WFH Gene Therapy Registry Introductory Webinar

9 November 2020

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WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
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SPEAKERS

- Dr. Glenn Pierce
  WFH VP Medical

- Dr. Barbara Konkle
  Bloodworks Northwest
  WFH Board of Directors

- Dr. Wolfgang Miesbach
  University Hospital Frankfurt
  GTR Steering Committee

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AGENDA

1. Importance of a global registry
2. GTR Oversight
3. Protocol & Core Data Set
4. Implementation
5. Next Steps
6. Questions & Answers

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Importance of long-term follow-up

Dr. Glenn Pierce

WFH VP Medical

2020-11-09

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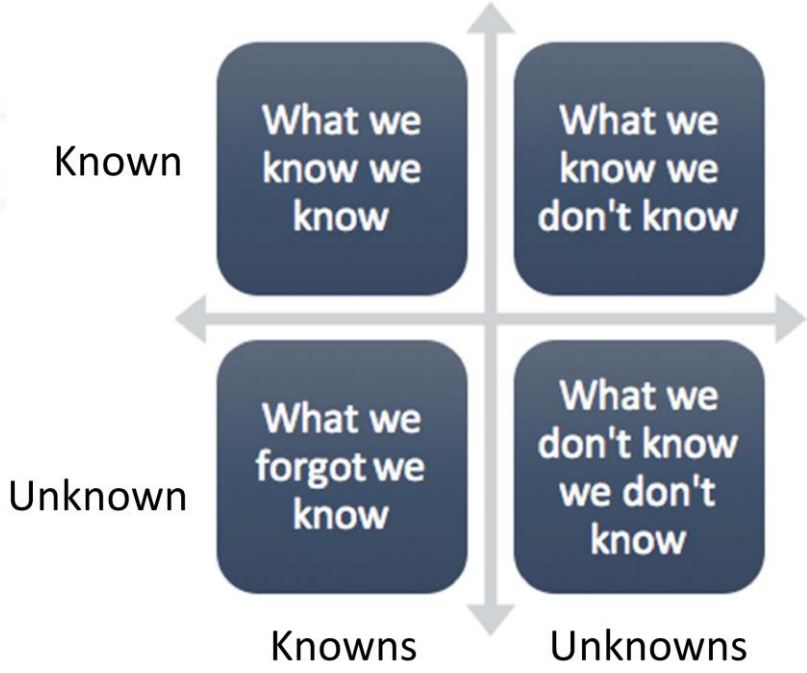
KNOWNS AND UNKNOWNS

Lifelong follow-up of gene therapy patients is crucial to monitor both known and yet unknown safety issues.



G. F. Pierce, A. Iorio. Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes. Haemophilia. 2018.

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CHALLENGES ASSOCIATED WITH RARE DISEASES

- Registries are an effective way to pool data to achieve the required sample size to conduct clinical research on rare disorders, such as hemophilia.

- Gene therapy recipients will be scattered around the world:
  - Essential to ensure the inclusion of a maximum number of patients, globally.

Increasing the likelihood of identifying low-incidence events.

LONG TERM FOLLOW-UP

- Regulatory agencies/FDA mandate 5 years of follow-up

  → incomplete or low-quality safety and efficacy data after the recommended 5-years.

