U.S. FOOD & DRUG ADMINISTRATION

The Critical Role of Patients In Advancing Gene Therapy Treatments for Rare Diseases

Wednesday, March 9, 2022, 11 a.m. – 12 p.m. ET

Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Virtual Meeting Considerations

- The webinar will be recorded and available online after the event.
- Closed captioning is available in Zoom.
- Use the Q&A box to submit questions throughout the webinar.
- Use the chat box to share general comments and report technical difficulties.

RegenMedEd Webinar Series

- OTAT's webinar series about regenerative medicine.
- Goals of the webinar series:

Discuss foundational information about regenerative medicine therapies, including gene therapy and cell therapy

Explore opportunities to engage with FDA and advance regenerative medicine research and drug development

Hear from FDA, patients, advocates, researchers, and other important stakeholders about their experiences

Rare Diseases and Gene Therapy

- 80 percent of rare diseases are caused by a single-gene defect.
- FDA has approved two gene therapies for single-gene disorders.
- More than 900 investigational new drug (IND) applications for ongoing gene and cell therapy clinical trials.
- Patient participation in clinical research is critical.

Featured Panelists

Debbie Drell
Director of Membership
National Organization for
Rare Disorders (NORD)

Brian O'Mahony
Chief Executive
Irish Haemophilia Society

Julienne Vaillancourt, RPh, MPH
Rare Disease Liaison, FDA CBER
Captain, U.S. Public Health
Service Commissioned Corps

SHOW YOUR STRIPES®

ON RARE DISEASE DAY®
FEBRUARY 28TH

MY PERSONAL JOURNEY

Conflict of Interest Disclosure

I have nothing to disclose except my love for my sister.

