Introduction:

Nurses are the cornerstone of the Hemophilia Treatment Center (HTC), often developing close relationships with their patients as they journey through their life with hemophilia. Many have watched their patients grow to adulthood and now care for multi-general families. Now, many senior HTC nurses, who have a rich history of working with their hemophilia patients, encountering many challenges and successes. These interactions can become close to the HTC nurse’s heart shaping their future and defining “who they are”. When HTC nurses retire or leave the field of hemophilia, those stories and learning opportunities will be lost, thus a forum is needed to demonstrate real live experiences and teachable moments that can be incorporated into the care provided by current and future HTC nurses as they continue to provide care.

Objective:

Capture the rich history of HTC nursing so that it can be shared with other hemophilia nurses for enrichment and learning opportunities inherent in the care of persons with hemophilia.

Methods

The Clinical Support Specialist team (CSS) of nurses with Bayer HealthCare identified this need and took on the challenge to preserve the stories of HTC nurses. Through direct contact, crafted emails, and direct mailings, HTC nurses were encouraged to submit their stories. These stories were then vetted by an independent marketing team and dedicated nurses from Bayer’s ad board with respect to content, preservation of anonymity of patients, and grammar. Submitted stories were then reviewed by the author for final approval and acceptance into the book.

Summary

The 2016 version of “Chronicles of Caring” was published in December 2016 and the Bayer CSS team has been actively distributing the book to HTC nurses throughout the country. Positive feedback has been received and thus the 2017 version is in progress.

Conclusions

This book has provided an excellent forum for HTC nurses to share personal experiences and provide learning opportunities for newer HTC nurses. The goal is to continue this format yearly.
Survey Finds Interest in Bleeding Disorder Social Work Specialty Credential

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Objective: The National Hemophilia Foundation (NHF) Social Work Working Group (SWWG) comprises SW leaders from the U.S. Hemophilia Treatment Center Network (USHTCN) aiming to enhance competencies/opportunities among USHTCN SWers. The Partners in Bleeding Disorders Education Program (“Partners”) promotes excellence in care through education by/for the USHTCN and supported development of the Hemostasis Nursing Board Certification Program, launched Dec 2015. In 2016, the SWWG and Partners surveyed USHTCN SWers’ interest in Bleeding Disorders Social Work Specialty Credentialing (BDSWSC).

Methods: The SWWG met with the National Association of Social Workers (NASW) in Sept 2014 then formed a Credentialing Committee to review existing SW specialty credentials. The SWWG conducted interviews with credentialed specialists on strategy, costs, and eligibility. In Sept 2016, USHTCN SWers were surveyed to measure interest in BDSWSC.

Summary: The survey was emailed to 259 USHTCN SWers. 118 (46%) opened the email; 93 (36%) participated. 31 responded via link on the NHF website, totalling 123 responses.

- 46% were interested in BDSWSC, 11% uninterested. 43% requested more information.
- Noninterest stemmed from a perception that achieving BDSWSC would not be rewarded.
- Most would not expect increased responsibilities/salary. 39% would expect more responsibility; 37% more pay.
- Content should include bleeding/clotting disorders and confer continuing education units.
- Preferred course formats included online webinars with ability to ask questions (68%); live workshops and online interactive case studies (59%); and coursepack/newsletters (58%).
- Time commitment ranged from 1 day to several hours per month over a finite period.
- >50% of respondents were willing to pay only ≤$100; 5% would pay ≤$400.
- 33% indicated their HTC would cover the cost; 58% were unsure.

Conclusions: BDSWSC would recognize professional achievement while assuring USHTCN SWers meet certain standards. USHTCN SWers desire to participate or obtain more information about BDSWSC. This possibility requires frank discussion of HTC capacity to support staff time and to compensate for the achievement. Most SWers were unwilling to pay >$100 and unsure if their HTC would cover the cost which may range up to $450.

To further investigate feasibility, we will survey HTC Medical Directors and Administrators about their interest/ability to support SWer time to achieve a BDSWSC and to financially support and/or compensate credentialing with increased pay/responsibility. This information will allow the SWWG to further discern USHTCN SWer interest and determine next steps.
A Study of Ethical Issues in the Bleeding Disorders Community (BDC)

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Objective:

At the request by the Social Work Working Group (SWWG) the National Hemophilia Foundation (NHF) agreed that an Ethics Working Group (EWG) within the Medical and Scientific Advisory Council (MASAC) could be formed. Since that time there has not been a clear definition of what are the ethical concerns in the bleeding disorders community. This study through the use of focus groups (FG) with physicians, nurses, social workers, physical therapists, consumers, and industry attempted to identify these concerns. A limitation of this study is that consumers did not respond to the request to participate.

Methods:

FG participants were asked to write a list of what they thought were primary ethical concerns. No food or special event was offered to participants and FG’s were held in three different physical locations.

Summary:

In every group there was concern about boundary issues between all members of the BDC. Of particular concern Pharma now directly markets to patients, Industry hiring patients and family members, conflicting ethical standards within professions, pharma, home care, and individual Hemophilia Treatment Centers (HTC). Additionally Industry did not know how to even start to address ethical breeches outside of their own companies and concern that other members of the BDC would not know how to address ethical breeches from their companies.

Conclusions:

- The limitation of not having consumer participation calls for more focus groups perhaps at NHF’s Annual Meeting, so this critical part of the BDC can be heard. In these new FG’s a list of possible concerns should be given to participants for them to rank order and then have a question that is open ended so that participants can express additional concerns. This would allow for more accurate measurement.

- The EWG needs to better advertise in the BDC that there is a place to ask ethical questions and to explain that their mission is not to make judgements, but to advise regarding what best practices should be considered for resolution. Over time the EWG can make recommendations for policy development to MASAC for resolution to chronic ethical issues.

- Consistent conversations and presentations regarding ethical issues and potential development of policies to prevent unethical behaviors is needed and encouraged.
Factors influencing uptake of evaluation among hemophilia carriers and potential carriers

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Objective: Hemophilia A and hemophilia B are X-linked bleeding disorders that have been primarily seen as diseases affecting only males; however, there is increasing evidence to show psychological, medical, and reproductive advantages for women to know their carrier status. There is limited knowledge regarding why only some women seek evaluation regarding their hemophilia carrier status; as such, this study explores factors that influence the decision to pursue evaluation among hemophilia carriers and potential carriers. Methods: A cross-sectional study was conducted using a web-based quantitative survey. Women with a family history of hemophilia were recruited at the National Hemophilia Foundation Annual Meeting and via Hemo Friends Facebook and Hemophilia Foundation of Oregon Facebook pages. Correlations between factors and establishment of care were explored using comparative statistics. Summary: Sixty-nine hemophilia carriers and potential carriers were included in this analysis. Individuals with a personal history of bleeding symptoms (27/41) and individuals who required treatment for a bleeding event (18/22) had significantly higher rates of establishing care (p=0.041, p=0.004, respectively). Individuals with a family history of severe hemophilia demonstrated higher levels of knowledge for hemophilia inheritance (24/34) and bleeding risks to carriers (12/30)(p=0.0007, p=0.035, respectively); they were also more likely to discuss hemophilia with family members (27/34). Conclusions: The findings suggest that hemophilia carriers and potential carriers are more likely to establish care after experiencing bleeding symptoms. Hemophilia severity may impact the retention of knowledge and motivation to discuss with relatives. This has implications for healthcare providers in how they enhance and promote care for hemophilia carriers.
ATTITUDES AND PERSPECTIVES ON ANKLE FUNCTION IN PEOPLE WITH HEMOPHILIA: A QUALITATIVE STUDY

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Background: For people with hemophilia, mild trauma can cause internal joint bleeding resulting in stiffness and pain, limited range of motion and irreversible bony changes. Ankle pain may occur early in life affecting the ability to participate in activities of daily living, work and leisure. The purpose of this study was to explore experiences and priorities of people with hemophilia regarding their foot and ankle function, activity and participation.

Methods: Eleven participants with hemophilia A or B, twenty-one years and older with a history of ankle pain, were recruited. Semi-structured interviews were recorded, transcribed and then analyzed for themes with NVivo 10 Software.

Results: Themes: (1) "Pain impacts my daily life, but I still have to get things done." (2) "Management of ankle function is highly individualized." (3) "Self-advocacy is crucial." (4) "I want healthcare providers who listen to me and respect my knowledge."

Conclusions: For our participants, ankle pain and dysfunction impact daily life. Expressed themes highlighted priorities for participation, health management and desired healthcare.

Discussion: As health care moves from volume-based to value-based care delivery, the patient’s voice is increasingly important in prioritizing interventions. The participant-identified priorities and experiences from our study can begin to inform healthcare providers, allowing them to deliver more targeted care for their patients with hemophilia.
Addressing issues of women and girls with blood disorders (WGBD) through a collaborative obstetrics/gynecology, adult and pediatric hematology lifespan clinic: a pilot project.

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Background: Women and girls with blood disorders experience unique issues through their lifespan that include reproductive tract bleeding, dysmenorrhea, pregnancy related bleeding, anemia and thrombosis. Based on the Foundation of Women and Girls with Blood Disorder (FWGBD) Learning Action Network (http://www.fwgbd.org/wgbd-learning-action-network-lan) concept, we developed an integrated team approach to address issues across the reproductive lifespan for females, that included an obstetrician/gynecologist (Ob-Gyn), adult and pediatric hematologists, nurse coordinators and more recently a social worker.

Objectives: Primary objective was to determine the spectrum of blood disorders in adult and pediatric patients who required combined Ob-Gyn and hematologic expertise. Secondary objective was to describe the process of instituting a collaborative/integrated clinic for WGBD.

Methods: Patient definition included females with diagnosed and undiagnosed blood disorders who required hematologic and Ob-Gyn consultation and management. The referral base was adult and pediatric hematology clinics and community Ob-Gyn referrals. The team consisted of Ob-Gyn, adult and pediatric hematologists, nurse and social worker. The dean’s office at Michigan State University (MSU) provided administrative support to address facility, personnel and billing issues.

Results: Over 1 1/2 years, the dean’s office facilitated in-person meetings of key stakeholders (administrators, physician specialists, nurse managers, information technology and billing) and site visits to address clinic space, personnel, billing, medical records, marketing and the target population. Since April 2016, we have conducted 12 clinics, with 37 unique patients (23 adults and 14 pediatric) and 10 follow-up patients; ages were 13-45 years; average number of patients per clinic was 3.8 (range 2-6). The average time in the clinic per patient was approximately 2 hours. Diagnoses included thrombophilia/thrombosis (15), von Willebrand disease (9), isolated heavy menstrual bleeding (HMB) and/or anemia (7), thrombocytopenia (3), platelet function defect (1), and sickle cell disease (1). Ob-Gyn consultation was obtained for hormonal therapy for HMB, pregnancy loss, dysmenorrhea, contraception counseling, and pregnancy management of severe maternal immune thrombocytopenia. Management plan was presented jointly and discussed with the patient. Thrombosis/thrombophilia in adults and HMB in adolescents were the most common diagnoses. Many patients presented with more than one diagnosis.

Conclusions: This pilot study demonstrates that a broad range of blood disorders among women and girls require collaborative hematologic and Ob-Gyn diagnosis and management. Most adult patients sought consultation for thrombophilia/thrombosis and most pediatric patients for HMB. Contraceptive/hormonal concerns and issues were common to both age groups. Administrative support was integral to the success of this clinic.
Patient Reported Outcomes, Burdens and Experiences (PROBE) Study Data Visualization and Analysis

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Introduction: The Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire assesses health status in patients with a bleeding disorder specifically, hemophilia. PROBE was developed with direct patient involvement in questionnaire design, conduct, and analysis using outcomes identified as important by patients. Feasibility and reproducibility of the PROBE questionnaire have been previously reported. Accessible, robust patient-reported data will strengthen advocacy efforts to improve and sustain care, and raise awareness within the hemophilia community and public of the impact of quality treatment and value of effective prevention.

Objective: Develop an analytics tool and visualization dashboard for PROBE study data allowing interactive selection of outcomes of interest. Implement a data platform that accommodates rapid update, a user-friendly interface and ease of presentation.

Methods: The PROBE dashboard was developed using Microsoft Power BI software, which includes a suite of business analytics tools. The first 2100 questionnaires collected by 20 national patient organizations worldwide were used in development of the pilot PROBE dashboard.

Summary: The dashboard is divided into two main components - filters and graphs (visualization views). The visualization views provide graphic results for the selected outcome of interest (e.g., pain, independence, education, employment, family life, mobility, and current health status). Filters allow refinement of the data sample for demographic variables (e.g., region of the world, diagnoses, disease severity, inhibitor history, treatment regimen, age group and gender). Comparator data from those not personally affected by a bleeding disorder are also depicted. The graphs are interactive allowing comparison of outcomes using the demographic variables.

Conclusions: The results of the feature-rich dashboard indicate an integral interaction between the analytical tool Power BI and PROBE study data. The dashboard will allow participating organizations easy, secure and large-scale external as well as internal access to PROBE study data. Real-time updates permit viewing progress and fluctuations of the data for outcomes both within each country and cross-sectional across countries. The PROBE dashboard framework and analytics will be further refined through beta testing with the participating organizations.
BAY 94-9027, a Site-Specifically PEGylated Recombinant Factor VIII: Preliminary Results From a Global Comparative Laboratory Field Study

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Background: Accurate measurement of factor VIII (FVIII) activity in patients with hemophilia A is important for patient monitoring and treatment decisions. Discrepancies in results using different assays or reagents to measure prolonged-half-life factor products have been recognized. BAY 94-9027 is a prolonged-half-life FVIII product site-specifically conjugated with a 60-kDa polyethylene glycol molecule (2×30 kDa branched).

Objective: A global field study was conducted to assess the ability of clinical laboratories to measure BAY 94-9027 activity in spiked hemophilic plasma samples using their in-house or specific assays.

Design/Method: In this 2-part study, laboratories received sample sets (3–4 per laboratory) of 26 blinded samples in randomized order for analysis. Each set consisted of triplicate test samples of BAY 94-9027 or a comparator (antihemophilic factor [recombinant] plasma/albumin-free method [rAHF-PFM (Advate®); Shire]) spiked at low (<10 IU/dL), medium (10–50 IU/dL), and high (50–100 IU/dL) concentrations in pooled hemophilic plasma. Normal control plasma and unspiked hemophilic plasma in triplicate were positive and negative controls, respectively. Two additional blinded samples matching 2 of the other 24 samples in the set were included in each set to decrease the predictability of each set. Laboratories analyzed test samples using their in-house assays (one-stage, chromogenic, or both), reagents, and standards (part 1). In part 2, all laboratories tested 2 additional sample sets using 2 activated partial thromboplastin time kits (Pathromtin® and HemosIL® SynthASil) previously shown to accurately measure BAY 94-9027 and full-length FVIII. FVIII recovery and FVIII levels were primary and secondary endpoints, respectively.

Results: Fifty-two laboratories in North America, Europe, and Israel participated in the study. In part 1, 49 laboratories tested samples using the one-stage assay, 16 used the chromogenic assay, and 13 used both assays. The reagents routinely used for measuring FVIII activity varied among participating laboratories. Mean FVIII recovery ranged from 75.1%–103.2% for BAY 94-9027 and 94.6%–114.7% for rAHF-PFM across all concentrations and reagents using the one-stage assay. As expected based on previously published data, the PTT-A and HemosIL® APTT-SP kits underestimated BAY 94-9027 at all concentrations. More accurate one-stage results were generated using the Pathromtin® and SynthASil kits, as shown in part 2 of the study. For the chromogenic assay, mean FVIII recovery ranged from 104.4%–117.1% for BAY 94-9027 and 87.7%–107.8% for rAHF-PFM across all concentrations.

Conclusion: BAY 94-9027 can be accurately monitored using the chromogenic assay and select commonly used one-stage assay kits without need of a conversion factor.
Pharmacokinetics and Prophylaxis Regimens and Relationship to Bleed Outcomes in Patients With Severe Hemophilia A Treated with BAY 81-8973

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Background: Factor VIII (FVIII) pharmacokinetic (PK) parameters and other patient characteristics may play a role in effectiveness of FVIII prophylaxis.

Objective: A post-hoc analysis was conducted to assess the association between PK parameters and BAY 81-8973 (Kovaltry®) prophylaxis regimen in patients with severe hemophilia A.