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GTR Oversight

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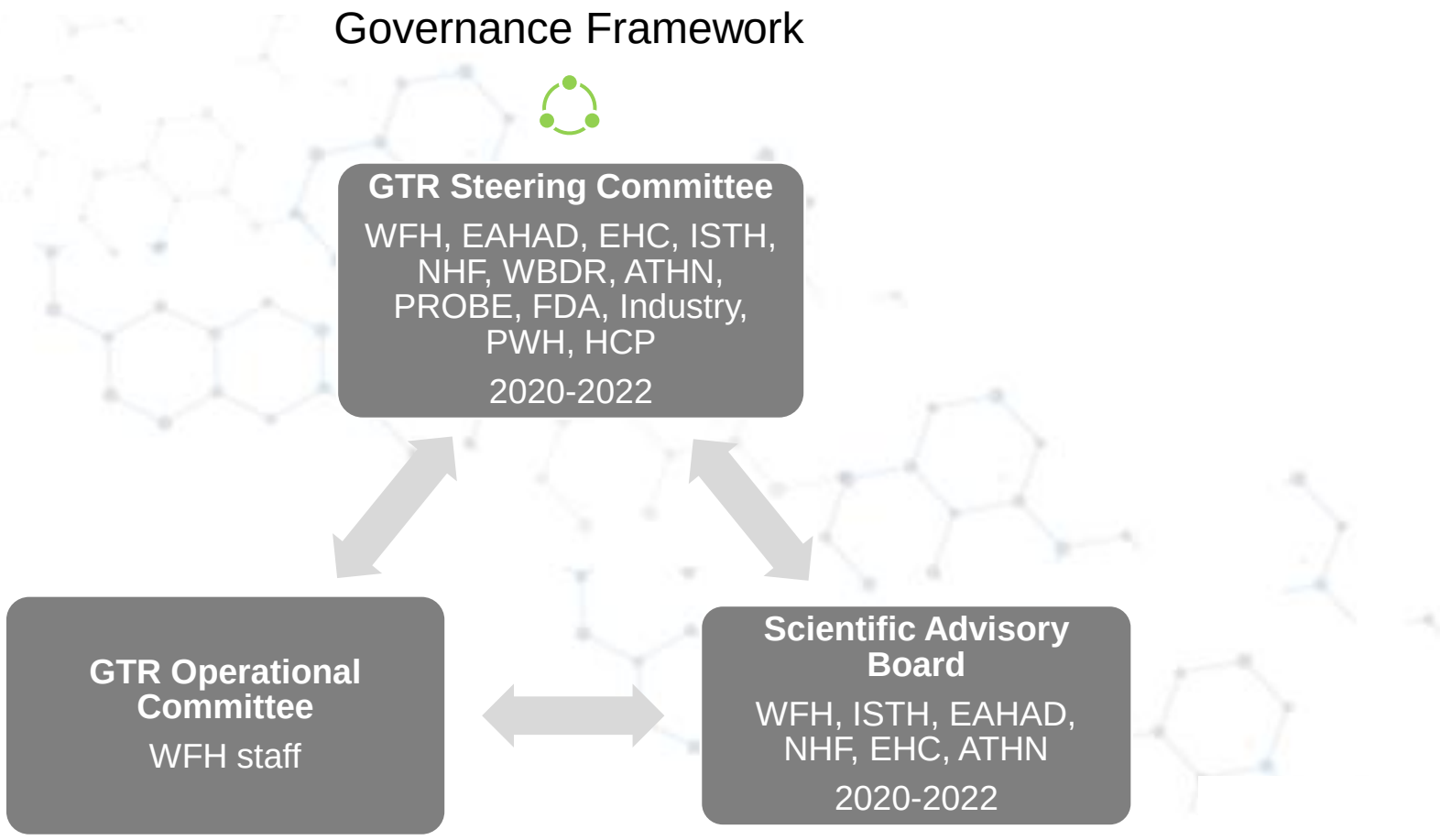
GTR OVERSIGHT



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GTR STEERING COMMITTEE

Name	Affiliation
Barbara Konkle	Chair , WFH WBDR SC Co-Chair
Glenn Pierce	WFH VP Medical
Mike Recht	ATHN
Bindu George	FDA Liaison
TBD	EMA Liaison
Vanessa Newmann	Industry - Biomarin
Ian Winburn	Industry - Pfizer
Bartholomew Tortella	Industry - Spark
Eileen Sawyer	Industry - Uniqure
Cary Clark	ISTH
Johnny Mahlangu	ISTH
Flora Peyvandi	ISTH
Lindsey George	Leader in the field, Children's Hospital of Philadelphia
Steve Pipe	NHF, MASAC
Wolfgang Miesbach	EAHAD
Declan Noone	Patient advocate, EHC
Mark Skinner	Patient advocate, coreHEM, PROBE
Alfonso Iorio	WFH WBDR SC Co-Chair
Donna Coffin	WFH Staff
Mayss Naccache	WFH Staff