SHOW YOUR STRIPES®

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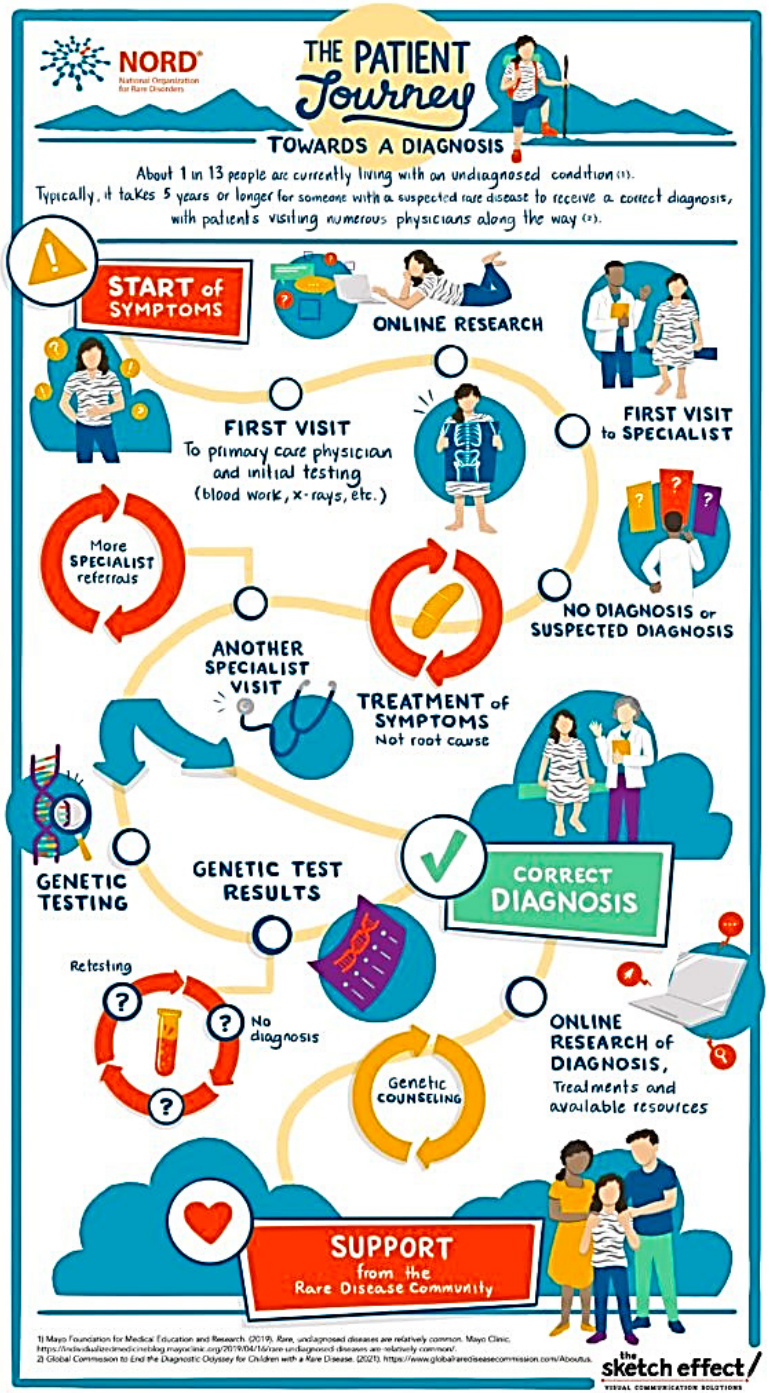
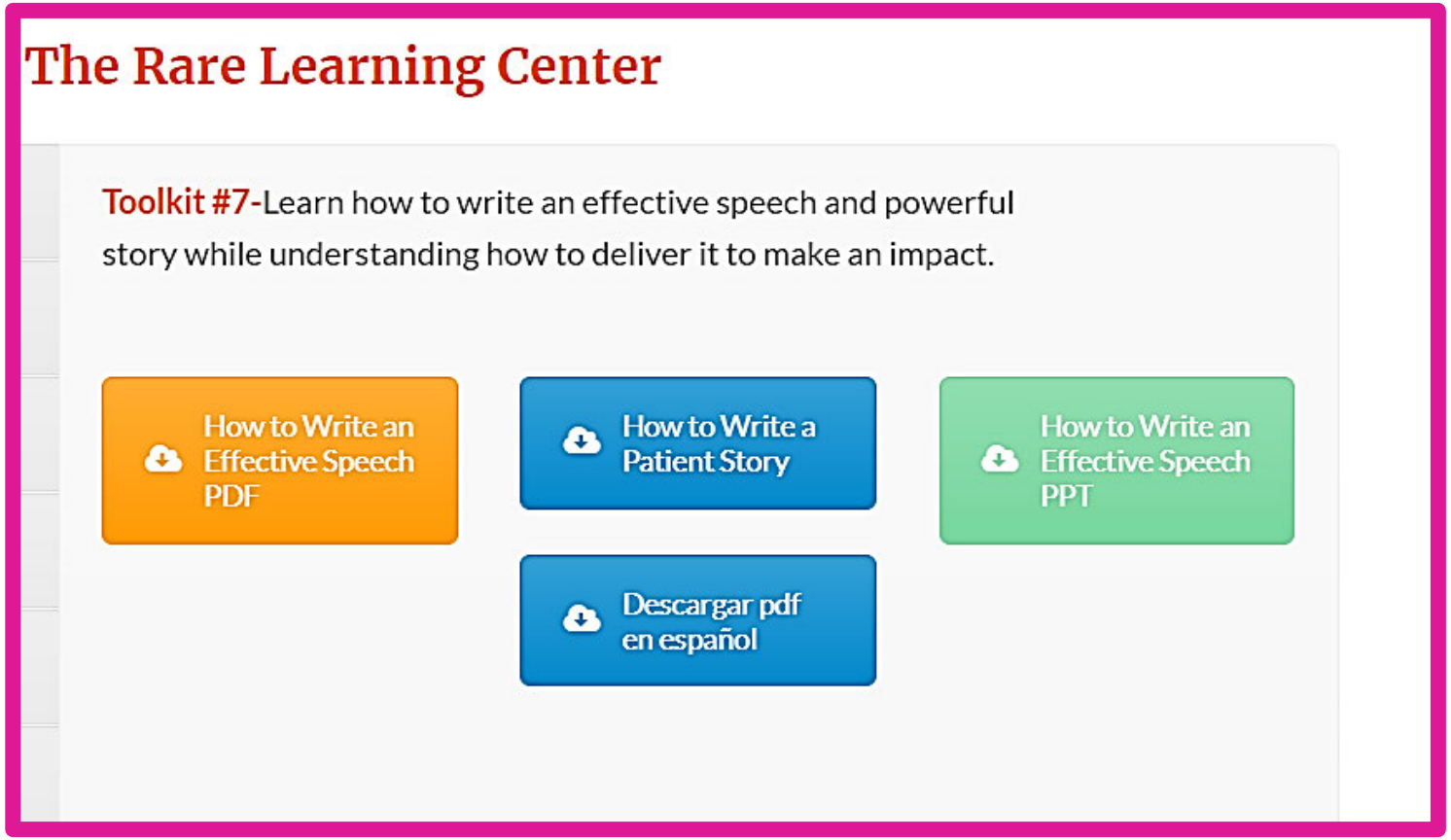
Your Diagnosis Journey

