HFA
Hemophilia Federation of America™

Hemophilia Federation of America's

RESEARCH AGENDA

For Females with Bleeding Disorders

TABLE OF CONTENTS

BACKGROUND

Inherited bleeding disorders, such as hemophilia, have long been recognized, tracked, and researched in males. However, the Centers for Disease Control and Prevention (CDC) currently estimates that inherited bleeding disorders affect up to 1% of all women and girls in the United States.[1] Through direct engagement with the bleeding disorders (BD) community, the Hemophilia Federation of America (HFA) has likewise identified a need for more support for females and individuals assigned female at birth, as well as intersex and non-binary individuals, with bleeding disorder diagnoses or symptoms. In response to this, the work of HFA's Engagement and Community Health Outcomes (ECHO) team (formerly Research) in recent years has placed a focus on females in the bleeding disorders community; this work has included assessing the needs of females as well as providing education around bleeding disorders in females. Through this work, HFA has identified a gap in bleeding disorders research specific to females. Because the presentation of bleeding disorders in females is often different than that of men, this lack of research represents a gender-based health disparity. In addition, HFA determined that females are often willing and interested in participating in research but have not been provided opportunities to do so thus far. Access to novel therapies for females has historically been limited, since trials have largely only been conducted on males; this further illustrates the need for the inclusion of females in bleeding disorders research overall. Additionally, trials that do not exclude females can further prioritize females in study participant recruitment. This can improve representation of females in existing studies, as well as highlight a desire from the community for researchers to approach study participants that they have not previously routinely considered.

With this in mind, HFA has engaged females in the bleeding disorders community through funding from the Eugene Washington PCORI Engagement Awards (Engagement Awards) program, an initiative of the Patient-Centered Outcomes Research Institute (PCORI); this engagement has been built upon a foundational belief that a focus on the perspective of stakeholders, including patients, throughout all stages of research will enhance research overall by improving its relevance to those upon whom it is focused.[2] For example, including the patient voice in planning phases will focus research questions around what patients feel is most important to their own quality of life and will inform patient engagement protocols by enumerating barriers study participants may experience and how they can be accommodated and fairly compensated, thus improving research recruitment and retention; meanwhile, patient input on dissemination of research findings can enhance accessibility of findings to those who are most directly affected. This engagement, completed by HFA between 2019 and 2021, aimed to educate females within the bleeding disorders community about patient-centered and comparative effectiveness research with the goal of further increasing their interest and capacity in participating in future research initiatives. After the completion of this engagement, a new module was launched on HFA's online learning management system (LMS), Learning Central, providing continued access to this educational content for patient audiences. Because of this work, HFA feels that the female bleeding disorders community is primed to participate in, and contribute to, research focused on their needs.

[1] https://www.cdc.gov/ncbddd/blooddisorders/women/features/state-of-science-and-cdc-programs.html
[2] https://jamanetwork.com/journals/jama/article-abstract/1901303

METHODS

To encourage research around females with bleedings disorders, a Community-Based Research Network (CBRN) was established in 2021 as part of HFA's Females in Research Sharing and Translation (FIRST) project, consisting of researchers, patients, and representatives of patient advocacy programs. The goal of the CBRN was to create a roadmap that outlines and addresses the unmet needs of females in the bleeding disorders community from both the patient and provider perspectives. To work toward that goal, the CBRN engaged in discussions to develop a shared research agenda that would guide current and future projects involving females with bleeding disorders. The research agenda, outlined below, is designed as a reference for research organizations to inform projects, with the aim of ensuring projects are directly useful to community members, supply research that informs policy and practice, and increase the capacity of stakeholders to conduct and use research. To that end, the CBRN identified research topics for females, listed in Appendix A, as areas of focus for work for the next three to five years. In addition, the CBRN outlined a few example research questions within these areas, listed below.

The research topics and questions created by the CBRN were then further refined, added to, and vetted in 2022 by a Steering Committee (SC) comprised of additional researchers, females with bleeding disorders, and other bleeding disorder stakeholders. The research agenda document was then shared more broadly among the colleagues/contacts of the SC to garner further input, refinement, and approval.