Methods: LEOPOLD I was a randomized, open-label, phase 2/3 trial to investigate use of BAY 81-8973 routine prophylaxis for treatment of bleeds in adolescents and adults with severe hemophilia A. In the efficacy part of the trial (part B), patients received BAY 81-8973 at a dose of 20-50 IU/kg 2x/week (n=18) or 3x/week (n=44) for 12 months. Prophylaxis regimens were determined by study investigators, independent of BAY 81-8973 PK data. A subset of 20 patients (2x/week, n=7; 3x/week, n=13) had data from an earlier PK study (part A), in which patients received a single 50-IU/kg injection of BAY 81-8973 and had blood samples collected over 48 hours to assess PK parameters, including area under the curve (AUC), half-life (t½), and clearance (CL). Estimates of PK parameters were also derived using a population PK model based on data from all patients. This analysis compared model-based PK parameters, baseline characteristics, total annual dosing, and bleed outcomes between 2x/week and 3x/week prophylaxis groups. A similar analysis was done among the subset of patients in part A who had PK data. Differences between 2x/week and 3x/week dosing were assessed using Wilcoxon rank sum tests for continuous variables, and chi-square or Fisher’s exact tests for categorical variables.

Results: In the full trial population, model-based AUC [mean (SD): 1957.1 (648.3) vs 2139.1 (875.7), 2x/week and 3x/week, respectively], t½ [15.0 (3.7) vs 15.9 (6.6)], and CL [0.028 (0.009) vs 0.027 (0.011)] were comparable between groups. The proportion of patients with ≥3 bleeds at 12 months was 33% for 2x/week and 48% for 3x/week. The 3x/week group had more bleeds in the past 12 months, higher baseline Gilbert bleeding scores, were more likely to have target joints at baseline, and received higher doses of BAY 81-8973 during the 12-month treatment period. In the part A subset analysis, observed and model-based AUC, t½, and CL were similar in both groups. The proportion of patients with ≥3 bleeds at 12 months was 0% for 2x/week and 46.2% for 3x/week (P=0.052).

Conclusions: The similarity of PK parameters in patients successfully treated with 2x/week and 3x/week regimens suggests that clinical factors other than t½, AUC, and CL are important in predicting success of prophylaxis with BAY 81-8973. Physician decisions, taking into consideration clinical factors to identify appropriate patients for specific prophylaxis regimens, appear to be an important factor for 2x/week or 3x/week dosing with BAY 81-8973. These factors should be considered when individualizing BAY 81-8973 prophylaxis frequency.
My Life Our Future Genotyping Days: On the Road Again to New Horizons

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Objective: To provide genotyping and enrollment into the My Life, Our Future research repository for individuals with Hemophilia and potential carriers by offering a community based outreach program.

Methods: Utilizing the ATHN dataset, potential participants who had not been previously genotyped were identified. In addition, a recruitment letter was prepared and sent to invitees of the local NHF Chapter Annual Dinner. Interested subjects were instructed to contact the genetic counselor, who discussed the project and scheduled them in 15 minute research timeslots. A hospital mobile unit, stocked with medical supplies and a centrifuge, was obtained to provide a site for registration, phlebotomy and processing of specimens. Staff for the event included the following: three staff to consent participants; four staff providing venipunctures, two staff to process specimens, two staff to assist with registration and a driver for the mobile unit. Funding was secured through NHF to support the genotyping day.

Summary: Fifteen subjects, including 3 males and 12 females, scheduled appointments for the 4-hour recruitment time period. In addition, three subjects were added the day of the project and a waiting list was started for those wishing to enroll at a future event. In total, 17 subjects were enrolled from 9 families. In several cases, family members from different generations enrolled, including an at-risk carrier female, her mother and grandmother. Ages of participants ranged from 4-91. All participants chose to participate in the research repository. One participant’s specimen had to be destroyed due to a mislabelled MLOF ID (an add-on subject). It took approximately 10 hours to prepare for the event including 2 hours of planning related to the mobile unit (5 staff) and 8 hours to develop the recruitment letter, prepare the IRB amendment, mail letters, schedule participants, prepare consent packets, obtain MLOF ID numbers, and arrange phlebotomy kits (4 staff). It took 5 hours and 12 staff to successfully implement the program on the genotyping day. In comparison, we typically process on average two patients per 4 hour comprehensive clinics held two times per month, with 2 staff involved with other concurrent job assignments.

Conclusions: The outreach program is an effective way to recruit individuals for genotyping and participation in the MLOF research repository. Participants were excited to participate and inquired about future events. The event provided a relaxed atmosphere with extended family members present, allowing for multi-generational and diverse recruitment. When considering a genotyping day versus scheduled clinic time, additional preparation time is needed to arrange logistics and avoid error, but the number of participants is significantly increased.
Journey To Best Outcomes in Hemophilia Transition: Passage to Independence

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Objectives: To streamline and standardize the transition process of care through improved collaborations with staff and for persons with hemophilia transferring from a pediatric to an adult HTC. Processes were developed to provide patients with documented transition skills in order to foster medical independence in a complex healthcare environment.

Methods: Continuous quality improvement tools were used to develop, implement and test a standardized transition tool for patients diagnosed with hemophilia A or B, ages fifteen to nineteen years of age. The transition tool was designed to assess the knowledge and skills of the adolescent in preparation for transition to adult care. Adherence to the administration of the tool in the pediatric HTC was the initial outcome measure. Key drivers included 1) improving communication between staff at the HTCs 2) transition tool development 3) educational resource content identification and 4) education of staff and families regarding the transition project. Communication was fostered through weekly team meetings to discuss and develop the transition tool in collaboration with the adult HTC. The adult HTC social worker would then attend the comprehensive clinic appointment at the pediatric HTC for those identified patients to assist in the preparation of transferring care. An excel spreadsheet, along with the ATN database, was utilized to track patients to provide continuity of care during the transfer. Additionally, quarterly meetings were implemented with both HTC teams to discuss transferring patients and the continuum of the transition process. The transition tool was developed after review of available transition tools and was designed to provide systematic assessment of patient knowledge for transition readiness. The tool was refined through a series of PDSAs and implemented at each comprehensive clinic. The patient responses to the transition tool highlighted educational opportunities and led to the development of a resource cart to provide readily accessible targeted educational tools. Family and staff were educated about the value of transition readiness through team meetings, community outreach and during clinic visits.

Summary: Use of the transition tool began in March 2016. Data was available through May 17, 2017. Thirty of 31 (97%) eligible patients completing the tool. Communication was improved between HTC teams. Educational tools were identified, obtained and provided to patients.

Conclusions: We have successfully streamlined and standardized the transition process, identified educational opportunities and improved communication with staff at our HTCs utilizing established quality improvement techniques. Next steps include measurement of answered transition tool questions to further enhance patient/family knowledge and promote successful transition, as well as expansion to other age appropriate transition tools, to facilitate the journey to medical independence.
Updated results from a dose-escalation study in adults with severe or moderate-severe hemophilia B treated with AMT-060 (AAV5-hFIX) gene therapy: up to 1.5 years follow-up

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Background: Gene transfer for hemophilia offers the potential to convert the disease from a severe to mild phenotype with a single treatment. AMT-060 consists of an AAV5 vector containing a codon-optimized wildtype hFIX gene under control of a liver-specific promoter.

Objective: This phase 1/2 study investigates the safety and efficacy of AMT-060 at 2 dose levels in adults with moderate-severe or severe hemophilia B.

Methods: Multi-national, open-label, dose-escalating study in patients with factor IX (FIX) activity ≤2% of normal, and a severe bleeding phenotype (prophylactic exogenous FIX; or on-demand exogenous FIX, plus ≥4 bleeds/year or hemophilic arthropathy). Patients received either 5x10¹² gc/kg (n=5) or 2x10¹³ gc/kg (n=5) of AMT-060 iv. Efficacy assessments include endogenous FIX activity (measured ≥10 days after use of exogenous FIX); reduction of exogenous FIX use; and annualized spontaneous bleeding rates. Safety assessments include treatment related adverse events, immunological and inflammatory biomarkers.

Summary: There were no screening failures due to AAV5 neutralizing antibodies. Mean FIX activity in the lower dose cohort was 5.2% (min-max, 3.0-6.8%; n=4; 1 patient remaining on prophylaxis excluded) during 1 year of follow-up, and 6.9% (min-max, 3.1-12.7%; n=5) in the higher dose cohort during 26 weeks follow-up. Eight of 9 patients on FIX prophylaxis discontinued use after AMT-060 infusion. Follow-up to up to 1.5 years will be presented, with annualized reduction of exogenous FIX use and spontaneous bleeding rates. Mild, temporary elevations in ALT were observed in 3 patients with higher mean FIX activity (6.3-12.7%; 1 in the lower and 2 in the higher dose cohort). Each received a tapering course of prednisolone. ALT elevations were not associated with changes in FIX activity or a capsid-specific T-cell response.

Conclusions: Patients continue to show sustained clinical benefit and endogenous FIX activity with no T-cell activation ≥1 year after a single infusion of AMT-060.
Characterization of Women and Girls with Hemophilia Treated in the US from A Claims Database

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Bioverativ, Waltham, MA, USA

Objective: Hemophilia A is an X-linked, inherited bleeding disorder that results from deficiency in coagulation factor VIII (FVIII). Inheritance of the severe disease is more common in males. However, women and girls commonly present with carrier status that may be asymptomatic or symptomatic, or with severe factor deficiency. Although men and symptomatic women have similar symptoms, such as bleeds into joints and tissues, women also experience complications during menstruation, pregnancy, labor and delivery. Healthcare providers may not be as familiar with bleeding disorders in women, leading to inadequate diagnosis and management. This study is aimed to provide real-world evidence on women and girls with hemophilia (WGH) treated in the US.

Methods: WGH were identified from a large US commercial claims database (Truven MarketScan) between January 2011 and November 2016. Eligible patients were women or girls who either had hemophilia A diagnosis (ICD-9/10: 286.0/D66) or received factor VIII treatment, including plasma-derived, conventional, and extended half-life (EHL) recombinant factors. WGH with coded Von Willebrand disease (VWD) diagnosis were excluded. The earliest date of factor use was defined as the index date, and patients were followed till the end of continuous enrollment or end of data, whichever happened earlier. Patient characteristics (e.g., age, region, and insurance type) and treatment patterns were derived. An algorithm based on proportion of days covered (PDC) during the follow-up period was used to classify factor use as prophylaxis (PDC>=70%) or on-demand (PDC<70%).

Summary: A total of 228 female patients used factor VIII treatment out of 557,391 patients with any coagulation disorders in the database. Forty-four of these were diagnosed with WGH and 184 had VWD diagnosis and were excluded from this study. The median age of WGH diagnosis and factor therapy initiation was 35 and 37 years old, respectively; the majority (>70%) of patients initiated factor therapy in adulthood. All WGH treated were covered by managed care plans (e.g., PPO: >60%). A total of 9% patients used plasma-derived factors, 84% used conventional recombinant factors, and 7% used EHL recombinant factors. Based on the algorithm using PDC, the majority (~80%) of WGH used factor therapy as on-demand treatment, and only 20% of them used it as prophylaxis.

Conclusions: Using this large US insurance claims database, more than half of the WGH patients received factor therapy in their mid-thirties, suggesting a delay in diagnosis and therapeutic intervention. The data support the unmet need that currently exists in management of this affected population, including appropriate and timely diagnosis.
Optimal dosing strategies evaluated using a model of the terminal half-life curves for 11 rFVIII products.

Robert Amand

BioTMG, Inc., Cary, NC, USA

Objective:

Physicians prescribing Factor VIII for haemophilia A patients are presented with an array of dose and dose frequency in the package insert making it difficult to precisely prescribe. To clarify the treatment outcome across products, a model of the published half-life was used to provide the expected % IU/dl +/- SD at 24, 48, 72, and 96 hours post dose at a normalized dose and at the high end of the recommended dosage (dose and freq.).

Methods:

Eleven FVIII products recently marketed in the US were assessed using a model of the half-life +/- SD to calculate the expected %IU/dl +/- SD at 24, 48, 72, and 96 hrs post-dose. Terminal half-life data for adults was obtained from each published package insert (PI). The one-stage clotting assay data was used for all except Afstyla® (chromogenic assay only). Variance reported as coefficient of variation or confidence intervals was converted to standard deviation.

The first comparison was made using a standard dose of 50 IU/kg across all products. The second comparison used the maximum recommended dose and frequency for routine prophylaxis defined in the PI. Full data sets and curves of %IU/dl +/-SD under standard doses of 50 IU/kg and under maximum dose and frequency for routine prophylaxis have been generated.

Summary:

Graphing the single dose comparison (50 iu/kg) revealed 3 general clusters and one outlier at 24 hrs post dose. The first cluster had 4 products with a mean range of 21-25 %IU/dl at 24 hrs post dose. The second cluster had 5 products with a range of 30-32 %IU/dl at 24 hrs. The third cluster had 1 product (Eloctate©) with 43 % IU/dl at 24 hrs. The outlier (Nuwiq©) showed exceptional variance compared to others and removed from discussion.

Expected %IU/dl was recalculated using the most frequent and highest dose recommended for individual products. Assessing the –SD value: 10 of 10 products achieved > 1% trough at 24 hrs; 8 of 10 at 48 hrs; 2 of 10 at 72 hrs; and 1 of 10 at 96 hrs. Note at 72hrs, only 2 of 10 products achieve minimal trough at –SD level when 4 of 10 claim q3day dosing.

Conclusions:

Initial dosing for routine prophylaxis relies on the mean half-life. The PK parameters are based on only 18 to 30 patients under well-controlled conditions. There is waste on both sides of the PK half-life distribution curve. Would it be reasonable to assure minimal breakthrough bleeds and less over-dosage by initiating treatment with a personal PK profile for each patient in order to identify the correct dose and frequency? This model could be used to find optimal dose and frequency with input from a personalized product half-life.
A Feasibility and Usability Study of a Nursing Orchestrated, Customized 3 Dimensional Virtual Reality Environment in Children with Hemophilia Undergoing Routine Intravenous Procedures

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Nationwide Children’s Hospital, Columbus, Ohio, USA

Objective: The over-arching hypothesis for our project was that a nurse orchestrated hemophilia customized; three-dimensional virtual reality (VR) environment during IV procedures could be integrated into a clinical setting when children with hemophilia underwent routine IV interventions during a comprehensive care visit without adversely disrupting clinic flow. We additionally hypothesized that VR would be more favourably viewed by patients, caregivers, and nurse orchestrators than standard of care distraction (SOC) one or two dimensional distraction techniques.

Methods: We designed a single-center, randomized pilot study to assess the feasibility and usability of a VR environment during IV procedures in a pediatric hemophilia clinic. Participants were children >6 years to <19 years with hemophilia A or B followed in a pediatric comprehensive hemophilia clinic. After informed consent, patients were block randomized 2:1 via computer generated randomization prior to a clinically indicated IV procedure to VR versus SOC and age cohorts were maintained so that 12 patients were in age cohort 1 and 12 were in age cohort 2 (age cohort 1=>6y-<13y; and age group 2=>13y-<19y). Each subject, one caregiver and the hemophilia nurse orchestrator assessed the distraction method using an appropriately anchored initial Visual Analog/FACES scale prior to the IV procedure. Each subject, one caregiver and the hemophilia nurse orchestrator assessed the distraction method using a Final Visual Analog/FACES scale at the completion of the IV procedure. Questions targeted usability, engagement, impact on procedural anxiety, impact on procedural pain, likability of the distraction technique, and procedural related nervousness. Additional data collected included type and severity of hemophilia, sex, historical use of prophylactic or on-demand therapy, and use of eyeglasses. To compare the length of procedure time between the two groups, the Wilcoxon Rank Sum test was used. The length of procedure times were summarized by presenting median and range.

Summary: We enrolled 25 children (table 1). The median VR procedure time was 12.5 minutes (mean 12.75 minutes) and the median SOC time was 9 minutes (mean 10.11 minutes). (p=0.6085).

Conclusion: We demonstrated that a nurse orchestrated hemophilia customized; three-dimensional VR environment during IV procedures could be integrated into a clinical setting when children with hemophilia underwent routine IV interventions during a comprehensive care visit without adversely disrupting clinic flow.