- 1 in 13 people are undiagnosed
- It takes 5 years or longer to receive a correct diagnosis
- Patients have to see multiple doctors
- Learn about diagnosis, genetic testing, and ways to support your best life



Share Your Story

- Write it for yourself
- Share it with someone you trust
- Consider sharing it with local media
- Share it with your rare disease organization
- Share it with NORD
- Share it with the world!



SHOW YOUR STRIPES®

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Learn About Research

- What is research, and why participate?
- Natural History Studies vs Clinical Trials
- Is there a study or registry for your disease?
- Should you get involved?
- Do you have doubts about research? Talk to others:
  - Your family
  - Your medical team (doctor/nurses)
  - Other patients
  - A nonprofit
  - Research coordinators

THANK YOU!

FOR PARTICIPATING IN RARE DISEASE DAY®

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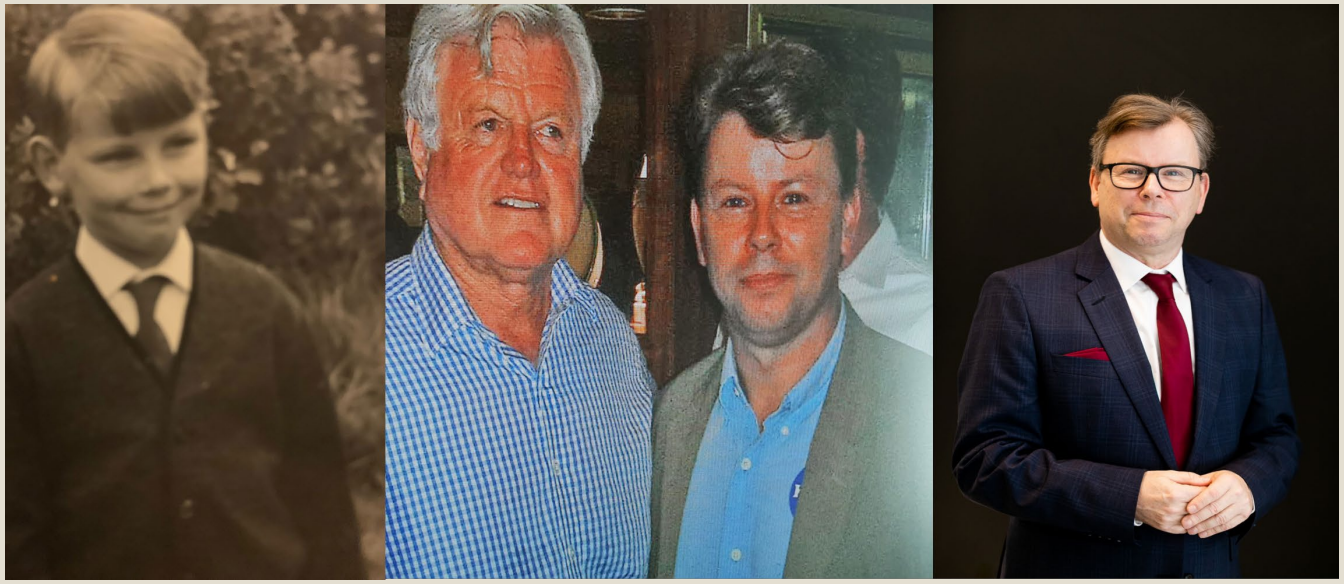
Personal Experience of Haemophilia Gene Therapy



