PROTOCOL SYNOPSIS

World Federation of Hemophilia Gene Therapy Registry

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WFH
WORLD FEDERATION OF HEMOPHILIA

GTR
WFH GENE THERAPY REGISTRY

Introduction and Rationale

Gene therapy for hemophilia is an evolving therapeutic modality, with many challenges and unresolved questions regarding safety and efficacy that will not be fully answered at the completion of current ongoing clinical trial programs.

The WFH has developed the WFH Gene Therapy Registry (GTR), designed to collect long-term data on all people with hemophilia (PWH) who receive gene therapy. Implementing the GTR requires support from the global bleeding disorders community, including regulatory agencies, hemophilia treatment centres (HTCs), PWH and industry partners. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have provided scientific advice on the design of the GTR, which has informed the methodology of the GTR.

The WFH GTR will ensure that rare adverse events, in a small patient population over a large geographical area, will be detected. The many unknowns of gene therapy for hemophilia make it critical that the bleeding disorders community ensures all patients are followed over their lifetimes.

Objectives

The **primary objective** of the WFH GTR is to determine the long-term safety of factor VIII and factor IX gene therapies in patients with hemophilia.

The **secondary objectives** of the WFH GTR are to determine the long-term efficacy and the durability of factor VIII and factor IX gene therapies in patients with hemophilia, assessed as bleeding rate and plasma factor activity level; and to assess the long-term quality of life, assessed by the EQ-5D-5L, PROBE, and coreHEM, mental health questionnaire (when finalized and available for use), post gene-therapy infusion.

Study Design

The WFH GTR study is a prospective, observational, and longitudinal registry of patients diagnosed with hemophilia, who have received gene therapy for hemophilia. Ideally, patients will be enrolled into the registry at the time of gene therapy infusion and data will be collected into the registry prospectively, therafter. For patients who enroll into the registry > 3 months after receiving their gene therapy infusion, the date of infusion will serve as baseline, and data collected between the date of infusion and the date of enrolment into the registry will be collected retrospectively.

Study Centers

All HTCs that will be administering gene therapy for PWH will be invited to participate. HTCs that will be providing follow up visits for PWH who receive gene therapy will either be invited to participate, or the patient data collected at the follow up site will be sent to the HTC administering gene therapy for inclusion in the registry.

Study Population

All PWH who have received gene therapy for hemophilia, via a clinical trial, compassionate use or as a marketed therapy, at any point in time, will be invited to participate. Clinical trial participants will be enrolled into the registry at completion of the clinical trial or earlier if permitted by the clinical trial criteria. There are no specific exclusion criteria for this registry.

Recruitment Process

Patient data will be included via 2 methods:

- Directly via HTCs**:** individual HTCs will be invited to participate in the registry directly. Eligible PWH will be enrolled into the GTR through participating HTCs.
- Data transfer from existing patient registries**:** to maximize the utility of data already being collected in existing registries, while avoiding duplicate data entry for HTCs, the WFH GTR has developed a Gene Therapy Data Integration Program, aiming to integrate gene therapy data collected in existing registries, directly into the WFH GTR, on at least a quarterly basis.

Participant Retention

Efforts to keep both HTCs and PWH engaged in the WFH GTR will be implemented. These will include financial compensation to participating HTCs for data management, and financial compensation to registry owners for the work required for direct linkage.

Withdrawal from WFH GTR

A participating PWH may withdraw from the WFH GTR at any time for any reason, or they may be withdrawn by the treating physician of the HTC.

Study Endpoints

The primary endpoint is safety events over the long-term. The number/proportion of patients experiencing at least one adverse event of interest, and the number of AEs of interest by type, deaths (related and unrelated), experienced by PWH post-gene therapy infusion, will be assessed at 3, 6, 9, 12, 18, and 24 months and annually thereafter.

The secondary endpoints are efficacy and durability of efficacy. The number/proportion of patients experiencing at least one bleed requiring treatment, from 1-month post-infusion to months 3, 6, 9, 12, 18, 24 and annually post-infusion thereafter will be assessed. The number/proportion of patients reaching pre-defined levels of factor expression (i.e., <5%, >5%-12%, >12%-20%, >20-50%, >50% and >150%) from diagnostic baseline factor level to month 3, 6, 9, 12, 18, and 24 months and annually thereafter, post gene therapy, will be assessed.

The number/proportion of patients who fail to maintain an achieved factor level category (<5%, >5%-12%, >12%-20%, >20%-50%, >50%) post gene therapy infusion will be assessed; defined as the time between first factor level assessment in which a patient reaches their highest factor level category and first factor assessment demonstrating a decrease to a lower category will be assessed.

The change in the composite health related quality of life scores of patients from the time they receive their infusion of a gene therapy product (baseline) will be reported as mean, median, standard deviation and interquartile range. The change in the PROBE scores of patients from the time they receive their infusion of a gene therapy product (baseline) will be reported as mean, median, standard deviation and interquartile range. The endpoint related to coreHEM will be determined once this questionnaire becomes available for use.

Data Collection

This is an observational registry and as such, there are no mandated tests or procedures. It is recommended that data be recorded in the registry at the time of gene therapy infusion, on a quarterly basis for the first year, twice in year 2, and annually thereafter.