FOCUS AREAS
Research topics and questions were built out within the following focus areas:

Lifespan
Topics outlined in this area are not specific to any particular age or stage in life but could affect females throughout their lifespan. This area also encompasses research topics related to underserved communities or groups and associated social health disparities and negative health outcomes. Example research questions generated include:

- What are the patient-centric clinical endpoints that should be utilized in every clinical trial?
- What is the burden of disease, especially in the context of clinical bleeding, quality of life, pain, and medication use?
- What gaps in care exist for females in various populations due to social-economic health disparities or geographic considerations?

- Does prophylaxis in non-severe hemophilia or von Willebrand Disease (VWD) reduce bleeding events?

Adolescence
This stage of life, from menarche (around 11-12 years of age) through adulthood (around 18-19 years of age) is unique due to the effect of bleeding on school-related issues such as attendance, special considerations/accommodations needed during bleeding, and emotional effects on grades and social life. In addition, the existence of menarche within this age group differentiates it from other age groups, lending to potential to improving the processes for screening and diagnosis of bleeding disorders, as menstrual bleeding during adolescence is often a first indication of bleeding disorders in females. Example research questions for this age range are:

- Can the institution of a universal screening tool for Heavy Menstrual Bleeding (HMB) improve health care professional awareness of signs/symptoms of bleeding disorders in females, increase the number of females diagnosed with bleeding disorders, increase the number of hematology referrals, and improve quality of life and school attendance in adolescent females experiencing HMB?
- Do adolescents and young adults with heavy menstrual bleeding and a high fatigue score have an increased risk for an underlying bleeding disorder compared to the general population risk?

Reproductive Age
This age range (from approximately 20-50 years old) is often defined by family planning, pregnancy/childbirth, and caregiving, as well as the progression of complications from joint bleeds over time. An example research question written for this age range is:

- Would prophylactic factor or non-factor treatment slow the progression of joint damage/arthritis for females who are diagnosed later in life, especially if microbleeds are suspected?

Menopause
This age group consists of females who are going through or have completed menopause (approximately 51 years of age and older). Special consideration is needed for this group who, due to the cessation of the menstrual cycle, can often be dismissed from treatment and care for their bleeding disorders. Example research questions for this life stage include:

- Do bleeding symptoms change as females age and go through menopause?
- Does menopause and its inherent hormonal changes alter hemostasis and factor levels?

Results

Appendix A lists topics of interest identified by the CBRN and refined by the SC within each focus area. These topics, not listed in any particular order, are provided with the hope that stakeholders will be able to further refine and focus their research on topics that are of interest to them, yet essential and relevant for the care of females with bleeding disorders. Appendix B lists suggested methods and strategies for carrying out research studies based on the example questions listed above.

A Note on the Importance of Dissemination

Too often, it takes years for useful new findings from clinical research to be taken up in practice and to influence health care. In addition, research results are typically not presented in formats or language that patients and their caregivers can easily understand.[3] Poised to change this landscape, HFA's work includes the patient in every step of the research process, including plans for dissemination of any findings.

Dissemination methods of any findings of research activities resulting from this agenda could include:
- White papers
- Research Journal publication
- Patient accessible Journal articles, HFA's Dateline
- Poster/conferences
- Professional and patient conference sessions
- Webpages on affiliated sites, promoted via social media

In addition, dissemination of any new tools and/or guidelines resulting from this research would be essential. For example,

in the case of the creation of a Heavy Menstrual Bleeding universal screening tool, it would be suggested that researchers:

- Provide patients with access to the tool and encourage them to take it to their Primary Care Provider (PCP) if their PCP isn't using one
  – Consider web-based platform for increased accessibility
  – Share with patient organizations such as National Hemophilia Federation (NHF) and HFA
  – Create a publicity campaign (posters, social media awareness, etc.)
- Share generally with organizations like the American Academy of Pediatrics, ACOG, MASAC to make policy change & recommendations
- Publish in journals wider than in the hematology space (to include OB/Gyns, family practice physicians, etc.)
- Disseminate at conferences
- Share results with medical schools and other health professional schools, encouraging them to include questions on medical school & board exams