<table>
<thead>
<tr>
<th>Variable</th>
<th>VR Group</th>
<th>SOC Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Age 5-12 (years)</td>
<td>8 (66.7%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Age 13-19 (years)</td>
<td>8 (66.7%)</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>8 (66.7%)</td>
<td>8 (88.9%)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (50%)</td>
<td>7 (77%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (16.7%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (16.7%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>8 (66.7%)</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>Mild</td>
<td>2 (16.7%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (16.7%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (25%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>On prophylactic therapy</td>
<td>12 (100%)</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>Median procedure time (minutes)</td>
<td>12.5</td>
<td>9</td>
</tr>
</tbody>
</table>
Verification of Effective Zika Virus Reduction by Production Steps Used in the Manufacture of Plasma-Derived Medicinal Products

Nathan Roth\(^1\), Wolfram Schafer\(^3\), Birgit Popp\(^3\), Martin Stucki\(^2\), Randel Fang\(^4\), Henry Mead\(^5\)

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BACKGROUND: The manufacturing processes for plasma-derived medicinal products include specific virus inactivation or removal steps designed to ensure a high safety margin with respect to virus transmission. The efficacy and robustness of the inactivation/removal steps is demonstrated through validation studies. Previous studies with Flaviviruses such as bovine viral diarrhoea virus (BVDV) and West Nile virus (WNV) clearly demonstrated the effectiveness of the manufacturing process(es) to reduce such viruses. Given the recent Zika virus epidemic, additional validation studies have now been conducted to verify the effectiveness of pasteurization, low pH treatment, solvent detergent (SD) treatment, and 20-nm virus filters against Zika virus. Blümel and colleagues [1] recently demonstrated that Zika virus is sensitive to these virus inactivation and removal procedures that are widely used during the manufacture of plasma-derived medicinal products. The data presented here corroborate and supplement that report.

STUDY DESIGN AND METHODS: Samples of production intermediates were obtained from commercially available plasma-derived medicinal products in the United States, Europe, Australia, and other parts of the world. Zika virus was spiked into these production intermediates and log virus reduction was evaluated based on virus titres at specific time points (feed volume for virus filtration) using a Vero cell culture based virus infectivity assay (TCID\(_{50}\)/mL).

RESULTS: Zika virus was highly susceptible to inactivation by heat treatment, SD treatment, and low pH incubation. Zika virus was almost instantaneously inactivated by SD treatment (1% polysorbate 80, 0.3% TNBP) reaching the limit of detection within 30 minutes. Zika virus was completely inactivated (to the limit of detection) within 2 hours by pasteurization (10 h at 60°C) in an aqueous, sucrose stabilized, von Willebrand factor/factor VIII solution. These results corroborate reported findings [1]. We also demonstrated that Zika virus is highly susceptible to low pH inactivation (pH 4.0 at 37°C) and was completely inactivated within 30 minutes. Zika virus was also completely removed by a 20-nm virus filter (≥ 7.0 log\(_{10}\)). These process-specific data demonstrate that common virus inactivation and removal processes are highly effective in eliminating Zika virus, as predicted by previous studies with WNV and BVDV.

CONCLUSIONS: These data provide additional evidence that current manufacturing processes effectively reduce Flaviviruses, including Zika. Therefore, if Zika virus or any lipid enveloped arbovirus 40-60 nm in diameter were present in a plasma manufacturing pool, it would be effectively inactivated or eliminated. Thus, the theoretical risk of Zika virus being transmitted by commercially available plasma-derived medicinal products is negligible.

Assessment of Current Clinical Practices in Integrating Treatment Guidelines for Hemophilia

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¹Medscape Education, New York, NY, USA, ²National Hemophilia Foundation, New York, NY, USA, ³Munson Medical Center, Traverse City, MI, USA

Objective: This study assessed current clinical practices of clinicians related to hemophilia treatment guidelines to identify knowledge, competency, practice gaps and barriers to optimal care of patients with inhibitors.

Methods: A continuing medical education (CME)-certified clinical practice assessment survey was developed comprising 24 knowledge- and case-based, multiple-choice questions. The survey assessed knowledge, attitudes, and confidence with regard to newly-developed hemophilia treatment guidelines emphasizing integrated care for patients with inhibitors, and the application of these guideline-based recommendations. The survey launched on the Medscape Education website on December 5, 2016 with participant responses collected through January 26, 2017. The data sample includes responses from 170 physicians who participated during the study period.

Summary of Results (n=170 physicians): Responses to questions on the screening for, and management of, inhibitor formation in patients with hemophilia undergoing prophylaxis, showed that: the majority of hematologists/oncologists correctly identified the factors that increase risk of inhibitor formation (71%), while less than half of pediatricians did so (46%); when asked regarding exposure days (EDs) and the formation of inhibitors, half of hematologists/oncologists correctly identified within 50 EDs, while only 25% of pediatricians did so; and both hematologists/oncologists (21%) and pediatricians (28%) incorrectly identified how often a patient should be tested for inhibitors. When surveyed specifically regarding immune tolerance induction (ITI), a slight majority of hematologists/oncologists and pediatricians correctly chose the time frame during which to initiate ITI (55% and 51%, respectively), and 50% of hematologists/oncologists knew the most powerful predictor of ITI success, while only 42% of pediatricians did so; only 14% of hematologists/oncologists and 4% of pediatricians knew that there is no optimal rFVIII to initiate for ITI; only 10% of hematologists/oncologists and 8% of pediatricians knew that there is not optimal dose of rFVIII to initiate for ITI.

Conclusions: The need for further education was observed for the following topics: best practices in the integrative care of patients using evidence-based guidelines and recommendations; current and emerging clinical data guiding acute and prophylactic management; risk factors for the development of inhibitors during prophylaxis; screening and management of inhibitor formation, including ITI. Further educational efforts tailored to address these gaps are warranted.
Ethics of Compensated Plasma Donation

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Introduction: Nearly 70% of the plasma-derived medicinal products (PDMPs) are derived from donors who are provided monetary compensation. Data demonstrate a large and increasing unmet demand for PDMPs worldwide. In 2010, an International Consensus Conference on Risk-Based Decision Making for Blood Safety noted, “As blood systems are focusing more on responsible use of health care resources, questions arise as to the most effective way to manage risk at a level that is tolerable and sustainable.” Subsequently, the Alliance of Blood Operators developed a risk-based decision-making framework for blood safety (Framework).

Objective: Considering these two parallel dimensions, we reanalyzed whether an absolutist position against donor compensation taken by some countries is any longer relevant or would be appropriate if evaluated utilizing a risk-based decision-making approach.

Methods: We used the Framework to integrate stakeholder concerns into an overall risk profile focusing on two elements most relevant to our analysis: the assessment component of the ethical discussion and the participation strategy for engaging relevant stakeholder (e.g. patients) that has been missing from past analyses. We also applied the analytical structure of the Nuffield Council on Bioethics.

Summary: We found notable distinctions between donor plasma destined for further manufacture into PDMPs and labile whole blood and its components (e.g., red blood cells [RBCs], platelets, and plasma) for direct transfusion. The latter does not routinely undergo significant processing designed to mitigate the risk from transfusion-transmitted infections. Our assessment differentiated the two and focused on ethical issues as they related to the unique features of compensating donors of plasma destined for manufacture into PDMPs when donated in countries with well-established regulatory structures.

Conclusions: We found in no case has the prevalence of an emerging infectious disease been linked to donor compensation for PDMPs. Most donations are motivated neither by pure altruism or by pure self-interest and that the most direct incentives, including compensation, are not alone reasons to prohibit an activity. The policy of some countries is to meet identified patient need for PDMPs by importing PDMPs produced from compensated donations while at the same time advocating a seemingly contradictory policy of prohibiting donor compensation within their own borders. Given advances in PDMPs and donor safety, one of the remaining threats to safety is a policy that undermines an adequate and sustainable supply of PDMPs. Actions that limit patient access to life-saving treatment without considering supply issues raise the possibility that global patient needs will be eclipsed in pursuit of ethical ideals that are both impractical and unnecessary.
**PROTECT VIII: Can Eligibility for Less-Frequent Prophylaxis Dosing Regimens Be Predicted by Patient Characteristics?**

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1 University Clinic Bonn, Bonn, Germany, 2 Bayer, Whippany, NJ, USA

**Background:** Efficacy of prophylaxis with BAY 94-9027, a prolonged–half-life recombinant factor VIII product, was shown using individually tailored dosing regimens (2x/wk, every 5th day, or every 7th day) in PROTECT VIII, a phase 2/3 study in which previously treated adolescents and adults with severe hemophilia A received BAY 94-9027 for 36 weeks on demand or as prophylaxis (Reding MT, et al. J Thromb Haemost 2017;15(3):411-419). Prophylaxis intervals were determined after a 10-week run-in period of 25 IU/kg 2x/wk BAY 94-9027 prophylaxis for preselection of patients suitable for less-frequent dosing. Patients with ≤1 spontaneous joint or muscle bleed during the run-in were defined as “eligible” for randomization to prophylaxis every 5th day (45–60 IU/kg) or every 7th day (60 IU/kg); patients with >1 spontaneous bleed were “ineligible” for randomization and subsequently received 30–40 IU/kg 2x/wk.

**Aims:** To identify baseline characteristics of PROTECT VIII patients that are potentially predictive of patients with hemophilia A who may be considered for every-5th-day or every-7th-day prophylaxis with BAY 94-9027.

**Methods:** In this post hoc analysis, baseline characteristics were compared for patients who were eligible vs ineligible for randomization to less-frequent prophylaxis dosing regimens in PROTECT VIII.

**Results:** Based on bleeds in the run-in period, 97/110 patients (88.2%; median age, 34 years) were eligible and 13 patients (median age, 32 years) were ineligible for randomization to less-frequent prophylaxis dosing. Eleven eligible patients were not randomized during the study because randomization arms were full. Patients eligible vs ineligible for randomization had fewer median (quartile [Q] 1; Q3) total bleeds and joint bleeds in the previous 12 months (total bleeds, 5.0 [1.0; 15.0] vs 15.0 [9.0; 25.0]; joint bleeds, 2.0 [0; 11.0] vs 10.0 [6.0; 19.0]) and fewer baseline target joints (1.0 [0; 2.0] vs 2.0 [1.0; 2.0]). Target joints were present at baseline in 69 (71.1%) vs 11 (84.6%) patients eligible vs ineligible for randomization. A higher proportion of patients eligible vs ineligible for randomization received prophylaxis before the study (81.4% vs 69.2%).

**Conclusion:** Based on PROTECT VIII data, number of previous joint bleeds and target joints are relevant indicators for predicting suitability of patients for less-frequent BAY 94-9027 prophylactic dosing regimens.
IMPACT QoL II—The relationship of depression and anxiety to control of chronic pain and adherence to clotting-factor treatment

Cynthia Nichols¹, Angela Lambing², James Munn³, Terry Anderson⁴, Bartholomew J. Tortella⁴, Michelle Witkop¹

¹Northern Regional Bleeding Disorder Center, Traverse City, MI, USA, ²Henry Ford Hemophilia and Thrombosis Treatment Center, Detroit, MI, USA, ³University of Michigan Hemophilia Treatment Center, Ann Arbor, MI, USA, ⁴Pfizer, Inc., Collegeville, PA, USA

Objectives: The primary aims of this study are to 1) evaluate the prevalence of depression and anxiety among adult persons with hemophilia (PWH) and 2) explore relationships between depression, anxiety, chronic pain, and adherence to clotting-factor treatment.

Method: This study used a subset of data from the IMPACT QoL II, a one-time, cross-sectional survey of 200 adults (age ≥18) with self-reported diagnosis of either Hemophilia A or B who were able to read, write, and speak English. The study was approved by the IRB in the primary investigator’s institution. Participants were a convenience sample recruited at bleeding disorders conferences in 2013-2014 and issued a randomly generated identification number to ensure anonymity. The 139-item survey was completed electronically through SurveyMonkey™ on a study computer tablet. Participants were given $20 upon completion of the survey, which took 15-45 minutes to complete. The subset of variables evaluated for this analysis included the Faces of Pain Scale-Revised (FPS-R) (chronic pain), level of control over pain each participant feels they have, adherence to clotting factor measured by total scores (higher score=lower adherence) on the VERITAS-PRO or VERITAS-PRN, anxiety measured by the GAD-7, depression measured by the PHQ-9, and self-report of ever receiving a diagnosis of depression and/or anxiety. The cut-off score for presence of moderate to severe depression or anxiety was 10 on both the PHQ-9 and the GAD-7, scores which have been validated by previous literature in other populations. Lower vs. higher adherence was defined by VERITAS scores in the highest and lowest quartile respectively.

Summary: Participants with lower treatment adherence (VERITAS score >57) were more likely to have PHQ-9 scores >10 (P=0.02). GAD-7 scores >10 also demonstrated a trend to be associated with lower treatment adherence (P=0.15). 28% of participants reported a diagnosis of depression, but 53% with PHQ-9 scores >10 had not been diagnosed with depression. Similarly, 22% reported a diagnosis of anxiety but 52% with GAD-7 scores >10 had not been diagnosed. Participants who reported non-control of pain were more likely to have PHQ-9 scores or GAD-7 scores >10 (P=0.001 and P=0.013 respectively). There were significant correlations between PHQ-9 and GAD-7 (Rho=0.76, P<0.0001), PHQ-9 and FPS-R (chronic pain) (Rho=0.31, P=0.003), and GAD-7 and VERITAS (P=0.005). These data indicate that depression and anxiety are associated with greater severity of chronic pain, and depression is associated with poorer adherence to clotting factor treatment regimen (prophylaxis or other regimen). Both depression and anxiety appear to be under-diagnosed in PWH.
Depression levels in patients with hemophilia and von willebrand

Ana Paola Abreu Bastar, Valeria Escobar Ruiz, Maria Fernanda Domínguez Ballesteros, Leydi Lizbhet Morales de la Cruz, Maria Laura Giselle Torres Chablé

Universidad Autónoma de Guadalajara, Villahermosa, Tabasco, Mexico

Bleeding disorders are a group of conditions that result when the blood cannot clot properly (American Society of Hematology, 2017). The most frequently occurring bleeding disorders include von Willebrand Disease (VWD), Hemophilia A, and Hemophilia B (FDA’s, 2016). Some studies show that it is important to consider the depression in the psychological approach of patients with a bleeding disorder (Recht, Batt, Witkop, Gut, Cooper, Kempton, 2016 and Osorio, Bazán, Izquierdo, 2016). Beck’s theory defined depression in cognitive terms. He saw the essential elements of the disorder as the “cognitive triad”: (a) negative view of self, (b) a negative view of the world, and (c) a negative view of the future. The depressed person views the world through an organized set of depressive schemata that distort experience about self, the world, and the future in a negative direction (Beck, A. 1972 in Lynn, P. 2015).

Objective: Compare depression levels in groups of patients with haemophilia, Von Willebrand (VWD) and apparently healthy people. Methods: The study design was quantitative, non-experimental, transactional and correlational in which the difference between three groups of participants was analyzed: 41 patients with hemophilia A or B, 10 patients with VW and 20 apparently healthy people. The sample was obtained from Tabasqueña de Hemofilia A.C. through a non-random sampling of subjects-type. Depression symptoms were obtained by Beck’s inventory and for control variables a questionnaire was applied. All of the findings were assessed by SPSS 21 for Windows program. Data were analysed using descriptive statistics, comparisons between groups were evaluated with Games-Howell coefficient and post hoc test. Summary: 71 participants with a mean age of 28.24. Considering the patients who have a bleeding disorder, 74.50% of the sample was deficient of factor VIII, 11.76% of factor von Willebrand, 11.76% of factor VII and 1.96% of factor IX; 82.35% of them have access to treatment while 17.64 have not access. Statistically significant differences were found only in apparently healthy people compared to haemophilia patients (p=0.031). A marginal difference was detected between the group of apparently healthy people and von Willebrand patients (p=0.081). Conclusions: The presence of a coagulation disease increase the levels of depression and the severity of the symptoms.

Key Words: Hemophilia, Von Willebrand, Depression.
Perceptions of Vulnerability, Protective Behaviors, and Reported Stress in Mothers of Sons with Hemophilia

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Background: The impact of family history on mothers of sons with hemophilia is unknown. The primary purpose of this study was to determine whether differences exist in perceived vulnerability of sons, protective behaviors toward sons and reported stress when comparing mothers of sons with hemophilia who have a known family history of hemophilia with mothers who have an unknown family history of hemophilia.

