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CLINICAL RESEARCH

Designing ATHN 7: Safety, effectiveness and practice of treatment of people with haemophilia in the United States through a natural history cohort study

Tyler W. Buckner, Nabil Daoud, Moses Miles, Carrie O'Neill, Crystal Watson, Michael Recht

TYLER W. BUCKNER
Hemophilia and Thrombosis Center, University of Colorado School of Medicine, Aurora, CO, United States

NABIL DAOUD
American Thrombosis and Hemostasis Network, Rochester, NY, United States

MOSES MILES
American Thrombosis and Hemostasis Network, Rochester, NY, United States

CARRIE O'NEILL
American Thrombosis and Hemostasis Network, Rochester, NY, United States

CRYSTAL WATSON
American Thrombosis and Hemostasis Network, Rochester, NY, United States

MICHAEL RECHT
American Thrombosis and Hemostasis Network, Rochester, NY, United States. Email: mrecht@athn.org

Background: Haemophilia A and B are X-linked inherited bleeding disorders, resulting in the deficiency of clotting factor VIII and IX, respectively. Since the introduction of recombinant clotting factor concentrates in the early 1990s, the major safety concern for haemophilia therapy has been the development of inhibitory antibodies, or inhibitors. Over the recent past, new therapies for the treatment and prevention of bleeding have received regulatory approval or are under study. **Objective:**

ATHN 7
RESEARCH STUDY

The American Thrombosis and Hemostasis Network (ATHN) is building a comprehensive dataset on treatment safety, effectiveness, regimens, target joints, and patient-reported outcomes for people with haemophilia in the United States

'ATHN 7: A Natural History Cohort Study of the Safety, Effectiveess, and Practice of Treatment for People with Hemophilia is designed to determine the safety of current haemophilia therapies when used for participants with haemophilia with or without inhibitors. Secondarily, ATHN 7 will describe the real-world effectiveness of current therapies by assessing bleeding rate and location, therapy utilisation, adherence, and patient-reported outcomes. **Methods:** This longitudinal, observational cohort study by the American Thrombosis and Hemostasis Network (ATHN) will follow participants with haemophilia with or without inhibitors for four years from the time of enrolment. Each participant is assessed every three months. All data are collected into ATHN Systems. The primary outcome measure is the incidence of safety

events as defined by the European Haemophilia Safety Surveillance (EUHASS) programme. Effectiveness will be described based on annualised bleeding rate, therapy utilisation, adherence, and patient-reported outcomes. **Conclusion:** As the first product-agnostic, real-world study of haemophilia therapy in the United States, ATHN 7 collects data to determine current intervention safety and effectiveness. Based on this success, ATHN will continue to collect these data longitudinally through the ATHN Transcends study.

Keywords: Haemophilia A, Haemophilia B, Therapeutics, Safety, Effectiveness, Natural history

Haemophilia A and B, X-chromosome-linked blood disorders characterised by the inability to form effective clots in response to injury, affects between 30,000 and 33,000 men in the United States [1]. Haemophilia A is caused by a deficiency of clotting factor VIII (FVIII), while haemophilia B is caused by a deficiency of clotting factor IX (FIX) [2]. Eighty percent of people with haemophilia (PwH) have haemophilia A (12 cases per 100,000 males) and 20% have haemophilia B (3.7 cases per 100,000 males). Haemophilia also affects women, underscoring the importance of including women, girls, and those with the potential to menstruate in any natural history study [3,4]. Haemophilia severity is classified based on an individual's baseline circulating factor levels: less than 1% of normal is classified as severe, 1% to 5% as moderate, and more than 5% to less than 50% as mild [5]. The direct and indirect costs of this lifelong condition have been described as 'staggering', with hospitalisations, outpatient visits, and drug treatments, as well as missed work and school, exacting a huge toll [6]. In addition, the lives of PwH can be impacted by acute and chronic pain [7], anxiety, and reduced quality of life [8], while their caregivers suffer constant stress [9].