The WFH GTR includes a core data set, that will be requested on all PWH from participating HTCs and existing registries that link with the WFH GTR. The GTR Core Data Set includes sections on:

- Demographics & Diagnosis
- Medical/Clinical History
- Gene Therapy Infusion Details
- Safety Data
- Efficacy Data
- Patient Reported Outcome Measures
- Mortality

myGTR Mobile Application

Patient reported outcome data will be collected through a patient mobile application, myGTR. myGTR will be a web-based application where patients will be asked to answer a short series of questions every 6 months and asked to complete EQ-5D-5L, PROBE, and coreHEM (when it becomes available) on a rotational basis.

WFH GTR Readiness Program

The WFH Readiness program will train participating HTCs and PWH on the WFH GTR. The program is aimed at providing investigators, physicians and data managers, as well as PWH who will be receiving gene therapy with training and education on the GTR, via on-line modules, presentation, guides and tools. This program will be offered in conjunction with general education on gene therapy for hemophilia.

Data Quality

The WFH GTR will include a comprehensive data quality program, which will be applied to all WFH GTR data entered into the gene therapy registry. All data will be evaluated on the following data quality dimensions:

- Completeness
- Accuracy
- Timeliness
- Source document validation

Data Governance, Access, and Reporting

Each HTC or country registry providing individual patient information, will own the data they enter in the registry. The combined data will be governed by the WFH. Data access and reporting plans are outlined in the WFH GTR Data Charter.

Database Hosting

The web-based data entry system for the WFH GTR will be developed, maintained, and hosted by United Biosource Corporation (UBC).

Privacy and Confidentiality

The database provider will provide a secure data centre with appropriate physical, administrative and technical safeguards in place. These procedures are aimed to protect information from misuse, unauthorized access, interference, alteration, loss and/or disclosure, which will meet or exceed the privacy and security regulation requirements in Canada, USA and Europe. Data policy guidelines must adhere to US, Canadian and European data privacy regulations.

Registry Governance

The WFH Gene Therapy Registry (GTR) has established a governance structure to ensure the continued success of the program (Appendix 1), including a Steering Committee, a Scientific Advisory Board, an Industry Consortium, and a Patient Advisory Group. The different governance entities are composed of multi stakeholder representatives from the following organizations: WFH, ATHN, EAHAD, EHC, Industry, ISTH, NHF, WBDR, in addition to PWH and clinical trialists.

Informed Consent

Eligible PWH must provide written informed consent or assent prior to participating in the WFH GTR.

Ethics Committee Approval

The protocol and the proposed informed consent form must be reviewed and approved by the Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) of the participating HTC prior to enrolling PWH.

Appendix 1: Registry Governance

WFH GTR Steering Committee members

Representation	Name	Affiliation
Chair, WFH Board of Directors member	Barbara Konkle	University of Washington, Seattle, USA
WFH VP Medical	Glenn Pierce	WFH
ATHN	Mike Recht	Oregon Health & Science University, Portland, USA
EAHAD	Wolfgang Miesbach	University Hospital Frankfurt, Frankfurt, Germany
ISTH	Cary Clark	ISTH
ISTH	Johnny Mahlangu	University of the Witwatersrand, Johannesburg, South Africa
ISTH	Flora Peyvandi	Università degli Studi di Milano, Milan, Italy
NHF	Len Valentino	NHF
NHF, MASAC	Steve Pipe	University of Michigan, Ann Arbor, USA
Leader in the field, Children's Hospital of Philadelphia	Lindsey George	The Children's Hospital of Philadelphia, Philadelphia, USA
Patient advocate, EHC	Declan Noone	EHC
Patient advocate, coreHEM, PROBE	Mark Skinner	Institute for Policy Advancement Ltd
Industry	Vanessa Newman	Biomarin
Industry	Ian Winburn	Pfizer
Industry	Paul Solari	Spark
Industry	Krupa Sivamurthy	CSL Behring
WFH WBDR SC Co-Chair	Alfonso Iorio	McMaster University, Hamilton, Canada

WFH GTR Scientific Advisory Board members

Representation	Name	Affiliation
Chair, WFH Gene Therapy Registry Steering Committee	Barbara Konkle	University of Washington, Seattle, United States
VP Medical, WFH	Glenn Pierce	WFH
EAHAD	Wolfgang Miesbach	University Hospital Frankfurt, Frankfurt, Germany
EHC Medical Advisory Group	Mike Makris	University of Sheffield, Sheffield, United Kingdom
ISTH	Flora Peyvandi	Università degli Studi di Milano, Milan, Italy

NHF MASAC	Steve Pipe	University of Michigan, Ann Arbor, United States
Patient advocate	Brian O'Mahony	Irish Haemophilia Society
Patient advocate	Mark Skinner	Institute for Policy Advancement Ltd

WFH GTR Industry Consortium

Representation	Name	Affiliation
Chair, WFH GTR Steering Committee	Barbara Konkle	University of Washington, Seattle, United States
VP Medical, WFH	Glenn Pierce	WFH
Industry	Vanessa Newman	Biomarin
Industry	Wendi Carroll	Biomarin
Industry	Ian Winburn	Pfizer
Industry	Lisa Wilcox	Pfizer
Industry	Paul Solari	Spark
Industry	Trupti Truvedi	Spark
Industry	Krupa Sivamurthy	CSL Behring
Industry	Blanca Salazar	CSL Behring

WFH GTR Patient Advisory Group

Name	Affiliation	Country
Bradley Rayner	South African Haemophilia Foundation	South Africa
Brendan Hayes	National Hemophilia Foundation	USA
Brian O'Mahony	Irish Haemophilia Society	Ireland
David Page	Canadian Hemophilia Society	Canada
Laurence Woollard	On The Pulse Consultancy	UK
Mark Skinner	Institute for Policy Advancement Ltd	USA