Methods: We performed a prospective, single visit study of mothers who have a son with hemophilia. Following informed consent, participants answered demographic and family history questions and completed three surveys: the Parent Protection Scale, the Child Vulnerability Scale and the Parenting Stress Index.

Results: A total of 39 participants completed the study, including 21 mothers with a known family history of hemophilia and 18 mothers with an unknown family history of hemophilia. No significant differences were found in perceived vulnerability, protective behavior and reported stress in mothers with a known family history of hemophilia compared to those without a known family history of hemophilia. However, the total Parent Protection Scale scores were significantly higher among mothers of sons with hemophilia with a history of inhibitor, compared to those without a history of inhibitor. Mothers of sons with hemophilia without siblings scored significantly higher on the Parent Protection Scale, Supervision and Control sub-scores, as well as the Parent Stress Index, Difficult Child sub-score. Child Vulnerability Scale scores increased along with the Parent Protection Scale, Dependence sub-scores and Separation sub-scores. Child Vulnerability Scale scores increased along with the total Parent Stress Index scores, as well as with increasing Parent Stress Index, Difficult Child sub-scores and Parent-child dysfunctional Interaction sub-scores.

Discussion: Historically, social workers in hemophilia programs have observed psychosocial differences between mothers of sons with hemophilia who have a known versus unknown family history. We did not find differences in the measures we utilized between groups. Instead, the results of this study demonstrated the complex system of behaviors exhibited by all mothers of sons with hemophilia, enriching the understanding of the impact of family history of hemophilia when providing comprehensive care services to mothers of sons with hemophilia and families.

Implications/Next Steps: The results of this study will lead to the improvement of hemophilia center clinical social work assessment of family functioning, specifically the mother-son relationship. Further research needs to be initiated to explore the complex psychosocial differences in individual mothers of sons with hemophilia, individual sons with hemophilia, family systems and social systems impacted by hemophilia.
Patient and Clinician Experience of Using Goal Attainment Scaling for Hemophilia (GAS-Hēm), an Innovative Patient-Centered Outcome Measure

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Background: The value of the patient perspective in guiding clinical care is increasingly recognized, but there are a limited number of tools available to facilitate and document this important aspect of care. GAS-Hēm is an innovative, patient-centered outcome measure and clinical engagement tool used to establish and measure progress towards patient goals. This method encourages patients to set measurable, personally meaningful goals and provides a framework for assessing the degree to which they are attained over specified intervals. This report describes the patient and clinician experience of using GAS-Hēm for setting goals and tracking goal attainment.

Methods: A 12-week feasibility study was carried out at 4 study sites in the US and Canada, between December 2015 and November 2016. Participants with severe hemophilia A or B (aged 5–65) took part in face-to-face GAS-Hēm-facilitated goal-setting interviews at baseline; goal attainment was assessed at 6 and 12 weeks (in person or by telephone) and rated separately by participants and clinicians. Participants' experience using the GAS-Hēm tool was captured using a 13-item, self-report end-of-study survey (P-ESS) administered at the final study visit; most questions were open ended (n=9), others were Yes/No or based on a 5-point Likert Scale. Clinician feedback on the GAS-Hēm tool was captured using a 25-item end-of-study survey (C-ESS) and during a post-study debrief meeting. Results: 38/42 participants (91%) completed the P-ESS. None reported having previously used anything similar to GAS-Hēm. Most (29/38) reported that GAS-Hēm was very/extremely useful. Participants' enthusiasm for personalizing their goals emerged as a clear theme, but some found the process time consuming (Table). Six clinicians completed the C-ESS and 8 participated in the debrief; all sites were represented. As a tool for care planning, case management, and measuring patient outcomes, all respondents rated GAS-Hēm as “somewhat or very useful” (Table). Discussion: These findings support the merit of the GAS-Hēm tool, suggesting patients and clinicians would find value in incorporating this approach in routine clinical practice. A revised tool (rebranded as “GOAL-Hēm”) integrating patient and clinician input from the feasibility study is currently in development and will be supported by a comprehensive clinician training program.

<table>
<thead>
<tr>
<th>Group</th>
<th>Selected Responses to Open-Ended Survey Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td><strong>Positive Feedback</strong></td>
</tr>
<tr>
<td>(P-ESS)</td>
<td>• I was able to choose my own goals</td>
</tr>
<tr>
<td></td>
<td>• Gave me motivation and a goal</td>
</tr>
<tr>
<td></td>
<td>• Holds you accountable</td>
</tr>
<tr>
<td></td>
<td>• Gave me a small push to actually change</td>
</tr>
<tr>
<td><strong>Clinicians</strong></td>
<td><strong>Incredibly useful</strong></td>
</tr>
<tr>
<td>(C-ESS)</td>
<td>• Facilitated productive interviewing</td>
</tr>
<tr>
<td></td>
<td>• Provided personalization and guidance</td>
</tr>
<tr>
<td></td>
<td>• A great conversation opener and motivator</td>
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</tbody>
</table>
Hereditary factor X (FX) deficiency in women and girls: treatment with a high purity plasma-derived factor X concentrate

Roshni Kulkarni1, Andra James2, Miranda Norton3, Amy Shapiro4

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Background: A high-purity plasma-derived FX concentrate (pdFX) has been developed for treatment of hereditary FX deficiency, an autosomal recessive disorder.

Aim: This post hoc analysis describes the pharmacokinetics, safety, and efficacy of pdFX in 10 women and girls with hereditary FX deficiency.

Methods: In this open-label study, subjects (10 women/girls, 6 men/boys) aged ≥12 years with moderate or severe FX deficiency (basal plasma FX activity ≤5 IU/dL) were enrolled and received 25 IU/kg pdFX for on-demand treatment of bleeding episodes or preventative use for up to 2 years. All subjects provided informed consent and the protocol was approved by appropriate independent ethics committees.

Results: Nine women and girls had severe and 1 had moderate FX deficiency, were aged 25.5 (median; range 14–58) y, and received a total of 267 pdFX infusions (178 for on-demand and 89 for preventative treatment). Men and boys (5 severe and 1 moderate FX deficiency) received a total of 159 pdFX infusions (64 on-demand; 95 preventative). The mean number of infusions per subject per month was higher among women/girls (2.48) than males (1.62). The mean pdFX incremental recovery was similar between women/girls and men/boys (2.05 vs 1.91 IU/dL per IU/kg, respectively), as was mean half-life (29.3 and 29.5 h, respectively). Among women and girls, 132 assessable bleeding episodes (61 heavy menstrual bleeding, 47 joint, 15 muscle, and 9 other) were treated with pdFX. Women and girls reported a treatment success rate (ie, subject rating of “excellent” or “good” response to pdFX) of 98%, comparable to the 100% treatment success rate among men and boys. After study completion, 2 subjects received pdFX for hemostatic cover during obstetric delivery. Additional infusion, bleed, and safety data will be presented.

Conclusion: These results show that, in women and girls with moderate or severe hereditary FX deficiency, who experience reproductive tract and other bleeding events, pdFX was safe and effective. The pharmacokinetic profile of pdFX in women and girls was similar to that of men and boys.

Funding: Bio Products Laboratory
Efficacy, safety, and pharmacokinetics of a high-purity plasma-derived factor X (pdFX) concentrate in the prophylaxis of bleeding episodes in children <12 years with moderate to severe congenital factor X deficiency (FXD)

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Background: Congenital FXD is a rare bleeding disorder characterized by spontaneous joint and mucocutaneous bleeding and gastrointestinal or intracranial hemorrhage. pdFX is a US- and EU-approved treatment for congenital FXD, but data in children <12 years have been unavailable.

Aims: To investigate pdFX efficacy, safety, and pharmacokinetics in children <12 years with moderate to severe congenital FXD.

Methods: In this 6-month, open-label, multicenter, phase 3, prospective study in children <12 years, all subjects had a confirmed diagnosis of moderate to severe congenital FXD (basal FX:C <5%), severe bleeding history, or an F10 gene mutation causing a documented severe bleeding type. Subjects received routine prophylaxis at recommended 40–50 IU/kg twice weekly to maintain trough FX:C levels ≥5%. Each investigator assessed efficacy based on standardized criteria and presence of breakthrough bleeding. All subjects provided informed consent and the protocol was approved by appropriate independent ethics committees.

Results: Mean age of the 9 trial completers was 6.8 years. Eight subjects had severe and 1 had moderate FXD. Overall, 537 prophylactic infusions were administered; mean dose/child was 38.6 IU/kg. Ten bleeds in 3 of 9 children were reported: 6 minor, 3 major, 1 unassessed. Investigators rated overall pdFX efficacy as excellent in all subjects. Overall mean incremental recovery was 1.74 IU/dL per IU/kg. FX trough levels were maintained ≥5% after visit 4 (days 29–42) in all subjects.

A total of 28 treatment-emergent adverse events (TEAEs) were reported in 8 children; none were considered pdFX related. No significant changes were noted in vital signs, physical exams, or laboratory measurements. No evidence of inhibitor development was seen.

Conclusion: pdFX is efficacious in the prophylaxis of bleeding episodes in subjects <12 years with moderate to severe FXD. Safety profile in this population is consistent with previous results in subjects ≥12 years.

Funding: Bio Products Laboratory
An Integrated Safety and Efficacy Analysis of Sofosbuvir-Based Regimens in Patients with Hereditary Bleeding Disorders

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Objective: Patients with hereditary bleeding disorders have been included in Phase 2 and 3 clinical trials of sofosbuvir (SOF), ledipasvir/sofosbuvir (LDV/SOF), sofosbuvir/velpatasvir (SOF/VEL), and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) as well as in a dedicated study (n = 120) in this patient population. This integrated analysis evaluates the safety and efficacy of SOF-based regimens in HCV-infected patients with hereditary bleeding disorders.

Methods: HCV-infected patients with a medical history of a hereditary bleeding disorder who participated in a SOF-based Phase 2 or 3 study were included in this pooled analysis. Medical history term(s) used to identify patients with bleeding disorders included variations of Hemophilia A or B, Von Willebrand’s Disease, Factor Deficiencies, or conditions associated with hemophilia.

Summary: A total of 201 patients (74 GT1, 10% GT2, 14% GT3, 2% GT4, <1% GT5) with bleeding disorders were identified across 19 studies. The majority were male (91%), Caucasian (82%), IL28B non-CC (70%), HCV treatment-naive (55%), and without cirrhosis (74%). Hemophilia A (65%) and B (26%) were the most common bleeding disorders. SVR12 results are shown in the below table by treatment regimen and genotype. The most frequently reported adverse events (>10%) were fatigue and headache; majority were mild or moderate in severity. One patient (<1%) discontinued LDV/SOF due to an adverse event and 11 patients (5%) experienced a serious adverse event. Hemarthrosis, muscle hemorrhage, epistaxis, hematoma, and hematuria were the only hemorrhagic events that occurred in >1 patient. Grade 3 or 4 laboratory abnormalities were infrequent with anemia and hyperbilirubinemia the most frequent Grade 3 laboratory abnormality consistent with RBV administration.

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<th>SVR12 (modified ITT), % (n/N)</th>
<th>SOF+PEG/RBV (n=3)</th>
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<th>LDV/SOF (n=119)</th>
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CRA0034
Conclusions: SOF-based regimens led to high rates of SVR in genotype 1–5 HCV infected patients with bleeding disorders. SOF-based regimens were safe and well tolerated with no new toxicity specific to patients with bleeding disorders emerging.

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Management of Hemophilia Carriers Around The Time of Their Delivery: Phenotypic Variation Requiring Customization of Management.

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Objective: Management of hemophilia carrier women during labor and postpartum is yet to be standardized. Most of these carriers have normal pregnancies without any bleeding. Levels of factor VIII usually increase significantly in pregnancy unlike levels of factor IX, which do not usually change significantly. After delivery, a carrier’s factor level drops down to pre-pregnancy levels, which increases the chance of postpartum hemorrhage (PPH). In some parts of the world, PPH remains a major cause of maternal death in this population of patients.

Methods: Our first patient is a 34 year old symptomatic hemophilia A carrier with baseline factor VIII of 20% that increased to 61% in the third trimester. She went into labor at 34 weeks of gestation. She received Xyntha an hour prior to epidural anesthesia, and 1 more dose 1-2 hours prior to delivery. She underwent spontaneous vaginal delivery of a baby girl complicated with atonic PPH and retained placenta that was removed manually in the OR, followed by dilation and curettage. Bleeding improved with uterine massage and utero tonics, after which she received another dose of Xyntha. She had no episiotomy, and suffered a 1st degree perineal laceration with repair. She received Xyntha daily postpartum for 2 days, during which time her factor levels were 94%, and 75%, respectively. After discharge she was placed on Eloctate twice weekly for 6 weeks. The second patient is a 31 year old asymptomatic hemophilia A carrier (a sister of our first patient), with a baseline level of 133% that increased to 212% in the third trimester. As she was known to have a male fetus, forceps, vacuum or fetal scalp electrodes were avoided. She had an epidural injection with no complications, without any need for factor infusion, and underwent an uncomplicated vaginal delivery at 40 weeks of an unaffected boy, with spontaneous delivery of her placenta. Her factor level was 152% on day 1 postpartum. Our third patient is a 34 year old symptomatic hemophilia A carrier with baseline level of 46% that increased to 96% in the third trimester. She is currently at 40 weeks of gestation. Her first pregnancy, 2 years ago, was managed by Xyntha at time of delivery; she reported heavy lochia for 6 weeks postpartum. Her first baby was a boy who was diagnosed with severe hemophilia A. Our plan for this pregnancy is Xyntha at delivery and twice weekly Eloctate postpartum.

Summary: These three cases demonstrate how phenotypic variation between patients can lead to different presentations requiring individual customization of management.

Conclusion: It is essential to close the gap in the care of hemophilia carrier women by raising awareness of the challenges they may face and managed in a collaborative multidisciplinary approach.
NPO0036

Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia A and B with and Without Inhibitors: Interim Results from a Phase 2 Extension Study

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Background/Objective: Hemophilia is a bleeding disorder caused by the body’s inability to accomplish the natural clotting process. People with hemophilia experience bleeds because there is an inadequate amount of thrombin due to a deficiency in factor VIII or IX. Thrombin is critical to clotting and sealing the wound; it converts fibrinogen into fibrin, establishing a network to help more platelets accumulate. Thrombin activity is regulated by antithrombin. Fitusiran is a subcutaneously administered investigational RNA interference (RNAi) therapeutic targeting antithrombin with the goal of improving thrombin generation to promote clotting in people with hemophilia A or B with and without inhibitors. Interim data from the Phase 1 study showed fitusiran was generally well tolerated and administration of monthly fitusiran led to dose-dependent antithrombin lowering, improvement in thrombin generation, and decrease in bleeding frequency. We will report interim safety, pharmacodynamics, and clinical activity of fitusiran from the Phase 2 extension study.

Methods: The Phase 2 extension study (NCT02554773) includes people with hemophilia A or B with and without inhibitors, previously dosed in the Phase 1 (NCT02035605) study. Participants receive monthly, fixed subcutaneous doses of fitusiran, 50 mg or 80 mg. Primary endpoints include safety and tolerability; secondary endpoints include antithrombin activity, thrombin generation and exploratory evaluation of bleed events.

Summary of Results: As of May 2017, 33 participants were enrolled in the study and had received continuous dosing of up to 14 months. Previously reported data showed that fitusiran was generally well tolerated, with no serious adverse events related to study drug and no thromboembolic events. Once-monthly subcutaneous dosing achieved dose-dependent antithrombin lowering of ~80% and thrombin generation levels approaching levels similar to participants without hemophilia. Exploratory post-hoc analysis of bleed events showed median annualized bleed rate (ABR)=1 in participants without inhibitors and median ABR=0 in participants with inhibitors. Bleed events were successfully managed with either replacement factors or bypassing agents. Updated safety, tolerability and clinical activity will be presented.

Conclusions: Emerging clinical data suggest that fitusiran may be a promising investigational prophylactic therapy to promote appropriate clotting and reduce the frequency of bleeding in people with hemophilia A or B with and without inhibitors.
Management of Bleed Events in the Phase 2 Study of Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia A and B with and Without Inhibitors

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**Background:** Hemophilia is an inherited bleeding disorder caused by an impairment in the body’s ability to accomplish the natural clotting process. People with hemophilia experience bleeds because there is an inadequate amount of thrombin due to a deficiency in factor VIII or IX. Thrombin is critical to clotting and sealing the wound by converting fibrinogen into fibrin, reinforcing the primary platelet plug. Thrombin activity is regulated by antithrombin.