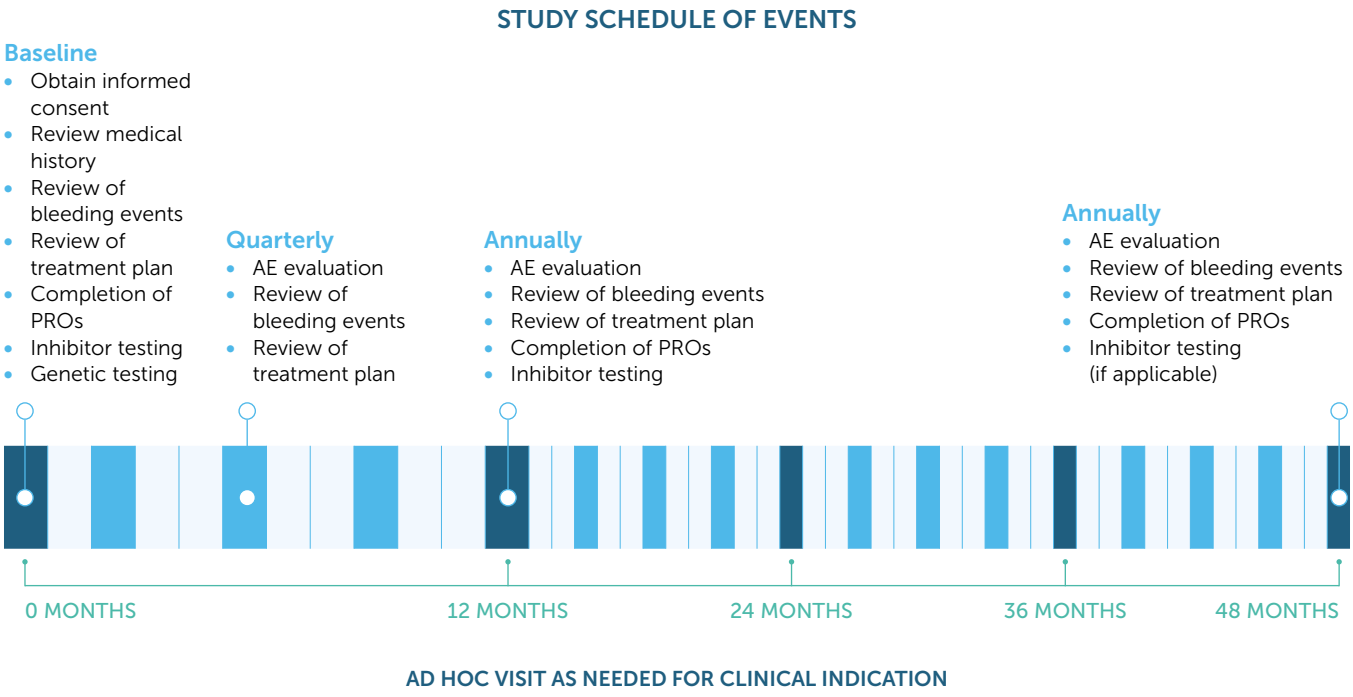
Treatment for PwH includes intravenous infusion of the missing clotting factor. These FVIII and FIX concentrates, initially purified from human plasma, may be administered either episodically (to stop a bleeding episode) or prophylactically (to prevent bleeding episodes). The first recombinant FVIII and FIX products received regulatory approval in 1992. Many products have been developed and marketed since that time. Most recently, emicizumab, a bi-specific antibody mimicking the action of factor VIII, was approved for the prevention of bleeding in people with haemophilia A with or without inhibitors [10,11]. Other therapies under study include therapies aiming to rebalance the coagulation system by reducing the actions of various endogenous anticoagulant proteins [12].

A significant challenge for PwH is the development of neutralising antibodies to infused factors. These antibodies, or inhibitors, reduce or eliminate the pro-coagulant effects of both infused, exogenous factor concentrates, as well as the patient's own endogenous FVIII or FIX (for those with non-severe haemophilia A or B). Approximately 20% of people with haemophilia A and 30% of those with severe disease develop an inhibitor at some point during their lifetimes [13]. A smaller proportion (7–10%) of people with haemophilia B develop inhibitors [14]. Modifiable risk factors for inhibitor development include type of clotting factor utilised, age at first treatment, treatment intensity, and the danger signal effect. In addition, null mutations in the F8 and F9 genes are the most important risk factor for inhibitor development. Various immune response genes and cytokines have been studied without definite confirmation of their role in inhibitor development [15]. Alternative therapies are required for PwH complicated by inhibitors, including high-dose clotting factor concentrates, bypassing factor concentrates (factors that bypass the inhibited factor in the clotting cascade), and emicizumab (for haemophilia A). Immune tolerance induction (ITI) therapy is the only current therapy to eliminate inhibitors [16]. Overall, treating PwH and inhibitors is lengthy, costly, and painful for PwH, as well as inconvenient and emotionally draining for both individuals with haemophilia and inhibitors and those who care for them [17].