Summary

Overall, the importance of research on females with bleeding disorders cannot be understated. The landscape of research on females with bleeding disorders has thus far remained largely unmapped, making it difficult to determine where to start. Our hope in creating this research agenda is to create a launchpad for this type of research while keeping patient needs and input at the center of the focus of research. Topics within the focus areas listed reflect the suggestions and needs of both patients in this community and physicians who provide care to it. Through this work, we hope to improve care for females with bleeding disorders across their lifespans and into future generations.

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[3] https://www.pcori.org/sites/default/files/PCORI-DisseminationImplementation.pdf

APPENDIX A:

Research Topics/Ideas Generated by the Community Based Research Network and Steering Committee

Research topics in red font are the top-priority research topics selected by females with bleeding disorders for each focus area

Theme	Research Category	Additional Information
Lifespan	Clinical Trial Endpoints	What are the routine endpoints that should be collected in every clinical trial? How should endpoints potentially be created or revised for various or underserved populations where bleeding disorders may present differently?
	Burden of Disorder	What is the burden of bleeding disorders in females? Measuring clinical bleeding; Measuring quality of life, pain, medication, limited mobility use; Measuring socioeconomic effects; Measuring impact of disease on employment, insurance, family
	Social health disparities	What gaps in care exist for females in various populations due to social-economic health disparities or geographic considerations?
	Non-severe prophylaxis	Does prophylaxis in non-severe hemophilia reduce bleeding events?
	Aging with BD	What is the natural progression of bleeding disorders for females?
	Family of Males with BD	Explore whether routine genetic testing for siblings/family of people diagnosed with hemophilia should be a best practice; use encounters with male patients as an opportunity to discuss genetic testing of all potentially affected members of the family
	Life experiences	Capturing the stories of the effects of bleeding disorders on a female life spectrum
	Addressing "normalization"	Address issues faced by generations of females with inherited bleeding disorders; define "normal" bleeding for a female with a bleeding disorder as well as "normal" bleeding for a femle without a bleeding disorder
	Mental Health	Explore the mental health impact of bleeding disorders on females (especially during adolescence and menopause life stages)
	Classification of disorder	Explore classification of bleeding disorders that reflects bleeding phenotype as well as factor levels, along with associated management recommendations for each classification
	Support	Identify support available during various stages of life (infancy, youth, adulthood, post-menopause) in non-clinical settings; evaluate current support available for females in HTCs and other hematology clinics

Theme	Research Category	Additional Information
Adolescence	Universal Screening tool	Can the institution of a universal screening tool for Heavy Menstrual Bleeding (HMB) improve health care professional awareness of signs/symptoms of bleeding disorders in females, increase the number of hematology referrals, and improve quality of life and school attendance in adolescents experiencing HMB?
	Assessing knowledge of parents, patients, and providers	Evaluating parent and patient knowledge and understanding of bleeding disorders; what is considered "normal," when to treat, etc.
	Quality of Life	Measure impact of being an adolescent female with a BD in daily life, especially considering missed days of school due to bleeding/cramps and/or special accommodations needed during menstrual bleeding, the effect on relationships/social life, and the impact of activities restricted to prevent injury; also consider whether there are intersections with compounding barriers to care, such as geographic, economic, or underserved community status
	Fatigue score for females with reported HMB	Do adolescents and young adults with heavy menstrual bleeding and a high fatigue score have an increased risk for an underlying bleeding disorder compared to the general population risk?
	School Policy	Assess need for policies and support while adolescent females w/BD are in school to have access to the bathroom to avoid missed days of school and ensure academic success is attainable for this demographic
Reproductive Age	Pregnancy	Explore difficulties in getting pregnant due to BD
	Childbirth Complications	Track bleeding after childbirth (including vaginal deliveries), potential need for transfusions, epidural anesthesia and factor level needed to be able to have epidural; also consider differences in care due to underserved community status
	Self-management	Self-management of females with BD who are caring for a child(ren) (with or without BD)
	Hormonal Therapy	What is the best line of hormonal therapy? Combined hormonal contraceptives, IUD, or other hormonal options; what should be the first line of therapy for females with BD?
	Prophylactic Treatment	Would prophylactic treatment slow the progression of joint damage/arthritis for females who are diagnosed later in life, especially if microbleeds are suspected?
	Burden of disease	Study the impact of the disease on females of reproductive age on employment, insurance, family planning, home life, caretaking, sex, overall quality of life