Fitusiran is a subcutaneously administered investigational RNA interference (RNAi) therapeutic targeting antithrombin with the goal of improving thrombin generation to promote clotting in people with hemophilia A or B with and without inhibitors. Fitusiran is currently being evaluated as a prophylactic agent for hemophilia A and B with and without inhibitors in an ongoing Phase 2 extension study. Breakthrough bleeds on the study are being managed using replacement factors (non-inhibitor patients) or bypassing agents (BPAs; inhibitor patients). The use of replacement factors or BPAs in the background of fitusiran treatment is of clinical interest and will be described.

**Methods:** The Phase 2 extension study (NCT02554773) includes people with hemophilia A or B with and without inhibitors, previously dosed in the Phase 1 (NCT02035605) study. Participants receive monthly, fixed subcutaneous doses of fitusiran, 50 mg or 80 mg. Data on breakthrough bleeds and how they were treated were collected by patient diary.

**Results:** As of May 2017, 33 participants were enrolled in the study. Previously reported data demonstrated that fitusiran was generally well tolerated and led to dose-dependent antithrombin lowering, thrombin generation increase, and decrease in bleeding frequency in participants with hemophilia A and B with or without inhibitors. Among those achieving target antithrombin lowering of >75%, few bleed events occurred during the observation period. Bleed events were treated with factor concentrates (FVIII or FIX) or bypassing agents (rFVIIa or aPCC), respectively, in doses according to or lower than recommended by the WFH guidelines. Detailed analyses of the frequency and management of bleed events in the Phase 2 study will be presented.

**Conclusions:** Clinical data suggest that fitusiran may be a promising investigational prophylactic therapy to promote appropriate clotting and reduce the frequency of bleeding in people with hemophilia A or B with and without inhibitors. Further, the initial limited experience in treating breakthrough bleeds with replacement factor or BPAs has been encouraging, demonstrating good treatment effect in the absence of identified safety concerns.
Centralized Inhibitor Testing in the United States: Laboratory Methods Used for the Community Counts Registry for Bleeding Disorders Surveillance

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Objective: Antibodies to factor replacement products, inhibitors, are the most pressing public health problem facing persons with factor VIII (FVIII) or factor IX (FIX) deficiency. Development of an inhibitor can lead to increased factor utilization, morbidity, healthcare costs, and risk of early mortality. The Division of Blood Disorders (DBD) at the U.S. Centers for Disease Control and Prevention funds a public health monitoring program (Community Counts) to gather and share information about health issues and causes of death that affect people with bleeding disorders cared for in U.S. Hemophilia Treatment Centers. The Registry for Bleeding Disorders Surveillance component collects detailed information and blood specimens to detect and monitor inhibitors. Regular testing for an inhibitor can lead to early detection which increases the chances for successful treatment to eradicate inhibitors. DBD’s Hemostasis Laboratory Branch (HLB) was tasked to design an inhibitor testing algorithm for Community Counts that is valid and consistent, avoids the need for factor wash-out, and minimizes reporting of false positive results.

Methods: HLB implemented a modified Nijmegen-Bethesda assay (NBA) that avoids the need for product wash-out. A cut-off for positivity of 0.5 NBU for FVIII inhibitors and 0.3 NBU for FIX inhibitors was established. False positives were most common in the low-positive range (0.5-1.9 NBU for FVIII, 0.3-0.9 NBU for FIX). All eligible specimens are screened for inhibitors using the modified NBA. Specimens with a low-positive FVIII inhibitor titer are further tested with more specific inhibitor tests, a chromogenic assay (CBA) and a fluorescence immunoassay (FLI), as well as a dilute Russell’s viper venom test (DRVVT) to screen for lupus anticoagulants. Specimens with a low-positive FIX inhibitor titer are further tested with a FIX FLI.

Summary: For 8,163 specimens collected for FVIII inhibitor surveillance prior to January 2017, 95% were negative (<0.5 NBU), 2% were low positive (0.5≤NBU<2.0), and 3% were positive (NBU≥2.0) via the modified NBA. Among those with a low positive inhibitor titer and sufficient volume for follow-up testing via chromogenic, FLI, and DRVVT, 7% were deemed false positive, 20% presented ambiguous results, and 73% were confirmed positive. For 804 specimens collected for FIX surveillance between September 2016 (date of FIX FLI availability) and April 2017, 98% were negative (<0.3 NBU), 1% were low positive (0.3≤NBU<1.0), and 1% were positive (NBU≥1.0) via the modified NBA. Among those with a low positive inhibitor titer, 20% were deemed false positive and 80% were confirmed positive by FLI testing. A repeat specimen was requested on new positive or ambiguous results.

Conclusions: The methods used to perform centralized inhibitor testing for Community Counts have been combined to produce a testing algorithm that is valid and consistent, avoids the need for factor wash-out, and minimizes reporting of false positive results.
Assessing the Availability and Use of Resources to Support Youth with Hemophilia, their Families and Care Teams during Transition to Adult Health Care

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Objective: Evidence from the literature reveals that young adults with hemophilia face unique challenges during the transition from pediatric to adult care. As part of a larger effort to systematically examine key areas of need during patients’ care transition, this project aimed to: (i) describe the availability, relevance, and use of resources to support transition in hemophilia care; (ii) identify gaps in the availability, awareness, uptake, and coordination of these resources; and (iii) provide recommendations for future research to describe barriers and promote more effective use of resources. Methods: Targeted web-based searches were conducted to identify English-language online transition resources, including both hemophilia-specific sources and widely-cited generic resources for patients with special health care needs. Results were complemented with findings from a literature review and systematic evaluation of transition readiness assessment tools. For each identified resource, information was synthesized on the purpose, content, relevance to hemophilia, and evidence of use and effectiveness. The Six Core Elements of Health Care Transition (Got Transition, 2014) served as a framework for assessing the extent to which existing resources address the needs of the hemophilia population. Summary: A total of 17 resource hubs, 19 toolkits, and 266 individual resources were assessed, including guidance reports, clinical tools, training resources, and educational materials. Hemophilia-specific resources are available for three of the six core elements (transition policy, transition readiness, and transition planning). For the remaining elements (transition tracking and monitoring, transfer of care, and transfer completion), generic resources were identified that could be used as is or easily adapted for use in the hemophilia population. Few process evaluations assessing the use of available resources have been conducted. While some studies successfully report implementation of specific transition programs, the overall adoption of transition policies, utilization of resources, care team coordination, use of process evaluation tools within hemophilia treatment centers and other practice settings is unknown. Challenges reported by patients suggest low use of resources, possibly related to low awareness and lack of guidance from providers. Literature suggests that providers underutilize resources due to low awareness, inadequate training and support, and poor coordination between pediatric and adult providers. A lack of validated hemophilia-specific measures prevents broad evaluation of transition-specific outcomes. Conclusions: There is a large amount of resources available in the public domain tailored to all stakeholders. However, little is known about whether or how these resources are being used to support youth with hemophilia who are transitioning to adult services. Evidence for strategies that effectively support these young people is severely lacking. Additional research is needed to gain insight into the awareness, access, and effective utilization of resources available for this population.
CHESS – Improving research and advocacy through an improved understanding of the economic and social burden of hemophilia

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Background

In 2014, a major study was conducted to quantify the Cost of Haemophilia across Europe from a socioeconomic perspective (CHESS). The objective of the study was to quantify the economic and societal cost of severe hemophilia A and B in adults across the five largest European countries; France, Germany, Italy, Spain and the UK (EU5). CHESS employed a ‘bottom-up’ methodology with the aim of quantifying the annual direct and indirect costs of severe hemophilia A and B in adults with severe hemophilia (factor level of <1%) across EU5.

Methods

A cross-section of hemophilia specialists provided demographic and clinical information and 12-month outpatient and secondary care activity for patients through an online survey. The responding physicians completed a patient record form (PRF) for the next 8-10 eligible patients and invited each patient to complete a corresponding patient self-completion (PSC). Patients provided corresponding direct and indirect cost information, including work loss and out-of-pocket expenses, as well as information on quality of life and adherence. The quality of life measure used within the study was the EQ-5D 3L.

The study was directed by a steering committee consisting of charity representatives from each participating country, physicians and health economists. The research was conducted in accordance with the Ephemra guidelines and approved by the University of Chester (UoC) Ethics Committee.

Results

139 physicians participated in the study across the EU5. Detailed clinical and health economic data from patient records were provided by physicians for 1,285 adult males (996 Hemophilia A, 289 Hemophilia B patients), 551 of whom completed corresponding patient questionnaires.

Conclusion

The CHESS study has produced a detailed cost, resource use and patient outcome database from which a comprehensive burden of disease study has been utilized on a scale far greater than previous studies. This evidence base has aided the medical and patient community, as well as policymakers. The CHESS study has made an impact through UK governmental support to develop a contaminated blood policy, utilization of data by various charities and universities for research and advocacy purposes and by liaising with various government decision makers globally to support development of outcomes consideration as part of reimbursement frameworks.

Based on the experience in Europe and interest in application of the data to policy making the CHESS research is now being conducted in the United States.
REAL-WORLD PHARMACY DISPENSATION AND EXPENDITURES ASSOCIATED WITH STANDARD AND EXTENDED HALF-LIFE RECOMBINANT FACTOR VIII PRODUCTS IN HEMOPHILIA A

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OBJECTIVES: Contemporary real-world data on units dispensed and expenditures associated with use of standard half-life (SHL) and extended half-life (EHL) factor VIII replacement products in U.S. patients with hemophilia A are limited. This exploratory analysis of real-world administrative data was conducted to determine units dispensed and factor replacement product-related direct expenditures associated with currently marketed recombinant SHL and EHL FVIII products, and to examine inter-product switches.

METHODS: De-identified claims data from the commercially available Truven Health MarketScan® Research US claims database were used to identify direct expenditures and number of international units (IUs) dispensed for all patients with a diagnosis code of ICD-9 286.0/ICD-10 D66 who used SHL (SHL group) and/or EHL (EHL group) during the study period from Aug 1, 2014 to Jan 31, 2017. Data on switching from an SHL to an EHL factor VIII replacement product were captured in patients with continuous pharmacy enrollment for whom claims data were available for at least 1 calendar quarter and up to 1 year before and after the index date of a product switch. Descriptive statistics were used to analyze results.

SUMMARY: Cross-sectional analysis. The SHL group comprised 415 patients, among whom six distinct SHL FVIII products had been dispensed, and the EHL group included 91 patients, among whom two EHL FVIII products had been dispensed. The age distribution of the two groups was similar (p =0.57), although the proportion of patients under 18 years of age was somewhat higher in the SHL group than in the EHL group (46.9% vs 36.2%). The median FVIII product dispensation per calendar quarter was 46,409 IU (IQR, 12,760-87,670 IU) (SHL) versus 67,375 IU (IQR, 50,524-98,264 IU) (EHL). Median expenditures per calendar quarter were substantially higher for EHL ($135,519; IQR, $100,320-186,557) than for SHL ($61,152; IQR, $18,593-115,845). Switching analysis. Of the patients in the EHL group, 29 had switched from one of three SHL FVIII products to one of two EHL FVIII products during the study period. The total median IU dispensation per calendar quarter increased following the switch from 58,598 IU (pre-switch, SHL) to 68,036 IU (post-switch, EHL; 16% increase), as did the factor-related expenditure ($76,553, SHL, versus $141,101, EHL; 84% increase).

CONCLUSION: Real-world data derived from a large claims database, unadjusted for treatment regimen or hemophilia severity, reveal marked differences in metric units and expenditures among hemophilia A patients to whom SHL and/or EHL products were dispensed. Switching from an SHL to an EHL FVIII replacement product was associated with a substantial increase in units dispensed and factor expenditures. Further analyses, incorporating essential clinical characteristics, should be explored.
Physician practice patterns in the US show significant variation in how PK parameters are currently used to personalize care for US hemophilia A patients

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Introduction & Objective: Standard approaches to prophylaxis may be further improved by taking into account individuals' pharmacokinetic (PK) profile, thereby increasing the likelihood of therapeutic success [Valentino 2012, Valentino 2014, Lissitckov 2017]. One study demonstrated an association between more time spent above higher FVIII levels (20 and 30%) and lower bleeding rates [Valentino 2016]. Furthermore, a consensus statement proposes to target specific factor levels to tailor treatment for different patient profiles [Iorio 2017]. Additionally, new extended half-life treatments provide physicians with another option to personalize therapy. As more data and therapeutic options become available, it is important to understand physicians’ current perceptions and practice patterns with respect to personalizing haemophilia A care in the US. Materials & Methods: Physicians in the US who treat persons with severe hemophilia A and provided informed consent were eligible to complete a cross-sectional, double-blinded web-based survey to evaluate physicians’ perceptions and practice patterns with respect to measuring PK and if/how they personalize treatment with this information, when and to what extent. This abstract presents results from the first half of the survey which focused on ways in which physicians measure FVIII pharmacokinetics and personalize care. Results: Ninety physicians completed the survey. The top three most important considerations for personalizing therapy in general were bleeding history, patient goals, and physical activity. The most commonly cited reason for conducting a PK assessment was product switch (74%) while the most common barrier was patient willingness/availability (60%). Physicians reported using a PK-based approach to personalize treatment in 25% (median) of their severe patients. Of physicians who use PK, trough levels (91%), half-life (58%), peak levels (56%) and Area Under the Curve (22%) were used. While 12% of these physicians reported using all PK parameters, 18% only used trough levels. 23% reported using peak, trough and half-life in combination. Most physicians (89%) indicated using PK data to adjust dose and 50% also used it as a patient education opportunity. Conclusions: There was significant variability across respondents as to how PK is assessed and how PK parameters are used in treatment decisions, suggesting an opportunity to increase awareness and use of PK-guided personalization to ultimately improve patient care. Additional education on the definitions and details of PK-guided dosing could help improve overall adoption of this treatment strategy and align the community on what it means to personalize therapy using PK information. More research studying the association between PK-guided prophylaxis and outcomes is encouraged to better understand how best to personalize PK-based prophylaxis for different patient scenarios.
Sports/Recreational Activity-Specific Range and Drivers of Risk in People With Hemophilia: Results of the Activity-Intensity-Risk (AIR) Survey and Consensus Meeting of US Physical Therapists

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Objective: Limited evidence supports activity-associated bleeding risk assessment for people with hemophilia (PWH), and consumer materials generically describe types of risk and a single activity risk score based on input from a few physical therapist (PT) authors. The aim of AIR was to assess activity-specific risk ranges, bleed-specific risks, and inherent/modifiable factors that increase risk based on survey/consensus of PT experts. Methods: Peer-nominated PTs from US hemophilia treatment centers (HTCs) were invited to participate in a survey regarding ~100 sports/recreational activities. For each activity, respondents provided a low (minimum) and high (maximum) risk assessment on a 5-point scale (low=1, high=5). Position-specific assessments were made for some team sports (eg, baseball pitcher, catcher, and field positions). Sports with distinctly different rules for contact were evaluated separately (eg, flag/tackle football, boys/girls lacrosse, Frisbee/ultimate). Drivers of risk were identified from free text comments and explored at a consensus meeting. Drivers of risk were categorized as inherent, modifiable, activity-driven, and patient-driven. Summary: Of 32 invited PTs, 17 responded to the survey with median 26.5 years as a PT and 15.5 years at an HTC; 8 participated in the full-day consensus meeting. Of the survey participants, majorities reported treating adults (94%) and treating children (88%), and most worked in the HTC full-time (29%) or nearly full-time (41%). Overall, few activities had low and high risk assessments both fall within the lower (1) or upper (5) end of the response range. For example, swimming is associated with low risk scores, even when including maximum risk with year-round competitive teams (median low 1, high 2), and tackle football had consistently high scores (median low 5, high 5). Risk scores (median low, high) for some common sports were as follows: baseball pitcher (3,4), catcher (3,4) or other position (2,3); basketball (2,4); hockey (4,5); skiing-downhill (2,4); soccer goalie (2,4) or other position (2,4); snowboarding (3,5). Risks for joint injuries were consistent with position and motion requirements for each sport, while head and muscle bleeds were associated with contact. Key drivers of risk that were identified included progression from seasonal participation to year-round play, overtraining, competitive level, participation in tournaments, and improper body mechanics. Inherent risks included impact with surface/ball/equipment (eg, soccer goalie), impact with players (eg, football), or falls (eg, horseback riding). Modifiable risks included tricks/stunts (eg, skateboarding) and use of safety equipment when not required. Conclusion: AIR provides insights into activity-specific risk for PWH including types of bleeding risk and drivers of increased risk. The results may provide a broader framework for assessing activities with respect to bleed site-specific risks and for recognizing how certain activities may be modified to decrease risk or to identify those with non-modifiable inherent risks for injury.
REAL-WORLD SPECIALTY PHARMACY DISPENSATION AND EXPENDITURES ASSOCIATED WITH PROPHYLACTIC REGIMENS USING STANDARD AND EXTENDED HALF-LIFE RECOMBINANT FACTOR IX PRODUCTS IN SEVERE HEMOPHILIA B

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OBJECTIVES: Scant data are available regarding real-world usage and costs associated with the management of hemophilia B, including contemporarily relevant data referencing standard half-life (SHL) and extended half-life (EHL) factor IX replacement products. In addition, administrative datasets typically lack correlation with patient-level characteristics, which may hamper the interpretation of the data. An analysis of real-world claims data was conducted to determine units dispensed and expenditures associated with nonacog alfa, an SHL product, and eftrenonacog alfa, an EHL product, among U.S. severe hemophilia B patients identified as receiving a prophylactic regimen.