The haemophilia treatment landscape is constantly evolving. Clinical data need to reflect this diversity as well as monitor effectiveness and safety. Comprehensive data from diverse populations and treatment products are sorely lacking. Previous published studies of haemophilia have included small population sizes and have been product-specific, often conducted as part of mandatory post-marketing surveillance programs. In addition, variations in study designs among these efforts make it difficult to compare outcomes across studies.

Founded in 2006, the American Thrombosis and Hemostasis Network (ATHN) has established a national informatics platform (ATHN Systems) to support clinical care and outcomes analysis, research, advocacy, and public health reporting in communities impacted by non-neoplastic hematologic disorders. ATHN partners with a nationwide network of federally supported haemophilia diagnostic and treatment centres

Figure 1. ATHN 7 schedule of events



AE: Adverse event PRO: Patient-reported outcome

(haemophilia treatment centres, or HTCs) established to provide comprehensive and integrated services for patients and families [18]. These efforts involve research, surveillance, and quality improvement (QI) initiatives. This paper describes the design and methods of the ATHN 7 study.

METHODS

Study design

ATHN 7 is an observational, longitudinal, natural history cohort study conducted at 26 ATHN-affiliated HTCs in the United States. Participants with either haemophilia A or B are followed for four years. ATHN's informatics platform (ATHN Systems) is in use for data capture by all ATHN Affiliates. Data are collected per a routine schedule of assessments and documented in electronic case report forms (eCRFs) in ATHN Systems. In addition, ATHN 7 participants are invited to contribute bleeding and treatment data via ATHN's mobile application.

Study oversight

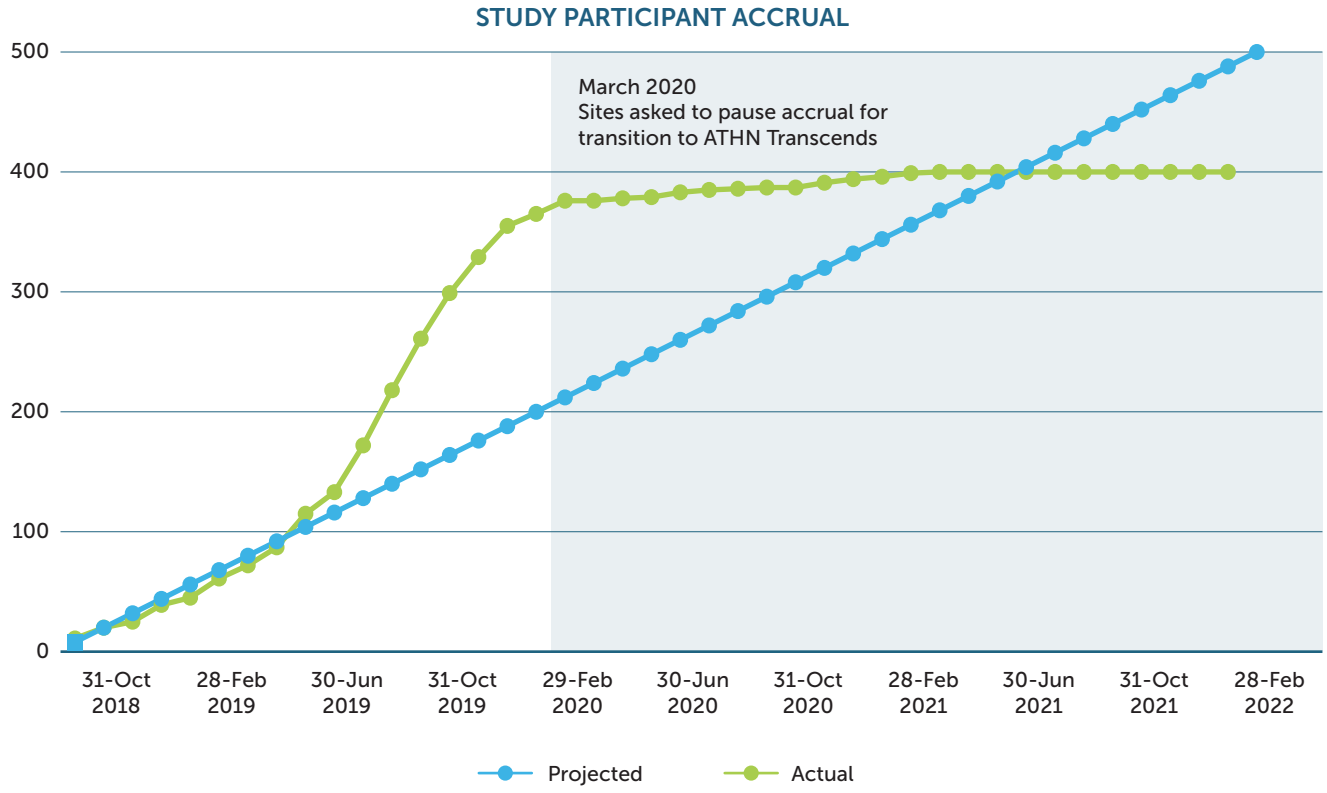
ATHN 7 is conducted in accordance with the ethical principles described in the Declaration of Helsinki [19]. The initial study protocol and all subsequent amendments were submitted to a centralised institutional research board. Participant identification code documentation is maintained by each institution to link participants to Study Subject Identifiers. An ATHN 7 study steering committee, whose membership consist of clinical, scientific, and consumer representatives, monitors the progress of the study.