Theme	Research Category	Additional Information
Menopause	Bleeding disorder symptoms over time	Do bleeding symptoms change as females get older and go through menopause?
	Menopause and hemostasis/factor levels	Does menopause and its hormonal changes alter hemostasis and factor levels?
	Bone health	Studies on bone health in females with platelet disorders and/or VWD
	Mental health	Is there a connection between receiving BD treatment and mental health for menopausal or post-menopausal females?

APPENDIX B:
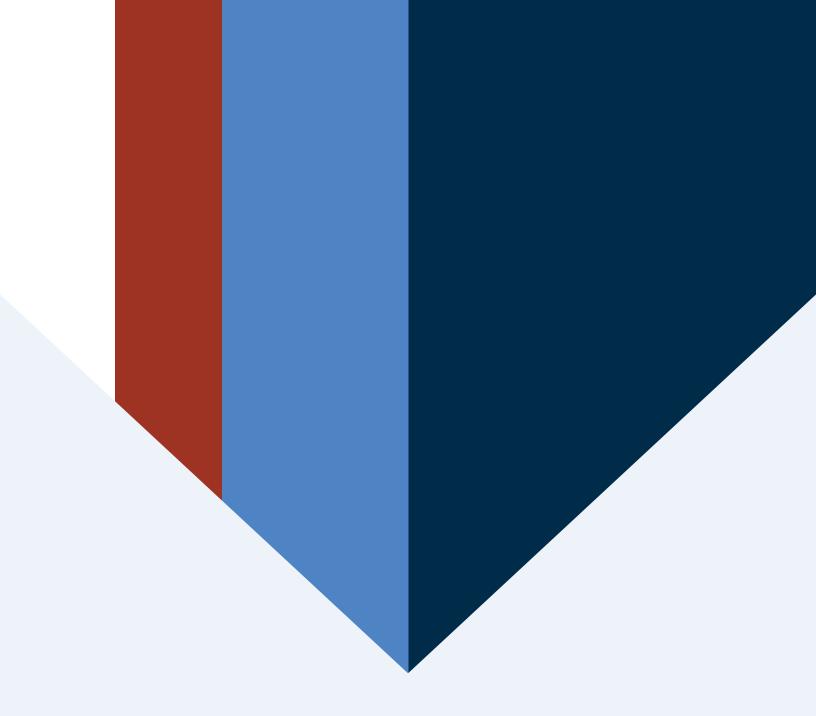
Suggested Methods/Strategies for Example Research Questions

Subtopic	Question	Method	Recruitment Strategy	Data Collection/ Analysis
Lifespan	What are the patient-centric clinical endpoints that should be utilized in every clinical trial?	Key informant interviews and/or focus groups, survey	Recruit females with Hemophilia A or B levels 1-40%, or VWD and hematologists at Hemophilia Treatment Centers (HTCs)	Primary data (surveys, interviews) analyzed via mixed methods with quantitative and qualitative evaluation
	What is the burden of disease? Measuring clinical bleeding, quality of life, pain, medication use	Observational study; Could apply to use Community Counts Data through American Thrombosis and Hemostasis Network (ATHN), or the PROBE study	Recruit females 18+ with a diagnosis of hemophilia A or B or VWD	Primary data, analyzed using descriptive statistics; use ATHN to access research sites; non-HTC patients register through a website
	Does prophylaxis in non-severe hemophilia or VWD reduce bleeding events?	Comparative research study	Recruit males and females, adolescent and older with a diagnosis of mild/moderate hemophilia, or Type 1 or Type 2 VWD	Primary, Secondary data; Single arm study design with 6-month lead in focusing on Annual Bleed Rate (ABR). Compare ABR lead in or pre-study ABR. Focus on Quality of Life (QoL) using the CATCH tool, fit for purpose Patient-Reported Outcome measures (PROs) and work productivity assessments