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GTR SCIENTIFIC ADVISORY BOARD

Position	Representative
Chair, WFH Gene Therapy Registry Steering Committee	Barbara Konkle
VP Medical, WFH	Glenn Pierce
ISTH	Flora Peyvandi
EAHAD	Wolfgang Miesbach
NHF MASAC	Steve Pipe
EHC Medical Advisory Group	Mike Makris
Patient advocate	Brian O'Mahony
Patient advocate	Mark Skinner

Support staff

Position	Representative
Director, Research & Public Policy, WFH	Donna Coffin
Gene Therapy Program Manager, WFH	Mayss Naccache

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Protocol & Core Data Set

Dr. Barbara Konkle

Bloodworks Northwest

WFH Board of Directors

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WFH GENE THERAPY REGISTRY

- Prospective, observational, and longitudinal registry.
- Goal: Data collection on all patients who receive gene therapy for hemophilia, via clinical trials and post-marketing
- Worldwide

Konkle BA, Pierce GF, Coffin D, Naccache M, Clark C, George LA, Iorio A, O'Mahony B, Pipe S, Skinner MW, Watson C, Peyvandi F, Mahlangu JN, for the ISTH subcommittee on Factor VIII, Factor IX and rare bleeding disorders. Core data set on safety, efficacy and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020 Oct. https://doi.org/10.1111/jth.15023

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PROTOCOL DEVELOPMENT

- Protocol developed with input from multi-stakeholder Steering Committee
- Submitted to CHMP EMA for Scientific Advice
- Submitted to FDA for comment and feedback
- Responses received and protocol updated according

Konkle BA, Pierce GF, Coffin D, Naccache M, Clark C, George LA, Iorio A, O'Mahony B, Pipe S, Skinner MW, Watson C, Peyvandi F, Mahlangu JN, for the ISTH subcommittee on Factor VIII, Factor IX and rare bleeding disorders. Core data set on safety, efficacy and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020 Oct. https://doi.org/10.1111/jth.15023

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GTR OBJECTIVES

- Primary objective:
  - to determine the long-term safety of factor VIII and factor IX gene therapies in patients with hemophilia.

- Secondary objectives:
  - to determine the long-term efficacy and the durability of factor VIII and factor IX gene therapies in patients with hemophilia;
  - to assess long-term quality of life (EQ-5D-5L) and burden of disease (PROBE) post gene-therapy infusion.

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CORE DATA SET DEVELOPMENT

- Development of the Core Data Set:
  - Steering Committee monthly teleconferences
  - Iterative process
  - Published in JTH as an ISTH SSC publication (Nov 2020)

Konkle BA, Pierce GF, Coffin D, Naccache M, Clark C, George LA, Iorio A, O'Mahony B, Pipe S, Skinner MW, Watson C, Peyvandi F, Mahlangu JN, for the ISTH subcommittee on Factor VIII, Factor IX and rare bleeding disorders. Core data set on safety, efficacy and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020 Oct. https://doi.org/10.1111/jth.15023

CORE DATA SET

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

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DEMOGRAPHICS & DIAGNOSIS

Demographics
Enrolment date
Date of birth
Sex at birth
Country of residence
Race
HTC for GT administration
HTC for follow-up data

Diagnosis
Hemophilia Type
Severity
Year of diagnosis
Baseline factor level
DNA Variant

MEDICAL HISTORY

Medical/Clinical History
Family history of hemophilia
Factor VIII or IX inhibitor?
Was patient on prescribed prophylaxis at time of GT?
Number of exposure days of factor replacement therapy prior to gene therapy infusion?
AAV Neutralizing Antibodies to product received (prior to infusion)
Test methodology
Date of test
Result
Titre (if recorded)
Concomitant medication
Any concomitant medication (prescription, over the counter (OTC), herbal medications, and supplements)?
Alcohol consumption