Study population

All individuals of any sex and/or gender who meet the following inclusion criteria are eligible for enrolment in ATHN 7: congenital haemophilia A or B of any severity, with or without inhibitors, who are receiving any clotting factor therapy or for whom the use of a non-factor product may be medically indicated; able (or via parent/authorised guardian) to give informed consent; and willing to opt-in to the ATHNdataset, which is a Health Insurance Portability and Accountability Act (HIPAA)-compliant, de-identified, voluntary dataset containing data contributed by over 43,000 participants with blood disorders in the United States.

Participants who meet any of the following exclusion criteria are not eligible for enrolment into the study: presence of any known bleeding disorder other than congenital haemophilia A or B; presence of concurrent haemophilia and a second haemostatic defect (those with low von Willebrand factor without von Willebrand disease diagnosis are not excluded); and an inability or unwillingness to consent to and comply with the study protocol.

Figure 2. ATNH 7 accrual
Actual versus projected accrual into ATHN 7. The shaded area represents the onset of the COVID-19 pandemic and the decision to pause accrual into ATHN 7 with the planned transition of participants into ATHN Transcends.



At launch, ATHN 7 targeted enrolment of at least 280 participants. This number was based on initial funding and not on a statistical power calculation, as the study was not designed to detect differences in safety or effectiveness of individual therapies.

Study objectives and endpoints

Primary objective: The primary objective of ATHN 7 is to determine the safety of treatments for people with haemophilia A and B, including bypassing agents, non-factor products, and clotting factor replacement products in participants with or without inhibitors. Standardised, mandatory reporting of common adverse events is conducted quarterly.

Secondary objectives and endpoints: ATHN 7 includes four secondary objectives focusing on the real-world use of haemophilia therapies, including:

1. Describing the effectiveness of non-factor products, bypassing agents, and clotting factor replacement products for preventing and treating bleeding in participants with haemophilia with or without inhibitors. Effectiveness is measured by overall annualised bleeding rate (ABR); annualised spontaneous bleeding rate; annualised traumatic bleeding rate; annualised joint bleeding rate; annualised non-joint bleeding rate; and prevalence of unexpected and treated bleeding with surgical procedures.
2. Describing the dosing regimens and total amount of product utilised by the study population including non-factor products, bypassing agents and clotting factor replacement products for prophylaxis and treatment of bleeding. This includes determining the number of participants who initiate and/or switch treatment from factor concentrates to a non-factor product and their reasons for initiating and/or switching treatment with non-factor products; the number of participants who do not initiate treatment with non-factor products; the number of participants who switch between different non-factor products and their reasons for switching; and the number of participants who discontinue treatment with non-factor products and their reasons for doing so.
3. Describing the number and location of target joints (as defined by International Society on Thrombosis and Haemostasis (ISTH) [20]) upon study entry and determining the incidence of target joint development and the proportion of resolved target joints following study enrolment.

4. Describing patient-reported outcomes in individuals treated with non-factor products, bypassing agents, and clotting factor replacement products, including health care utilisation (number and types of visits and/or hospitalisations per year), health-related quality of life (HRQoL, as measured by EQ-5D-5L and the age-appropriate PROMIS Profile questionnaire), and treatment adherence as measured by Global Adherence Rating (Table 1).