METHODS: Claims from a large, U.S. national specialty pharmacy database were used to identify monthly expenditures and number of international units (IUs) dispensed for male patients with a diagnosis code of ICD-9 286.1/ICD-10 D67 who used nonacog alfa and/or eftrenonacog alfa from April 2015 to December 2016. Availability of clinical characteristics allowed for restriction of the analyses to severe hemophilia B and prophylactic regimens only. Monthly averages were calculated for each patient considering the months in which the first and last prescriptions occurred, and intervening months. Descriptive statistics were used to analyze results.

SUMMARY: A total of 151 patients meeting the above criteria were identified. The nonacog alfa group and the eftrenonacog alfa group comprised 101 and 75 patients, respectively; each group included 25 patients who had received both products during the study period. A slightly higher proportion of patients were less than 18 years old in the nonacog alfa group (53.5%) than in the eftrenonacog alfa group (42.7%), although the overall age distribution in the two groups was similar (p = 0.57). The median monthly average of FIX product dispensation was 26,050 IU (nonacog alfa) versus 15,412 IU (eftrenonacog alfa) (p< 0.0001). Considerable variability was present in the range of monthly units dispensed in both groups (nonacog alfa, IQR 16,218 – 42,406 IU; eftrenonacog alfa, IQR 10897– 25,296IU). Median monthly expenditures were higher in the eftrenonacog alfa group than in the nonacog alfa group (45,673 USD [IQR = 31,621-74,505] versus 34,874 USD [IQR = 21,812-57,304]; p=0.0031).

CONCLUSION: Contemporary observations may be tailored through incorporation of clinical parameters into analyses of real-world claims data. This study suggests that contemporary SHL to EHL transitions may not incur a sufficiently substantial reduction in units dispensed so as to lead to preservation of “cost parity” among severe hemophilia B patients receiving prophylactic management. Further analyses to validate these findings across additional patient populations should be explored.
Impact of targeted education on obesity in children with hemophilia—a single HTC quality project

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Introduction Prevalence of obese, overweight or at risk individuals in the hemophilia population is now more than 50% despite improvements in health care to lead normal lives. Obesity has several adverse effects; it is harder to establish vascular access, it necessitates increased dosing of pharmacological agents, and accelerates joint degeneration due to hemophilic arthropathy. Studies show that periodic behavioral reinforcement in the form of dietary and health counseling incorporated in clinic visits at the HTC is associated with significant weight loss and weight maintenance. Objective The objective of this project was to foster healthy eating practices and exercise in children with hemophilia and monitor the impact of educational intervention on BMI in obese/overweight and at risk children. Methods This single center pilot project commenced in June 2016 and will conclude in June 2018. The target group was all children with hemophilia with a sub-group of obese/overweight/at risk population. They were identified utilizing the ATHN patient database (Clinical Manager) based on weight/BMI. Thirty seven percent (N=33) of the children in our program were identified as obese or overweight. The project was divided into three stages and included 1. Content development, 2. Implementation and 3. Program evaluation. Three primary education modalities utilized to achieve our objective were educational videos, healthy snack cooking demonstrations, and a health fair. Video content included “Impact of Obesity on Joint Function/health and Safe Exercise Options” and “Healthy Eating” filmed by HTC staff. Professional cooking group demonstrations took place on scheduled bleeding disorder clinic days throughout the year. The annual hematology healthy Living Fair will be the final educational modality used in this project. All families also received informational brochures and healthy snacks on clinic days to foster healthy food choices. Data collected are 1. Extent of participation 2. Feedback regarding adoption of behavioral modification 3. Changes in BMI. Results We have completed the content development phase and are in our implementation phase of the project. All children presenting to our HTC this year (N=50) were given informational brochures on healthy tips/eating and healthy snacks. In addition 20 children have watched the “Impact of Obesity on Joint Function/health and Safe Exercise Options” video. The implementation phase will continue until June 2018. BMI of obese/overweight children over a 2 year period will be compared to BMI prior to initiative and tabulation of feedback on sustainable lifestyle changes by families will be done. Conclusions The knowledge gained from this evaluation will be used to create and optimize training modules for other HTCs to improve weight management practices and reduce the prevalence of overweight and obesity in people with hemophilia. An increased stakeholder involvement and participation will lead to improved health and optimization of long-term outcomes in children with hemophilia.
Mild-Severe Hemophilia B Impacts Relationships for US Adults and Children With Hemophilia B and Their Families: Results From the Bridging Hemophilia B Experiences, Results, and Opportunities Into Solutions (B-HERO-S) Study

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Objective: The B-HERO-S study evaluated the impact of mild-severe hemophilia B on the lives of affected adults and children. Here we assess the impact of hemophilia B on relationships.

Methods: US adults with hemophilia B and caregivers of affected children completed separate 1-hour online surveys that included questions regarding impact on interpersonal relationships.

Summary: Most (88%) of the 299 adults completing the survey had mild-moderate hemophilia B. Of those, 54% were married or in a long-term relationship, and 44% were single. Most adults (87%) reported that hemophilia impacted their ability to form close relationships with partners or prospective partners; 35% were very/quite dissatisfied with the support received from a previous partner. Ninety percent reported that their experiences in a prior relationship, including satisfaction with support from their previous partner, impacted their decision to enter a relationship with their current partner. Nearly all participants (98%) were very/quite satisfied with the support received from their current partner. The top reason for satisfaction was "my partner takes the lead in providing financial security" (45%). Most were very/quite satisfied with the support from family (87%) and friends (96%). Most participants reported a negative reaction or experience as a result of disclosing their hemophilia (friend/colleague/employer, 76%/80%/82%); some reported having felt bullied by peers/colleagues (69%/66%). Majorities reported that past experiences impacted which friends/colleagues they told about their hemophilia, and how or when they disclosed their hemophilia status to these individuals (97%/95%). Seventy-four percent of participants indicated that hemophilia has affected the quality of their sex life; only 54% were extremely/moderately satisfied with their overall sexual relationship. Many reported having had a bleed during sex (40%). Of 150 caregivers of children with mostly mild-moderate hemophilia (74%), 89% were married or in a long-term relationship, and most felt very/quite supported by their partner (98%) and family (87%). Impact on unaffected siblings was more often mixed (49%) than negative (18%). Most felt very/quite satisfied with support of teachers (91%), children at school (80%), and other adults in regular contact (72%). Most caregivers reported negative experiences telling a friend (76%) or having their child tell a friend (69%) about the child’s hemophilia; 43% reported that their child was bullied as a result of having hemophilia. Conclusion: While the impact of severe hemophilia on relationships has been reported in HERO and other studies, B-HERO-S suggests that mild-moderate hemophilia B also significantly impacts relationships of affected men/women and boys/girls, especially in terms of disclosure, intimacy, and feeling bullied by peers/colleagues. Opportunities may be explored to more proactively counsel individuals with mild-moderate hemophilia B and families in the setting of comprehensive care to better navigate interpersonal relationships and improve quality of life.
Objective:

Through the Annual Global Survey (AGS), the World Federation of Hemophilia (WFH) has been collecting national aggregate data on people with bleeding disorders since 1999. Lack of diagnosis and treatment for women and girls with bleeding disorders remains a challenge in the bleeding disorder community. Highlighting gender data from the AGS can help bring awareness to the issues facing women and girls.

Methods:

The Report on the AGS 2015 includes demographic and treatment-related data from 111 countries, representing 91% of the world population. The AGS began collecting data on gender distribution in 2007. Gender data from 2007 to 2015 is summarized.

Summary:

The Report on the AGS 2015 demonstrates that 65,284 women were identified as having a bleeding disorder. The five types of hereditary bleeding disorders with the largest proportion of women are: platelet disorders (65%), von Willebrand disease (VWD) (61%), Fibrinogen deficiency (56%), FXI deficiency (55%), and FV deficiency (54%) (Figure 1). A gender breakdown for hemophilia A and B indicates that there are women who are affected by hemophilia (N=3,988 (3%), N=1,328 (5%) for hemophilia A and B, respectively) (Figure 1). The most common bleeding disorder for women and girls is VWD. From 2007 to 2015, the reported number of women with VWD increased by 17,220 (21,710 – year 2007, 38,930 – year 2015). This is a 79% increase in the number of women identified with VWD compared to a 65% increase in men identified with VWD during the same time period.

Conclusions:

AGS data recognizes the women and girls around the world who are affected by bleeding disorders. The WFH Annual Global Survey data is available to the bleeding disorder community as an advocacy tool.
The WFH Launches World Bleeding Disorders Registry to Expand Knowledge Base Worldwide

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Objective: WFH's vision of treatment for all, establishes that collecting data and generating evidence is an essential activity in achieving this goal. The WFH collects country level data on the epidemiology of hemophilia and care around the world through the Annual Global Survey (AGS). The number of identified patients in the USA has increased from 13,523 to 18,596 between 2000-2015; and the amount of Factor VIII and IX used has increased from 5.08 and 0.814 IU/capita to 8.25 to 1.53 IU/capita, respectively, between 2006-2015 (Figure 1).

World Bleeding Disorders Registry Pilot Study

To meet the challenge of increasing the amount and type of data available on people with hemophilia, the WFH is developing a World Bleeding Disorders Registry (WBDR), which will complement the AGS data, by providing patient level data from individual Hemophilia Treatment Centers (HTCs). This registry is intended to collect prospective and longitudinal real world data on the patient clinical experience around the globe, allowing researchers to use patient data to generate evidence and build advocacy initiatives aimed at health policy decision makers. A pilot study was conducted to assess the feasibility of implementing a global patient registry in countries around the world.

Methods: A 9-month observational, global registry of people with hemophilia A or B, using the methodology under consideration for the planned WBDR, including the use of a web-based data entry system (McMaster University, Canada). The feasibility was assessed on the following performance indicators: proportion of HTCs invited who participated; proportion of participating HTCs that obtained a favorable ethics review; proportion of patients approached who consented to participate proportion of enrolled patients on which data collection and database entry was successful.

Summary: Thirty-one of the 40 invited HTCs agreed to participate in the pilot study (78% participation rate). Two HTCs withdrew before applying for ethics, 2 HTCs were declined ethics approval, and 1 was still pending at study closure. Twenty-six of the 29 (90%) HTCs who applied, were successful at obtaining ethics approval. 356 patients were enrolled in the pilot, with only 7 patients declining participation (98%). 92% of data fields were complete and entered into the database.

Conclusions: This pilot confirms the interest of HTCs and patients in participating in a global registry, as well as the ethical acceptability and technological feasibility of a worldwide web-based patient registry.
Management of Hemophilia B in US Women and Its Impact on Education, Employment, and Activities: Results From the Bridging Hemophilia B Experiences, Results, and Opportunities Into Solutions (B-HERO-S) Study

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Objective: The B-HERO-S study assessed the impact of hemophilia on US adults with hemophilia B, including affected females. Here we describe the symptoms, management, and impact on education, employment, and engagement in recreational activities in women. Methods: Adults aged ≥18 years with hemophilia B (factor IX <40%) completed a survey including questions about bleeding, treatment, and psychosocial impact. Summary: Of 299 respondents, 86 were women (median age, 29 years; 6% were aged >45 years) with mild (29%), moderate (65%), or severe (6%) hemophilia. The majority reported arthritis (66%) and anxiety/depression (57%); 19% reported acute and/or chronic pain. Most (86%) were treated with some form of “routine infusions to prevent bleeding”; 16% reported self-infusing, 31%/17% by partners/family. Self-infusion was initiated at median age of 18, and learned from HTCs (86%), camps (71%), or parents (57%). Most reported difficulty with access to factor due to affordability/availability in the past 5 years (72%) or expected in the next 5 years (85%). Women reported a median (mean) of 4 (3.86) bleeds in prior year; 83% bled within the last 4 weeks with most recent bleeding in joints (73%) or muscles (21%). Twenty-five percent reported one specific “bad” joint, most commonly the knee (69%). Nearly all went past high school with 55% completing 4-year college and 24% graduate degrees. Most (94%) reported some negative impact on completing their education (7% very large/69% moderate/19% small impact), most commonly due to difficulties concentrating at school due to bleeds or pain (81%). Most employed full-time (71%) or part-time (10%), commonly in office work (71%). Most (94%) reported a negative impact on their working life (3% very large/71% moderate/20% small impact); 36% reported leaving a job because of their hemophilia. Nearly all (99%) indicated some negative impact on their ability to engage in recreational activities (3% large/83% moderate/13% small impact). From a list of predetermined activities, dancing (50%) and walking (48%) were the most common current activities; bicycling (20%), dancing (17%), and swimming (16%) were the most common discontinued activities. Most reported treatment changes around activities (21% started prophylaxis, 52% revised time of doses, 38% added doses, 34% changed amount of doses); 8% reported no change and 3% no moderate/vigorous activities. Conclusion: Clinical presentation and treatment in women mirrored that reported by men except for greater anxiety/depression and more issues with access to treatment. Nearly all affected women reported a negative impact on their education, employment, and activities. While these results may be limited by bias in recruitment selecting those most symptomatic, the data reveal opportunities to improve awareness of and guidance around management and counselling of affected women.
Lessons Learned in the Assessment of Pain in US Adults With Hemophilia in the Pain, Functional Impairment, and Quality of Life (P-FiQ) Study: Importance of More Formalized Discussions Around Pain in the Comprehensive Care Setting

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Objective: People with hemophilia frequently experience joint bleeds, resulting in pain and functional impairment. The P-FiQ study formally evaluated patient-reported pain descriptions, responses to standardized patient-reported outcomes (PROs) related to pain, and pain management strategies.

Methods: Participants completed a pain/hemophilia history and 5 PRO instruments. Pain was assessed via 3 PRO instruments: EQ-5D-5L, Brief Pain Inventory v2 Short Form (BPI), and Short Form-36 v2 (SF-36v2), and these instruments were assessed for reliability, consistency, and correlation with factors including patient-reported characteristics.

Summary: P-FiQ enrolled 381 adult males with mild-severe hemophilia and a history of pain and/or joint bleeding. Most (65%) self-reported having arthritis/bone/joint problems. Thirty-two percent of participants reported experiencing both acute and chronic pain, 35% chronic pain only, and 15% no pain. Of those reporting acute pain, most described the sensation as “sharp” (77%) or “aching” (65%); for those reporting chronic pain, most described the pain as “aching” (80%) or “nagging” (50%). Ankles (37%) and knees (24%) were commonly reported as the most painful joints. Many participants with acute/chronic pain reported using acetaminophen (62%/55%) or nonsteroidal anti-inflammatory drugs (34%/49%) to treat their pain in the past 6 months. Some participants indicated having moderate/severe/extreme (28%/12%/2%) pain/discomfort “today” as measured by the EQ-5D-5L pain/discomfort domain. For BPI (scale 0-10, 10 is most severe pain), median pain severity scores were 6.0 for worst pain, 3.0 for average pain, 2.0 for current pain, and 1.0 for least pain. Median BPI pain interference scores indicated interference with general activity (3.0), mood (3.0), walking ability (3.0), normal work (3.0), and enjoyment of life (2.0). On SF-36, most participants (90%) reported experiencing bodily pain, and 75% indicated that pain interfered with normal work in the last 4 weeks. Assessments of pain on PROs were highly correlated with one another. The following formal PRO assessments were associated with self-reported pain: pain/discomfort domain of EQ-5D-5L, BPI worst pain, least pain, average pain, and current pain, and SF-36 bodily pain. Greater extent of lifetime routine infusions was also associated with EQ-5D-5L pain/discomfort and SF-36 bodily pain.