Brian O'Mahony

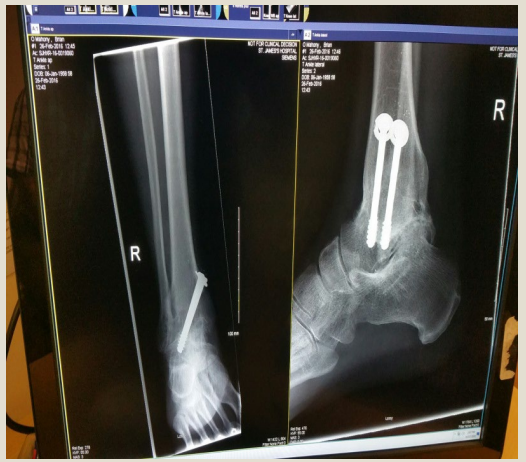
Chief Executive of the Irish Haemophilia Society,
Past President of WFH and EHC

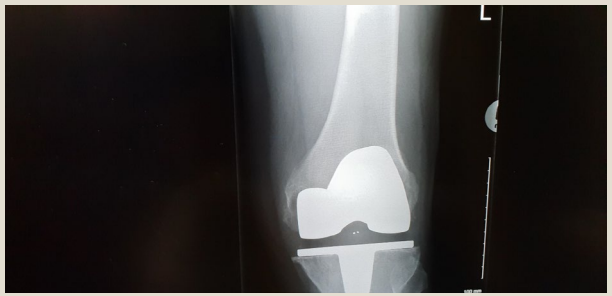
Disclosures

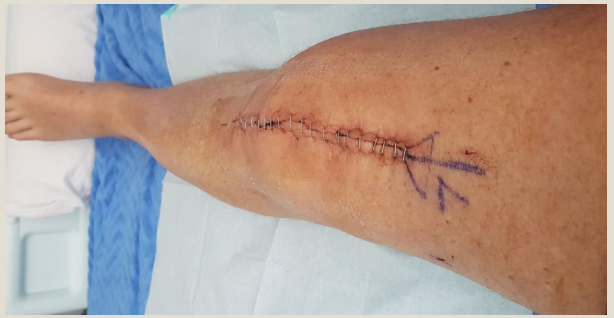
- Advisory Board: BioMarin
- Honoraria: Freeline

Treatment History: Severe Haemophilia B

- Childhood: No treatment, many bleeds into joints muscles, nosebleeds
- Age 14–17: Plasma
- Age 18–41: PCC or plasma-derived factor concentrate
- Age 41–58: Recombinant FIX
- Age 58–59: Recombinant FIX clinical trial
- Age 59–62: Extended half-life FIX
- Age 62: FIX gene therapy







Gene Therapy: My Expectations & Hopes

- **Duration of expression**: At least 10 years
- **Factor Expression**: Hoped for 20%–60%
- **Chronic Pain**: Hoped for less pain in damaged joints and reduced subclinical bleeding
- **Mental Health**: Freedom from burden of regular intravenous infusions and reduced time dealing with my personal haemophilia
- **ABR**: 0 or close to 0 (previously down to 0–1)
- **Factor Use**: Required only for surgery or major trauma
- **Activity Level**: Hoped to increase my physical activity level/fitness

Had to be prepared for a range of possible outcomes

Accepted: 19 June 2017
DOI: 10.1111/hae.13313

EDITORIAL

WILEY Haemophilia

Establishing the appropriate primary endpoint in haemophilia gene therapy pivotal studies

Over the past decade, the annualized bleeding rate (ABR) has been used as the primary endpoint in preliceensure studies of new factor VIII and IX products. We propose that for gene therapy trials, clotting factor activity is a more accurate and objective primary endpoint to assess efficacy than ABR. This recommendation is timely, anticipating that several gene therapy programs are likely beginning discussions with regulatory agencies around the design of their Phase 3 pivotal trials.