Figure 3. List of participating HTCs and accruals by site

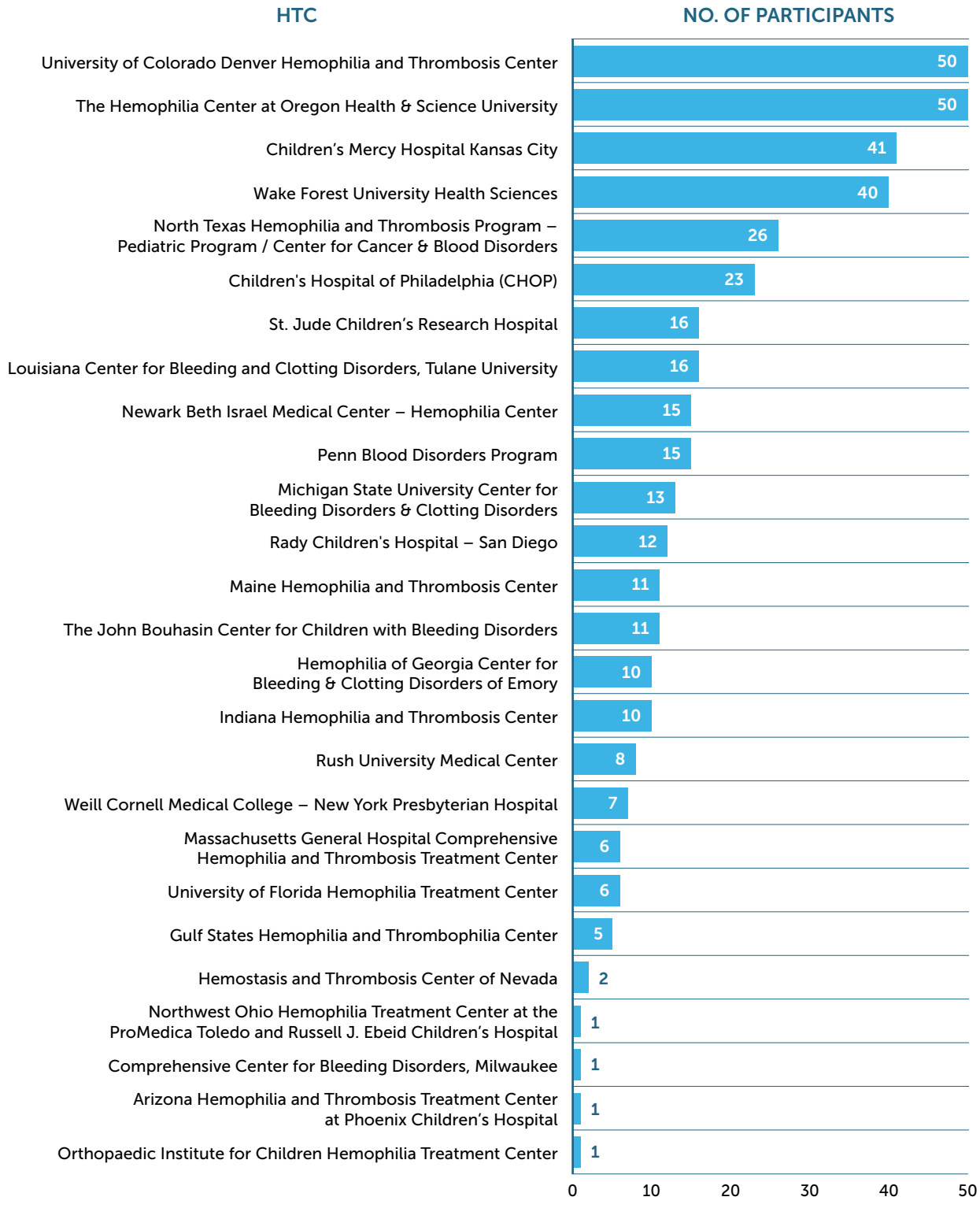


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Table 1. Patient-reported outcomes data collected from participants (or parent proxies) at enrolment in ATHN 7

AGE OF PARTICIPANT (YEARS)	0-4	5-7	8-11	12-17	>18
EQ-5D-5L				X	X
PROMIS-29					X
PROMIS-25			X	X	
PROMIS-25 parent proxy		X			
GAR				X	X
GAR parent proxy	X	X	X		