Pre-existing / co-morbidities (select all that apply)
Thromboembolic event(s)
Autoimmune disorders
History of cancer (any)
HIV-positive
Liver related medical history
Pre-existing liver disease
History of hepatitis C infection
History of hepatitis B infection
Liver assessment in the last 2 years

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GENE THERAPY INFUSION DETAILS

Vector infusion details
Vector product
Batch number
Lot number
Date of infusion
Dose – total vector genomes
Dosing weight (kg)
Vector genomes/kg
Complications at time of infusion (24 hours)
Complications during the following 2 weeks

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SAFETY DATA

Safety fields
Adverse events of special interest • Adverse event (FVIII inhibitors, FIX inhibitors, Thromboembolic events, Autoimmune disorders, Malignancies, Liver disease, Other) • Date of onset • Date of resolution • Description
Inhibitors tested against FVIII/FIX
Liver function tests • ALT • AST • Bilirubin • Other
If elevated enzymes: are there alternative diagnoses?
Has patient been diagnosed liver disease?

Safety fields
Liver biopsies?
Have you received non-vector related immunosuppressive therapy since last follow-up?
Onset of any other new co-morbidities

EFFICACY DATA

Efficacy fields
Bleeding events • Date • Reason • Treatment • Location
FVIII/FIX activity level test *ability to enter >1 test result
Use of any hemostatic treatment (factor, emicizumab, other) • Date • Drug • Dose, units • Frequency
Any change in concomitant medications since last visit (prescription, over-the-counter (OTC), herbal medications, and supplements)?

Surgeries
Surgeries • Type • Date • Severity • Factor use • Bleeding complication

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PATIENT REPORTED OUTCOME MEASURES

Patient Reported Outcome Measures
EQ-5D-5L
PROBE

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MORTALITY

Mortality
Date of death
Death related to gene therapy
Primary cause of death

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DATA COLLECTION SCHEDULE

Data will be collected at:

- Baseline/Infusion
- Follow-up visits
  - Month 3, 6, 12, 18, 24
  - Annually thereafter

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REGULATORY RELATIONSHIPS

- Core Data Set
  - Informed by in-person meeting with the EMA and feedback from FDA
  - Provided scientific advice on the protocol and core data set

- Data will partially meet regulatory requirements on safety and efficacy

Implementation

Dr Wolfgang Miesbach

University Hospital Frankfurt

GTR Steering Committee

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IMPLEMENTATION

Implementation

- Individual HTCs
  - Outreach to individual HTCs has began
- Linking with existing registries
  - USA (ATHN)
  - European registries if possible

Clinical trial patients

- Working with companies to determine process to obtain clinical trial data/enroll participants once trial completed
- Recruit previous clinical trial participants 1999-2005 (N=40)

DATABASE DEVELOPMENT & LAUNCH

Consent & Ethics

- Every patient enrolled must provide written informed consent
- Each HTC participating must obtain ethics approval from their local IRB

Timeline

- Database ready to receive data in mid-2021

WFH GTR HTC EDUCATIONAL PROGRAM

In development:

- HCP and Data Manager GTR Readiness Program
  - Training modules, resources and guides (On-line Learning Series, user guide, webinars, virtual & in-person training sessions and meetings)

- PWH GTR Readiness Program

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ADVANTAGES OF PARTICIPATION

Advantages include:

- Per patient funding for data entry
- Data visualization (patient summary, data dashboard, etc.)
- Contributing critical data on benefits and risks of gene therapy in hemophilia

Next Steps

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NEXT STEPS

- IRB approval
  - Ethics package available at gtr@wfh.org

- Site initiation visit (virtual)

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Questions & Answers

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THANK YOU

For more information contact us at:

gtr@wfh.org

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