Although ABR has served the community well as a primary endpoint in prolatin replacement trials, where dosing regimens that manage peaks and troughs need to be established, we believe it is not the appropriate endpoint for future pivotal studies in haemophilia gene therapy. Treatment advances, such as gene therapy, bring the prospect of greater efficacy and improved outcomes for people living with haemophilia. ABR alone does not have the capacity or sensitivity to distinguish the improved outcomes and efficacy possible with gene therapies.[1] As we move closer to achieving a cure for haemophilia, we need a drug evaluation standard that can directly measure the effect of the applied gene therapy.

Factor VIII and factor IX activity levels have long been established as direct measures of severity of haemophilia (reviewed in Ref. [2]). Factor levels are a direct manifestation of the gene defect, as they are directly linked to the pathophysiology of the disease. Patients with mild (>5%), moderate (1%-5%) and severe (<1%) disease have distinct and separable phenotypes based upon activity levels.[3,4] These are measured by bleeding rates, severity of bleeding, severity of sequelae including joint damage and risk of mortality. The natural history of progressive crippling in haemophilia based on clotting factor levels is well established. While there is interlaboratory variability in the assays, the use of centralized testing in clinical studies obviates this concern.[5,6]

ABR has a major subjective component, in that the patient or the physician needs to distinguish a bleeding episode from arthritic pain. False positive and false negative rates between the patient's perceptions of joint bleeding and arthritis compared with concurrent ultrasound evaluation are high.[7] The current joint disease status of a patient is largely based on his treatment history and has a large influence on the accurate reporting of ABR.

Recently, the FDA has affirmed its intention to focus more on outcomes important to patients. In Prescription Drug User Fee Act (PDUFA) V, FDA committed to a new initiative called Patient-Focused Drug Development with the goal of obtaining the patient perspective on certain disease areas during the 5-year period of PDUFA V. This information was deemed a critical aspect of decision making by the FDA as it establishes the context in which the regulatory decision is made.[8,9] Further, the National Hemophilia Foundation-McMaster treatment guidelines on care models for haemophilia specifically reviewed outcomes important to assessing care. Outcomes such as bleeding and bleeding rate were considered important, but judged not important enough to be included in the final list of patient important outcomes.[11] Greater patient involvement can drive the development of innovative medicines that deliver more relevant and impactful patient outcomes.[12]

In 2016, for the first time, therapeutic levels of FVIII and FIX activity expected to abrogate all bleeding events were achieved through gene therapy.[13,14] The establishment, through in vivo delivery of the clotting factor gene, of long-term, normal or near-normal circulating clotting factor activity levels, absent the peaks and troughs of protein replacement therapy, has underlying scientific validity since breakthrough bleeding occurs more frequently as clotting factor levels approach troughs.[15] Changing patients with severe or moderate disease to mild or normal phenotype makes ABR a useful secondary endpoint and clotting factor levels a more informative primary endpoint.

The availability of a new gene delivery modality which abrogates peaks and troughs, frequent repeat infusions, adherence issues and permits assumption of a normal lifestyle are all important to establish as secondary endpoints. Success or failure of gene therapy studies should be based on the establishment of safety, and clotting factor activity as the primary endpoint.

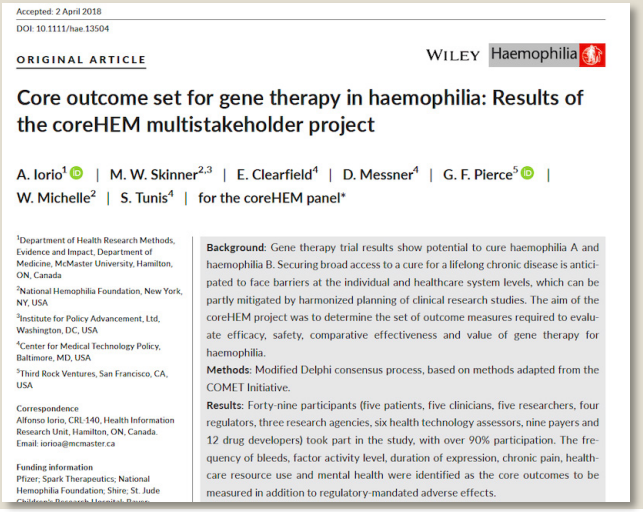
We call upon regulatory agencies to consider their scientific positions on this fundamental issue prior to the initiation of licensure studies.

