. The HTRS can provide an ideal setting where the combination of patients and expertise may help to conduct well-designed studies.

Areas of interest are:

- a) Prevalence of bleeding disorders in this population with adequate controls
- b) Prevalence of genetic and environmental factors that predispose to menorrhagia in the absence of a diagnosed bleeding disorder
- c) New therapies

Other disorders

- Novel strategies for DIC
- Novo7 for coumadin toxicity

Society Goals (please look at them and send your opinion in terms of including this in the strategy)

- Development of a registry or database of HTRS members interested in participating in clinical research and their numbers of patients with a variety of hemostasis disorders broken down by ages and severity.

This information would be helpful to investigators planning a specific study as well as in convincing funding agencies that studies could reasonably be performed by the HTRS network. If one, for instance, wanted to study some aspect of mild hemophilia in children, it would be very helpful to know that there was access to 1000 such patients through the HTRS. Or if someone wished to study something about Bernard Soulier Syndrome, it would be helpful to rapidly identify those sites having such patients.

- Development of a mechanism for developing and disseminating RFPs. Do we have a clear and fair policy for this?

Example: If Aventis wishes to fund a vWD study, how do we negotiate? I see 3 possibilities: 1) We issue an RFP for the specific study that Aventis requests; 2) We negotiate the specifics of the RFP with Aventis, emphasizing the society's highest priorities in vWD; or 3) We demand unrestricted funding for a vWD RFP with no input from Aventis. Option #1 reduces the HTRS to a clearinghouse for

industry sponsored trials with little room for our input and influence. Option #3 would likely not be acceptable to industry. Option # 2 seems the best compromise and allows the HTRS to lobby for the studies deemed to be highest priority by its membership. This is the real value of having a priority list of those topics of greatest concern to our membership.

- Develop a mechanism through the society for statistical support, particularly in study design and/or analysis – while this is something that may be very helpful, funding for this may have to wait until the society has an established track record in clinical trials.