Conclusion: Pain severity and interference in people with hemophilia were identified consistently across several PROs, and correlated with patient-reported pain. In the comprehensive care setting, greater use of formalized assessment tools over time would improve dialogue and pain assessment between healthcare professionals and patients, document and validate the presence and extent of pain, establish and monitor individual goals for pain management interventions, and encourage the exploration of various pain management strategies and the evaluation of their overall quality and effectiveness.
Lessons Learned From the Assessment and Prevalence of Anxiety and Depression in US Adults With Hemophilia in the Pain, Functional Impairment, and Quality of Life (P-FiQ) Study: Importance of Routine Screening and Comprehensive Approaches to Management

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Objective: Pain and functional impairment resulting from joint disease in patients with hemophilia (PWH) may impact emotional well-being, resulting in consistent reports of anxiety/depression. The P-FiQ study formally evaluated patient-reported anxiety/depression symptoms and treatment as well as responses to standardized patient-reported outcomes (PROs), and evaluated reliability, validity, and consistency of responses. Methods: At a comprehensive care visit, adult male PWH with a history of joint bleeding or pain completed a hemophilia history and 3 patient-reported outcomes (PROs) assessing anxiety/depression and quality of life (QoL): EQ-5D-5L, Brief Pain Inventory (BPI), and SF-36v2. PROs were assessed for reliability, consistency, and correlation with factors including patient-reported characteristics. Summary: A total of 381 PWH (median age, 34 years) were enrolled in P-FiQ; 77% had hemophilia A, 23% had hemophilia B, and 9% had inhibitors. Fewer than half (44%) were currently receiving routine infusions to prevent bleeding. More than half were employed full-time (53%), and 65% were married or had a long-term partner. Depression was reported by 19% and anxiety by 14%. On the EQ-5D-5L anxiety/depression item, 43% reported feeling anxious or depressed “today.” On BPI, most participants indicated that pain interfered in the previous week with mood, sleep, and enjoyment of life, and more than half (54%) indicated interference with relations with other people. On SF-36v2 (range 0-100, higher scores indicate better QoL), median mental health summary score was 50.7; subdomains were similar (vitality, 49.0; social functioning, 45.6; role emotional, 55.9; mental health, 52.8). Emotional problems resulted in reduced time spent on work/activities (40%) and accomplishing less than they would like (47%). More than half (55%) had felt downhearted or depressed, and a large majority (93%) had felt tired in the past 4 weeks. Sixty percent of participants indicated that their physical or emotional problems had interfered with their normal social activities with family, friends, and other contacts. Similar items across PROs correlated with one another, and PRO scores (EQ-5D-5L anxiety/depression, SF-36 mental health) were significantly (P<0.05) correlated with self-reported anxiety/depression. Conclusion: Anxiety and depression in adults with hemophilia have been consistently reported in other studies and were identified in P-FiQ by self-report and across several PRO instruments. Emotional problems were reported to interfere with normal social activities and productivity. While the unmet need to address mental health in PWH has received increased recognition, it is not typically assessed formally. When compared with pain, management strategies and/or referral relationships may also not be as formally established. The findings presented here highlight the potential value of simple screening tools (eg, EQ-5D-5L) and opportunities to encourage patient dialogue about mental health within the comprehensive care setting and in referral networks.
Lessons Learned in the Assessment of Functional Status in US Adults With Hemophilia in the Pain, Functional Impairment, and Quality of Life (P-FiQ) Study: Importance of More Formalized Assessment of Function in the Comprehensive Care Setting

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Objective: Functional impairment from recurrent joint bleeding in people with hemophilia results in joint pain and reduces quality of life. The P-FiQ study formally evaluated patient- and site-reported functional assessment including responses to generic and hemophilia-specific patient-reported outcomes (PROs) tools. Psychometric analyses were used to evaluate reliability, validity, and consistency of responses.

Methods: Adult males with hemophilia and a history of joint pain or bleeding completed a hemophilia history and 5 PROs assessing function: EQ-5D-5L, Brief Pain Inventory v2 Short Form (BPI), International Physical Activity Questionnaire (IPAQ), Short Form-36 v2 (SF-36v2), and Hemophilia Activities List (HAL). PROs were assessed for reliability, consistency, and correlation, with factors including patient-reported characteristics.

Summary: A total of 381 adults (median age, 34 years; range, 18-86 years) were enrolled in P-FiQ. Most participants (66%) and sites (59%) reported functional disability in the past 6 months (CDC-UDC scale). Patients self-reported arthritis/bone/joint problems (65%) and history of joint procedures or surgeries (50%). On EQ-5D-5L, most reported problems “today” with mobility (61%) and usual activities (53%) but fewer with self-care (19%). On BPI, similar median pain interference scores (0-10 scale, 10 is complete interference) were reported with general activity (3.0), walking ability (3.0), and normal work (3.0). On IPAQ, physical activity was reported by 49% of respondents over the prior week, with more reporting walking (35%) than moderate (16%) or vigorous (16%) activities. On SF-36v2, activities in the past 4 weeks that were most frequently limited were vigorous activities (80%), bending, kneeling, or stooping (67%), walking more than a mile (61%), and climbing several flights of stairs (59%). Physical problems caused participants to limit kinds of work/activities (69%), accomplish less than they would like (66%), have difficulty in performing work/activities (65%), and reduce time spent on work/activities (62%). On HAL, greater difficulties were seen for lower vs upper extremity functions/activities; within the lying/sitting/kneeling/standing domain, the most frequent problems in the previous month were squatting for a long time (74%), kneeling (73%) or standing (72%), and kneeling/squatting (70%). Similar items across different PROs were correlated with one another. Self-reported functional impairment was significantly differentiated by BPI pain interference, IPAQ total activity, SF-36v2 physical functioning, and all HAL domains and summary scores.

Conclusion: PRO instruments assessing functional status range from simple/generic (EQ-5D-5L) to complex/disease-specific (HAL) and provide varying levels of detail. Greater use of formal PRO instruments in the clinical setting may improve dialogue between health care professionals and patients/caregivers and inform proactive approaches to specifically target patient identified functional limitations (eg, HAL) and identify areas for further targeted management strategies.
Prevalence of gross motor delays in boys with hemophilia ages 4-14: single site study.

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Objective

The aim of this study was to determine if the young boys with hemophilia at our clinic have gross motor delays that may have been missed during the annual physical therapy evaluation. By identifying delays, our clinic can improve the standard of care and promote gross motor development in our patients to enhance their ability to be physically active and protect their joints and muscles from injury.

Method

Over a one year period, boys with hemophilia A or B between the ages of 4 to 14 were tested by the physical therapist at our clinic using the Bruinink’s-Oseretsky Test of Motor Proficiency, Second Addition, BOT2. The BOT2 is a valid and reliable gross motor test for 4 to 21 year olds and is widely used to detect mild to moderate motor delays. The five gross motor subtests used in this study included upper extremity (UE) coordination, bilateral coordination, balance, strength, running speed and agility (run/agility). A total of 42 boys completed the study with scores distributed between three age groups: Group 1=4-7 year olds; Group 2=8-11 year olds; and Group 3=12-14 year olds. Exclusion criteria included a bleed within the last week that was unresolved or other physical limitation preventing participation. All severities of hemophilia were included in the study, but were not separately analysed in the results.

Results

Each age group mean scores for the subtests were within the normal mean range of 15±4 except for strength in Group 2. Group 1 had some participants score above average for four of the subtests, while Group 2 and 3 only scored above average on one subtest. Group 1 had 6-18% score below average on four of the subtests while Group 2 had 27-47% and Group 3 had 30-50% score below average on all 5 subtests. No adverse events or bleeds occurred during or as a result of the gross motor testing.

Conclusion

At our Hemophilia Treatment Center, more than 50% of the boys tested had gross motor delays. The percentage of boys showing deficits increased and persisted after age 7. This reinforces the need to include some standardized gross motor testing during the annual physical therapy evaluation of our patients with hemophilia to identify boys with scores below average and make referrals at an early age to prevent persisting gross motor delays.
Assessment of numeracy, genetic knowledge and perceptions of genetic testing in carriers of Hemophilia A and B

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Objective: Hemophilia A and Hemophilia B are X-linked recessive genetic disorders thus typically affecting males, but female hemophilia carriers may have varying bleeding symptoms associated with varying clotting levels. Recently our research group has demonstrated an increased bleeding tendency in hemophilia carriers which is associated with reduced quality of life. There are ongoing efforts to improve identification and access to hemophilia treatment centers and thus genetic counselors for education. Numeracy and genetic knowledge have not been previously evaluated in this population. We sought to evaluate the perceptions that obligate carriers of hemophilia A and B have regarding genetic testing to identify quality of life concerns, and to assess the general genetic knowledge and numeracy skills of this population.

Methods: We administered a 38-question survey to obligate (but not genetically verified) hemophilia A and B carriers identified from the Comprehensive Bleeding Disorders clinic at Children’s Healthcare of Atlanta between August 2016 and April 2017. All participants were enrolled in ATHN and had genetic testing performed via the My Life Our Future project. Our survey gathered demographic data, evaluated numeracy using the validated Schwartz-Woloshin test, basic knowledge of genetic concepts and quality of life using five questions from the previously validated Hemo-QOL survey in female carriers of hemophilia A and B. Descriptive statistics, Chi-square analysis, and student’s t-test were performed.

Summary: Over 9 months, the survey was completed by 93 obligate carriers of hemophilia A and B. The median age was 35.5 years of age (range 29-43) with the majority being Caucasian and Non-Hispanic (46%), carriers of a severe mutation (57%) and educated with the majority with some technical, vocational or college degree (84%). 12% of participants were considered numerate (answering all three questions correctly) while genetics knowledge was poor with only 15% of responders correctly answering all 5 genetic knowledge questions. As expected, being previously educated by a genetic counselor was associated with being more knowledgeable than those that had not been counseled (p=0.02). Furthermore, 52% (14/27) of the participants who responded reported feeling parental guilt as a result of passing this genetic mutation to their son(s). Of note 71% (66/93) of the participants declined to answer this question.

Conclusions: This study illustrates that hemophilia A and B carriers at baseline have poor numeracy skills, limited genetic knowledge, and report poor quality of life, including guilt as a result of passing this condition to their son(s). This is the first study to evaluate numeracy of caregivers of hemophilia patients. This information is critical in informing educational efforts focused on improving numeracy skills, knowledge and psychosocial adaptation in this population.
Estimating the prevalence of symptomatic, undiagnosed von Willebrand disease: analysis of medical insurance claims data

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Objectives: Von Willebrand disease (VWD) is a common inherited bleeding disorder, but awareness among healthcare professionals is low. Timely and proper diagnosis is integral for reducing VWD burden, access to proper therapies, and avoidance of improper medication. Hence, we sought to estimate the prevalence of undiagnosed VWD among commercially insured patients in the United States with a recent history of bleeding events.

Methods: Patients with a VWD diagnosis who were users of or candidates for von Willebrand factor were identified from the IMS PharMetrics Plus Database (2006–2015). We constructed a unary patient-finding model based on 12 prediagnosis variables that best defined this population, and applied to a set of undiagnosed patients with recent bleeding events from the same database. ‘Best fit’ (confidence level 5/6) and ‘good fit’ (confidence level 3/4) patients were identified. Prevalence of symptomatic undiagnosed VWD in the commercially insured population was estimated from the best-fit and good-fit population size (projection factor 10.4).

Summary: Overall, 507,668 undiagnosed patients with recent bleeding events were identified (86% female, 14% male). Application of the VWD model identified 3318 best-fit and 37,163 good-fit patients; 91% of best-fit patients were females aged <46 years, with heavy menstrual bleeding the most common claim. Projection to the full commercially insured US population provided an estimate of 35,000 - 387,000 symptomatic, undiagnosed patients with VWD.

Conclusion: There is a high prevalence of symptomatic, undiagnosed VWD (undiagnosed bleeding disorder patients that likely have VWD) in the commercially insured population. This data underscores the importance of improved disease education to both patients and the first line treaters, including OBGYN, emergency room, and pediatricians. Enhanced awareness of VWD symptoms and their impact, and of screening and testing procedures, may improve diagnosis of VWD and reduce the disease burden.
A Cumulative Review on Four Decades of Thrombo-Embolic Events Reported with the Use of Activated Prothrombin Complex Concentrate (APCC) in Congenital Haemophilia

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**Background:** Bypassing agents have contributed to better management of bleeding in persons with haemophilia (PWH) and inhibitors. While bypassing therapy has been proven effective, it also has introduced a potentially increased risk of thrombo-embolic events associated with the treatment (TEEs). **Objectives:** The small size of clinical trials and post-authorization studies in PWH with inhibitors limits the capability to ascertain risk factors for APCC-associated TEEs. This review provides an overview of all TEE cases that have occurred with the use of APCC in congenital haemophilia as reported spontaneously and in literature, and documented in the Company’s global safety database (GSD). **Methods:** The GSD was reviewed for all spontaneous and literature adverse events reports of APCC from 1975 to July 2016, addressing patient demographics, dosing regimens, confounding and risk factors considered relevant for the development of TEEs in temporal association with APCC treatment. **Results:** APCC became commercially available in 1975. More than 7 billion units of APCC (beyond 2 million infusions) were distributed during the review period. 85 reports including one or more TEE events were received for PWH, aged 0-76 years (median 22) (see table):

<table>
<thead>
<tr>
<th>Table</th>
<th>Number of cases</th>
<th>Median age (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All reported TEEs in Patients with Congenital Haemophilia</td>
<td>85</td>
<td>22 years (0-76)</td>
</tr>
<tr>
<td>Deep vein thrombosis and/or pulmonary embolism</td>
<td>18</td>
<td>11 years (1-22)</td>
</tr>
<tr>
<td>Myocardial infarction / ischemia</td>
<td>17</td>
<td>41 years (8-73)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>18</td>
<td>55 years (2.5-70)</td>
</tr>
<tr>
<td>DIC</td>
<td>18</td>
<td>49 years (0-71)</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>30 years (3-57)</td>
</tr>
</tbody>
</table>

rFVIIa was reported to be administered in temporal relationship with APCC in 32/85 (37.7%) of TEEs. No thrombotic microangiopathic events have been reported. From 01 February 2000 to 31 July 2016, 73 TEEs for all indications were received from spontaneous sources (excluding literature), resulting in a reporting rate of approximately 3.5 TEEs/10⁵ infusions (3000 U per infusion). **Conclusion:** The reporting rate of TEEs associated with APCC is comparable with published data and confirms its long-time overall safety profile. A clinically relevant portion of the TEEs occurred in the presence of additional/confounding risk factors such as underlying disease and concomitant medications. The review of all TEEs reported in temporal association with the use of APCC is a valuable resource for the understanding and perhaps the prevention of such events.
What Symptoms of Hemophilia Most Impact Quality of Life – A Quantitative Survey of People Living with or Caring for Someone with Hemophilia A

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Background: While people with hemophilia are known to suffer from bleeding, numerous concomitant symptoms also burden these patients, including pain, mobility impairments, depression, and anxiety. These symptoms can have a significant impact on quality of life, limiting work and school attendance, causing social withdrawal, and encouraging inactivity. Additionally, available treatment options can sometimes fall short in treating the totality of hemophilia symptoms.

Objectives: To better understand what symptoms beyond bleeds are experienced, as well as the depth of impact of these symptoms and how they uniquely impact people living with hemophilia on a daily basis. Additionally, the study aims to better understand patients’ satisfaction with current treatments in addressing their hemophilia needs.

Design/Method: An email invitation was sent to all U.S. members affiliated with hemophilia A of MyHemophiliaTeam, a social network of people diagnosed with or caring for someone with hemophilia. 54 members responded to a 24 question survey between April 19 and May 1, 2017.

Results: Hemophilia had a significant negative impact on the day-to-day life of adults (72%) and children (52%). Pain was the most broadly and acutely experienced symptom: 60% of adults and 28% of caregivers felt that pain had a major impact on their lives and 33% of adults and 25% of caregivers considered mobility to be significantly impacted by hemophilia.