EQ-5D-5L: EuroQol, five-level EQ-5D; comprises five dimensions covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression

PROMIS 29: National Institutes of Health (NIH) Common Fund, Patient-Reported Outcomes Measurement Information System; 29-item short form HRQoL tool assessing seven HRQoL domains: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain (interference and intensity)

PROMIS 25: NIH Common Fund, Patient-Reported Outcomes Measurement Information System; 25-item paediatric short form HRQoL tool, six HRQoL domains: mobility, anxiety, depression, fatigue, peer relationships, and pain (interference and intensity). Designed for children aged 8-18.

GAR: Global Adherence Rating; a non-validated single-question assessment of adherence to current therapy extracted from VERITAS-PRO.

In addition to the primary and secondary objectives, ATHN 7 supports treatment-product-specific sub-study modules (Product Specific Modules or PSMs). PSMs are optional for study participants. PSMs, are administered in conjunction with the other ATHN 7 study assessments. Participants may agree to share product-specific information with investigators, including clinical researchers and pharmaceutical companies.

Study schedule (see Figure 1)

All study visits, procedures, and follow-up encounters are timed to coincide with routine, scheduled haemophilia care whenever possible. Participants are followed every three months for four years from time of enrolment.

The study schedule includes the following events:

1. Study enrolment/baseline – Study activities will begin after consent and relevant authorisations are signed
2. Quarterly follow-up (every three months) will occur in person or by telephone
3. Ad hoc follow-up for study-specific safety events and product switches
4. Annual visit
5. Study exit

Data collection

Data are collected based on the following data sources: participant report (in person and/or by telephone); review of the medical record; and participants' bleed and infusion logs. Data are then entered into electronic case report forms (eCRFs) in ATHN Systems. The following subject-level data are collected at the time of enrolment: 1) demographic data; 2) bleeding disorder history and family history of haemophilia; 3) inhibitor titres; 4) haemophilia genotype (if previously performed); 5) a comprehensive medical history, including modifiable risk factors for inhibitor development; 6) comprehensive history of medication use; 7) lifetime history of any target joints; 8) all surgical procedures; 9) a panel of patient-reported outcomes (see Table 1).

Safety is measured by those events in the prospective adverse event reporting system for Europe developed by EUHASS [21]. Events include death, factor inhibitor development, venous thrombosis, allergic reactions and treatment-emergent side effects of therapy, malignancy, cardiovascular events, and blood-borne infections. In addition to the EUHASS safety endpoints, ATHN 7 includes the following as safety endpoints: thrombotic microangiopathies, injection site reactions, cases of potential drug-induced liver injury, and additional safety events of interest, such as development of anti-drug antibodies.

Adverse events must be reported to ATHN by the study site team within seven days of study site awareness for EUHASS adverse events and adverse events of special interest, and within 15 days of site awareness for all other reportable events. These timeframes have been established to ensure that: 1) the study sponsor can meet their contractual obligations to the study funders for safety surveillance; and 2) drug manufacturers can meet their regulatory obligations to the US Food and Drug Administration (FDA) for post-marketing safety surveillance. Immediate, real-

time (e.g., 24 hour) reporting of serious adverse events or other events not meeting EUHASS criteria is not required for this study. Regulatory reporting is the responsibility of individual clinicians and is governed by the clinician's institutional policies and procedures.

Laboratory assessments

FVIII or FIX genotyping is offered to all participants who have not yet undergone such testing at the time of enrolment. Genetic testing is conducted at ATHN's central genetic testing laboratory service at Versiti Blood Center of Wisconsin.

Inhibitor titre testing results are collected at the following time points: baseline; each annual visit; the time of product switch; the time of suspected development of an inhibitor; the time of a confirmatory test for a previously elevated inhibitor test result; and at study exit. Any inhibitor test resulting in a positive titre is repeated within 10 days for confirmation. The Centers for Disease Control and Prevention (CDC) serves as the central laboratory for inhibitor testing, utilising their pre-analytical heat treatment method previously described [22]. Many ATHN 7 participants are also enrolled in the national CDC's Community Counts bleeding disorders surveillance project, for which ATHN is the national grantee. CDC and ATHN have designed these projects to allow the Community Counts inhibitor test results to be used for both Community Counts and ATHN 7 to minimise the number of blood draws for a participant.