Subtopic	Question	Method	Recruitment Strategy	Data Collection/ Analysis
Adolescence	Can the institution of a universal screening tool for Heavy Menstrual Bleeding (HMB) improve health care professional awareness of signs/symptoms of bleeding disorders in females, increase the number of females diagnosed with bleeding disorders, increase the number of hematology referrals, and improve quality of life and school attendance in adolescent females experiencing HMB?	Mixed methods: **Qualitative:** focus groups with adolescents to understand the impact of HMB on their quality of life & school. How to start and have conversations around menstruation. What questions should we be asking? **Experimental:** use a control group Create a tool to screen the provider as to what they would do with abnormal results on the bleeding assessment.	School-based health clinics General pediatrics clinics OB/Gyn clinics Messaging through various period apps Patient orgs-HFA & NHF	Primary; would require the development and validation of a universal screening tool for HMB (validated by a psychometrician) that could be disseminated and implemented in clinics across the country. Secondary; collect the electronic health record (EHR) data needed for the study; statistically analyze quantitative data gathered
	Do adolescents and young adults with reported heavy menstrual bleeding and a high fatigue score have an increased risk for an underlying bleeding disorder compared to the general population risk?	Literature review, Comparative observational study	Recruit from gynecology clinics, pediatric clinics, and family medicine clinics. Exclusion criteria: patient with diagnosed blood disorder, patient with other medical diagnoses that may cause chronic fatigue (chronic fatigue syndrome, anemia of other cause, etc.)	Primary (Laboratory analysis: PT, PTT, TT, CBC, Ferritin, VWF [Von Willebrand Factor] Antigen, VWF Activity, Factor VIII Assay), platelet function. Secondary (results of literature review); statistically compare fatigue scores of females without underlying BD with those who have BD

Subtopic	Question	Method	Recruitment Strategy	Data Collection/ Analysis
Reproductive Age	Would prophylactic factor or non-factor treatment slow the progression of joint damage/ arthritis for females who are diagnosed later in life, especially if microbleeds are suspected?	Comparative observational study	Recruit small cohort of post-menopausal females who were diagnosed in their 20s or 30s from hematology clinics	Primary, secondary (EHR); determine whether prophylactic treatment has been prescribed and compare development of joint damage/arthritis between females on prophylaxis and females not on prophylaxis over time using descriptive statistics
Menopause	Do bleeding symptoms change as females age and go through menopause?	Mixed methods: Qualitative: Focus groups can explore female issues and the best way to capture female experiences in a quantitative survey. Quantitative: Survey on post-menopausal females: demographics, symptoms, BD diagnosis, quality of life, factor levels over time, how anemia and iron deficiency affect daily lives, comorbidities, joint range of motion change	Recruit females in their 30s, 40s, 50s with bleeding disorders and with or without a history of hysterectomy from HTCs, Hematologists, and Ob/Gyn offices	Primary- Large prospective study following females over 2 years (with visits every 6 months) focused on those with low VWF, VWD, hemophilia carriers, rare bleeding disorders, qualitative platelet dysfunction, and other factor deficiencies. Collect bleeding symptoms and how they changed over time correlating with possible check factor levels over time. Also collect quality of life and evaluate how anemia affects daily lives, comorbidities, range of motion scores, bleeding scores. Use focus group to inform survey development and statistical analysis for survey results and medical records.
	Does menopause and its inherent hormonal changes alter hemostasis and factor levels?	Quantitative: measure factor levels and perform coagulation testing in representative group of pre-menopausal females with bleeding disorders and compare to post-menopausal females with bleeding disorders	Recruit from hematology clinics	Primary data (lab testing) statistically analyzed along with medical records