For adults, both pain and mobility limitations impacted sleep (71% and 45%, respectively), being able to perform chores (71% and 65%), and the ability to work (48% and 45%). For children, these conditions impacted school attendance (61% and 58%) and participation in high impact activities like running or playing soccer (56% and 75%).

Depression and anxiety were also common symptoms that impacted sleep across adults (71%, 61%) and children (60%, 55%). Adults most commonly reported feeling negative ones: stress (38%), fatigue (38%) and annoyance (35%).

81% of adults and 86% of caregivers were extremely or very satisfied with current treatment. However, needs beyond treating bleeds are currently not being met. Few felt their pain was adequately addressed by current therapies (74% of adults and 57% of children reported no relief). Mobility impairment issues were also not being adequately addressed. Time spent on treatment impacted people with hemophilia (39% of adults and 43% of children, respectively were not satisfied with the frequency of treatment).

Conclusions: People with hemophilia have many challenges beyond bleeds that are not currently being well addressed. This is particularly true for the pain experienced. As such, a more holistic approach to treating hemophilia beyond bleeds would be beneficial to patients.
living with hemophilia. Additionally, therapies that reduce the need and frequency for
treatment could potentially lower the burden of disease.
Efficacy, safety and pharmacokinetics of emicizumab (ACE910) prophylaxis in persons with hemophilia A with inhibitors: randomized, multicenter, open-label, phase 3 study (HAVEN 1)

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\textbf{Objectives:} Emicizumab, a bispecific humanized monoclonal antibody in development to address unmet medical needs in persons with hemophilia A with inhibitors (PwHAwI), bridges FIXa and FX to replace the function of missing FVIIa, needed for effective hemostasis. This study assessed efficacy, safety and PK of emicizumab prophylaxis in PwHAwI. \textbf{Methods:} Study NCT02622321 was conducted at 43 centers/sites, and enrolled PwHAwI ≥12 y.o. Participants (pts) receiving prior episodic bypassing agents (BPAs) were randomized (2:1) to emicizumab prophylaxis vs no prophylaxis (Arm A vs B). Primary endpoint compared treated bleed rates in Arm A vs B. PwHAwI receiving prior prophylactic BPA received emicizumab prophylaxis in Arm C. Emicizumab was injected subcutaneously at 3 mg/kg/wk for 4 wks, and 1.5 mg/kg/wk thereafter. \textbf{Summary:} 109 male PwHAwI were enrolled; median age 28 (range 12–75) yrs. Median (range) emicizumab treatment exposure was 24.0 (3.0–47.9) wk overall and 29.5 (3.3–47.9) wk in Arm A. Statistically significant, clinically meaningful reductions (87%) in treated bleed rates were observed between emicizumab prophylaxis vs no prophylaxis (Arm A vs B) (annualized bleeding rate [95% confidence interval] 2.9 [1.69 to 5.02] versus 23.3 [12.33 to 43.89], $P<0.0001$), and in all secondary bleed-related endpoints (spontaneous, joint, target joint, and all bleeds). Of note, a 79% reduction in treated bleed rate was seen with emicizumab prophylaxis (Arm C) vs BPA prophylaxis prior to study entry in a non-interventional study (NCT02476942; intra-individual comparison, $P=0.0003$). Overall, 67.3% of PwHAwI on emicizumab prophylaxis had zero treated bleeds. Statistically significant, clinically meaningful improvements in health-related quality of life (HRQoL) and health status were seen for Arm A vs B. Emicizumab was well tolerated. Total of 198 adverse events (AEs) were reported in 103 pts; most common AEs were injection-site reactions (15%), and 12 serious AEs were reported in 9 (8.7%) pts. Thrombotic microangiopathy and thrombosis (2 pts each in primary analysis) were reported and associated with high cumulative aPCC doses averaging >100 U/kg daily for >24 hr prior to event onset. No events occurred with emicizumab prophylaxis alone. Both TMA events resolved once aPCC treatment was stopped, and the thrombotic events did not require anticoagulation; 2 pts resumed emicizumab without sequelae (1 with TMA, 1 with thrombosis). No antidrug antibodies were detected. Mean trough emicizumab concentrations >50 µg/mL were achieved after 4 loading doses (3 mg/kg/wk) and sustained with maintenance doses of 1.5 mg/kg/wk.

\textbf{Conclusion:} Emicizumab prophylaxis prevented or substantially reduced bleeds in PwHAwI and meaningfully improved HRQoL. Emicizumab had acceptable safety without excess thrombotic risk in the absence of concomitant aPCC. PK levels were sustained with once-weekly maintenance doses. These promising data could support a paradigm shift in the management and lives of PwHAwI.
Efficacy, safety and pharmacokinetics of once-weekly prophylactic emicizumab (ACE910) in pediatric persons (<12 years) with hemophilia A with inhibitors: interim analysis of single-arm, multicenter, open-label, phase 3 study (HAVEN 2)

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Objectives: Emicizumab, a novel bispecific humanized monoclonal antibody promotes coagulation by bridging FIXa and FX to replace the function of missing activated FVIII, and has potential to address unmet medical needs in pediatric persons with hemophilia A (PwHA) with inhibitors. This study assessed efficacy, safety and pharmacokinetics of once-weekly subcutaneous emicizumab prophylaxis in pediatric PwHA with inhibitors. Methods: The study (NCT02795767) enrolled PwHA with inhibitors aged <12 years (or 12–17 years if <40 kg) previously treated with bypassing agents to receive emicizumab prophylaxis for ≥52 weeks. Emicizumab was administered subcutaneously at 3 mg/kg/week for 4 weeks, followed by 1.5 mg/kg/week thereafter. Efficacy objectives included bleed rate, and comparison of the bleed rate on emicizumab prophylaxis vs historical bleed rate obtained from a prospective, non-interventional study (NIS; NCT02476942). The NIS collected detailed, high-quality real-world data on bleeds and safety outcomes from a cohort of pediatric PwHA with inhibitors treated according to local, routine clinical practice. Participants from the NIS could subsequently enter the HAVEN 2 study, which permitted intra-individual comparisons. Summary: This interim analysis included 20 PwHA with inhibitors aged 3–12 years (median 8.5); 19 aged <12 years were included in the efficacy analyses. The median observation time was 12.1 weeks (range 7–14). In total, 18/19 (94.7%) participants had zero treated bleeds and 12/19 (63.2%) did not bleed while on study. Overall, 14 bleeds were reported in 7 participants, with none occurring in a joint or muscle. No participants have required up-titration of emicizumab. A substantial reduction in ABR on study vs ABR on prior treatment with bypassing agents (non-interventional study) was observed in 8 participants included in the intra-individual comparison; all 8 participants reported zero bleeds with emicizumab prophylaxis (efficacy period 85–99 days). Emicizumab was well tolerated; most common AEs were mild injection-site reactions (15%) and nasopharyngitis (15%). Three unrelated serious AEs were observed (mouth hemorrhage, appendicitis, catheter site infection). No thromboembolic or thrombotic microangiopathy events were reported. No anti-drug antibodies were detected. Mean trough emicizumab concentrations of >50 µg/mL were achieved after 4 loading doses of 3 mg/kg/week and sustained with maintenance doses of 1.5 mg/kg/week, and were consistent across age groups and body weight. Conclusion: Emicizumab prophylaxis was well tolerated and prevented/reduced bleeds in pediatric PwHA with inhibitors. Clinically meaningful reductions in ABR were observed compared with ABR on prior treatment with bypassing agents. The pharmacokinetic profile of emicizumab was similar to that seen in adolescent/adult PwHA with inhibitors. These interim data show the potential for emicizumab to reduce the disease and treatment burden for pediatric PwHA with inhibitors.
Living with hemophilia B: examining quality of life and associated characteristics in the Hemophilia Utilization Group Studies (HUGS Vb) cohort

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Objective: To identify sociodemographic, clinical and treatment characteristics associated with the quality of life (QoL) of individuals with hemophilia B (HB) using longitudinal data in the HUGS Vb cohort.

Methods: Between 2009-2012, 148 persons with HB were enrolled into HUGS Vb, a prospective cohort study examining individuals seen at ten federally supported U.S. hemophilia treatment centers (HTCs). Participants or parents of pediatric enrollees completed periodic surveys; data from 107 individuals with at least three follow-up surveys, clinician charts and dispensing records were included in the analyses. Data were analyzed at baseline and 6-month intervals across 2 years, yielding 5 time points. Periodic QoL assessments (SF-12 for adults and PedsQL for children), self-reported pain, employment and insurance status, time lost from work/school and treatment regimen were collected. Descriptive statistics and Spearman's correlation coefficient test were used to examine the associations. Summary: Forty-six percent of the sample had severe HB; 50% were children (2-17 years). Among those with severe HB, 64% of children and 50% of adults treated prophylactically. 58% of adults were employed full-time. Individuals with mild hemophilia missed more work/school days due to disease-related issues (8 days) than those with moderate hemophilia (2 days) or severe hemophilia (3 days, P=0.03). QoL scores were similar over time among those using prophylactic and on-demand treatment for both adults and children. Median adult Mental Component Scores (MCS) and Physical Component Scores (PCS) measured at 5 time points ranged from 53.0 to 55.1 for MCS and 45.5 to 50.5 for PCS, with no significant changes observed over time. However, adults employed full-time had significantly higher median PCS at each time point than those working less than full-time (all Ps<0.05). Adults who reported pain had significantly lower median PCS than those who reported no pain/pain only when bleeding at each time point (all Ps<0.03). Median MCS remained similar between the two groups. Overall, we observed no longitudinal differences in children's total PedsQL scores (range of median: 81.2-92.4) or in functioning subscales. However, among 18 children with QoL scores at both baseline and 24 months, missed school days were significantly correlated with decreased social functioning over time (rho=0.73, P<0.001). 8% of children who reported pain had consistently lower median total QoL scores than those reporting no pain/pain only when bleeding, despite having access to insurance and prophylactic treatment. Conclusions: Longitudinal data collected by HUGS Vb provide a valuable opportunity to examine the association of HB patient characteristics with measures of QoL in a multi-state sample. These data demonstrate that lower QoL was consistently associated over time with multiple factors, including absence from school, unemployment and pain. Continued analysis of this cohort will increase our understanding of the challenges faced by persons with HB.
Qualitative findings from bleeding disorders camp

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Camping programs for individuals with chronic illness are increasingly common. Unfortunately, few studies have been conducted to empirically evaluate whether camping programs are meeting their intended goals or having the positive outcomes that are expected of them. The current study was conducted as an evaluation of a bleeding disorder camp for patients with bleeding disorders and their siblings.

Participants in the current study included 77 participants, ages 7-20 (mean 11.58, SD = 3.21). The sample was 62.3% male and 63.6% patients (36.4% siblings). Most of the patients (52.6%) had severe bleeding disorders. Participants were administered the Children's Hope Scale (CHS; Snyder et al., 1991), which evaluates two dimensions of hope (1. Agency, the ability to identify positive goals and 2. Pathways, the ability to find ways to meet identified goals) and overall hope. Participants demonstrated a significant improvement on the agency subscale of the CHS, t(35) = -2.16, p < .05. Participants reported qualitative aspects of living with bleeding disorders, including differences in their lives, aspects of their lives that are better, aspects about bleeding disorders that are often misunderstood, and advice for others with bleeding disorders. Responses to qualitative were analysed across groups (patients and siblings; severe and mild patients) and were found to be very consistent across these groups. This information has helped to provide information about experiences of youth affected by bleeding disorders and will be used to help inform upcoming camp programming. These findings have also demonstrated positive psychosocial outcomes associated with camp attendance.
Staying on TRAQ: Determining transition readiness from pediatric to adult care in adolescents and young adults with hemophilia.

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Advancements in medical care for the hemophilia patients has created the need for an active and intentional process of transition from pediatric-oriented health care to adult-oriented health care. Instruments to measure transition “readiness” have not been validated in the adolescent and young adult (AYA) hemophilia population. The primary aim of this study was to identify the baseline state of transition readiness of hemophilia males in their ability to take charge of their own care as they transition from pediatrics to adult care using a validated Transition Readiness Assessment Questionnaire (TRAQ). Our secondary objective was: 1) To compare transition readiness between young adults who are transitioned to an adult hemophilia clinic in a separate facility versus those who continue to receive care in the same facility but transitioned to an adult provider. METHODS: For this purpose, we conducted a cross-sectional study at the Hemophilia study of Western New York (HCWNY), Buffalo (same facility) and at Children’s Hospital of Michigan (CHM), Detroit (separate facility). Inclusion criteria: 1) males who are currently 16-21 years old, 2) diagnosis of hemophilia A and B regardless of severity, 3) ability to read English at a grade 8 level. TRAQ is a 20-item, 5-domain patient-reported assessment of health and health care self-management skills with possible scores ranging from 1 (low) to 5 (optimal). Parents/legal guardians of patients aged 16 to 17 and patients aged 18-21 were mailed a letter explaining the study in detail. The willing participants were directed to the questionnaire link. The responses were anonymous which were directly imported into excel spreadsheet without collecting any identifying information of the participants. RESULTS: A total of 13 individuals at the two sites participated. amongst these, there were 5 from the HCWNY site, 1 with mild hemophilia and 1 patient reported unknown severity. The mean overall TRAQ score was 4±0.8. The mean scores for the different subscales were: managing medications (4.2±0.8), appointment keeping (4.1±0.9), tracking health issues (3.6±1.2), talking with providers (4.4±1.2) and managing daily activities (4.1±1.1). No differences in the overall and the subscales scores was noted between the two centers (Wilcoxon rank sum for all p>0.05). CONCLUSIONS: Our results suggest that the hemophilia youth in our population appear to have good readiness to transition from pediatric to adult care. We did not find a difference between the two different clinical care settings. The tracking health issues portion of TRAQ demonstrated the least readiness. Our study demonstrates that transition readiness assessments can be implemented in the hemophilia treatment centers, which can be used to guide clinical care.
OBJECTIVE: My Life, Our Future (MLOF) seeks to advance understanding of hemophilia by developing the MLOF Research Repository, a resource for use in scientific study. To strengthen the database and improve clinical care for females, MLOF expanded in 2016 to collect data and samples from potential and confirmed carriers. METHODS: MLOF is a collaboration between the American Thrombosis and Hemostasis Network (ATHN) (educates HCPs, collects and protects genetic data, manages ATHNdataset, manages research review committee), Bloodworks Northwest (BWNW) (performs genetic testing and analysis, manages MLOF Research Repository), National Hemophilia Foundation (educates patients and the community), and Bioverativ (provides scientific collaboration and sponsorship). Patients enrolled in MLOF can contribute their de-identified clinical information and specimens (DNA, RNA, plasma and serum) to the MLOF Research Repository. The patients’ hemophilic genetic data (F8 or F9 variant) and specimens are stored at BWNW and their clinical data in the ATHN dataset. For carrier project participants, an ISTH Bleeding Assessment Tool score is determined, and for confirmed carriers factor levels are obtained and recorded in ATHN Clinical Manager. Upon enrollment of 5,000 participants, the MLOF Research Repository was opened to U.S.-based investigators in February 2017. Investigators were encouraged to partner with a participating hemophilia treatment center (HTC) on projects for clinical translational support. An independent, international, multidisciplinary panel of experts was convened to review research proposals, evaluating project feasibility, scientific merit and potential contribution to the bleeding disorders community. SUMMARY: To date, 97 HTCs are actively participating in MLOF and have enrolled 8,246 patients. Of those, 83% (6,857), including 723 confirmed carriers, have consented to research. The samples of 427 additional females consenting to research are pending evaluation; 1,643 females have participated in MLOF. The first MLOF Research Repository cycle received 9 Letters of Intent and 7 were chosen for full proposal review. The final selection of studies will be announced to the community in June 2017. CONCLUSIONS: Combining and analyzing genetic and clinical data via this database may allow researchers to solve unmet needs in patients with hemophilia, including understanding inhibitor development, bleeding severity or aiding in identifying new therapeutic targets. By considering molecular drivers of disease and genetic variability, this approach could lead to more individualized treatment through advancement of precision medicine. Global expansion of the MLOF Research Repository is planned for 2018. Carrier testing may help females manage their bleeding disorder and may aid in family planning. Related to research, females provide a unique control group for males with hemophilia on natural history, modifier genes inside and outside the coagulation system, and epigenetic factors affecting outcomes.