STATISTICAL ANALYSIS

Descriptive statistics will be used to analyse ATHN 7 data. The study is not designed to detect differences in safety or efficacy among individual factor or non-factor products and its results will not be used for this purpose. The frequency and percentages for each categorical variable will be reported. Other outcomes, such as HRQoL, will be treated as continuous variables, and the mean, median, standard deviation, interquartile range, and the minimum and maximum values of each will be presented. In addition, ATHN 7's safety endpoints will be reported as incidence rates (i.e., the number of reported events per participant-year) every four months for the length of the study. In addition, we will analyse patient-reported outcome data, such as the EQ-5D-5L index score and PROMIS scores, longitudinally.

LIMITATIONS OF ATHN 7

Although designed to be the largest natural history study of people with haemophilia in the United States, ATHN 7's design has some important limitations potentially impacting the generalisability of results. First, we did not design the study to represent the population of people with haemophilia receiving care through ATHN Affiliates. Rather, we targeted specific populations for enrolment. Specifically, we attempted to enrol approximately half of all participants on novel therapies to determine if there were any unique safety signals emerging from the use of these new agents. Second, we did not enrol consecutive participants. Rather, we allowed individual sites to choose individuals for participation based on site-specific criteria. Third, sites participating early in ATHN 7 were able to enrol up to 50 participants. As these early enrolling sites were among the larger sites in the US, bias was introduced potentially effecting generalisability of results. Finally, the 26 sites participating in ATHN 7 do not necessarily reflect the practices of all ATHN Affiliates as a whole.

CURRENT STATUS

ATHN 7 is currently underway at 26 ATHN-affiliated sites in the United States (see Figure 3). The study exceeded enrolment expectations within the first 18 months, with 397 participants enrolled to date (see Figure 2). In March 2020, ATHN 7 closed to enrolment for two reasons. First, because of ATHN 7's success in participant enrolment, ATHN designed a natural history study inclusive of all inherited and acquired bleeding disorders, ATHN Transcends (clinicaltrials.gov identifier: NCT04398628). ATHN is currently working with all ATHN-affiliated sites to transition participants in ATHN 7 to ATHN Transcends to ensure the continuity of the longitudinal data collected for as long as ATHN Transcends remains open (currently proposed for 15 years). Enrolment into ATHN Transcends requires ending participation in ATHN 7 and signing a new consent. As part of the ATHN Transcends consent, participants are given the option of linking data from the two studies. Second, the world-wide SARS-CoV-2 pandemic seriously impaired the study's ability to enrol new participants, largely due to policy changes at the institutional, state, and local levels necessary to respond to the public health emergency.

CONCLUSIONS

Treatment options for those affected by haemophilia A or B have greatly expanded since the approval of plasma-derived factor concentrates more than five decades ago. It remains imperative to ensure that all new therapies are safe as well as effective. The ATHN 7 haemophilia natural history study aims to address the

need for ongoing evaluation of haemophilia therapies being used in real-world settings. The results of ATHN 7 will be disseminated both through the peer-reviewed medical literature as well as directly to the inherited bleeding disorders community.

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Disclosures

Tyler W. Buckner has worked as a consultant to uniQure, BioMarin, and Tremeau Pharmaceuticals. He has served on advisory boards for Spark, Tremeau, Bayer, CSL Behring, Novo Nordisk, Genentech, Takeda, and HEMA Biologics. He is a member of the Board of Directors of the American Thrombosis and Hemostasis Network.

Research funding to Moses Miles's employers has come from Bayer, BioMarin, CSL Behring, Genentech, Grifols, HEMA Biologics, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, and uniQure.

Research funding to Michael Recht's employers has come from Bayer, BioMarin, CSL Behring, Genentech, Grifols, HEMA Biologics, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, and uniQure. Dr. Recht has worked as a consultant for Catalyst Biosciences, CSL Behring, Genentech, HEMA Biologics, Kedrion, Novo Nordisk, Pfizer, Sanofi, Takeda, and uniQure. Dr. Recht sits on the board of directors of the Foundation for Women, Girls with Blood Disorders and Partners in Bleeding Disorders and Thrombosis and Hemostasis Societies of North America.

ORCID

Tyler W. Buckner https://orcid.org/0000-0003-1954-4385
Michael Recht https://orcid.org/0000-0002-2805-1016

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