DISCLOSURES

GFP is a consultant for BioMarin and St. Jude Children's Research Hospital. BDM has served on an advisory board for Freeline. SWP is a consultant for Dimension Therapeutics, uniQure and Bayer. MWS is a consultant for Spark and Bayer. All authors wrote and edited the paper.

Keywords
annualized bleeding rate, clinical trials, factor IX, factor VIII, gene therapy, haemophilia

G. F. Pierce[1,2]
M. V. Ragni[2]
H. M. van den Berg[3]
A. Weyl[4]
B. O'Mahony[1]
M. W. Skinner[1]
S. W. Pipe[5]



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ORIGINAL ARTICLE

WILEY Haemophilia

Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project

A. Iorio[1] | M. W. Skinner[2,3] | E. Clearfield[4] | D. Messner[4] | G. F. Pierce[5] | W. Michelle[2] | S. Tunis[4] | for the coreHEM panel*

[1]Department of Health Research Methods, Evidence and Impact, Department of Medicine, McMaster University, Hamilton, ON, Canada
[2]National Hemophilia Foundation, New York, NY, USA
[3]Institute for Policy Advancement, Ltd, Washington, DC, USA
[4]Center for Medical Technology Policy, Baltimore, MD, USA
[5]Third Rock Ventures, San Francisco, CA, USA

Correspondence
Alfonso Iorio, CRL 140, Health Information Research Unit, Hamilton, ON, Canada.
Email: iorioa@mcmaster.ca

Funding information
Pfizer; Spark Therapeutics; National Hemophilia Foundation; Shire; St. Jude Children's Research Hospital; Bayer

Background: Gene therapy trial results show potential to cure haemophilia A and haemophilia B. Securing broad access to a cure for a lifelong chronic disease is anticipated to face barriers at the individual and healthcare system levels, which can be partly mitigated by harmonized planning of clinical research studies. The aim of the coreHEM project was to determine the set of outcome measures required to evaluate efficacy, safety, comparative effectiveness and value of gene therapy for haemophilia.

Methods: Modified Delphi consensus process, based on methods adapted from the COMET Initiative.

Results: Forty-nine participants (five patients, five clinicians, five researchers, four regulators, three research agencies, six health technology assessors, nine payers and 12 drug developers) took part in the study, with over 90% participation. The frequency of bleeds, factor activity level, duration of expression, chronic pain, healthcare resource use and mental health were identified as the core outcomes to be measured in addition to regulatory-mandated adverse effects.

Gene Therapy: My Concerns

- Transaminitis being missed, resulting in loss of expression
- Transaminitis requiring medium- to long-term steroid use
- Risk of cancer from insertional mutagenesis
- Risk of loss of expression achieved

Molecular Therapy
Opinion

Eliminating Panglossian thinking in development of AAV therapeutics

Radoslaw Kaczmarek,[1] Glenn F. Pierce,[2] Declan Noone,[3] Brian O'Mahony,[4] David Page,[5] and Mark W. Skinner[6]

https://doi.org/10.1016/j.ymthe.2021.10.025

The US Food and Drug Administration (FDA) held a 2-day meeting (September 2–3, 2021) of the Cellular, Tissue and Gene Therapies Advisory Committee to consider toxicity risks of adeno-associated virus

extraordinarily inefficient, with doses employed to achieve therapeutic results that are logs greater than the total number of cells within the human body and logs greater than viral loads ever encountered in the course of

ings, but the long-term clinical implications of these findings are unknown. While it is hypothesized to be related to transgene overexpression and not capsid toxicity, this has not been well established.

Oncogenicity has so far been only a theoretical risk in humans, but preclinical studies continue to show that it is possible (https://investors.biomarin.com/2021-09-06-U-S-FDA-Placed-a-Clinical-Hold-on-BMN-307-Phearless-Phase-1-2-Gene-Therapy-Study-in-Adults-with-PKU-Based-on-Interim-Preclinical-Study-Findings). Contrary to the stubborn misconception, AAV vectors do integrate at a rate resulting in tens of millions of integrations with the currently used vector doses. AAV integration can trigger hepato-

My Rationale

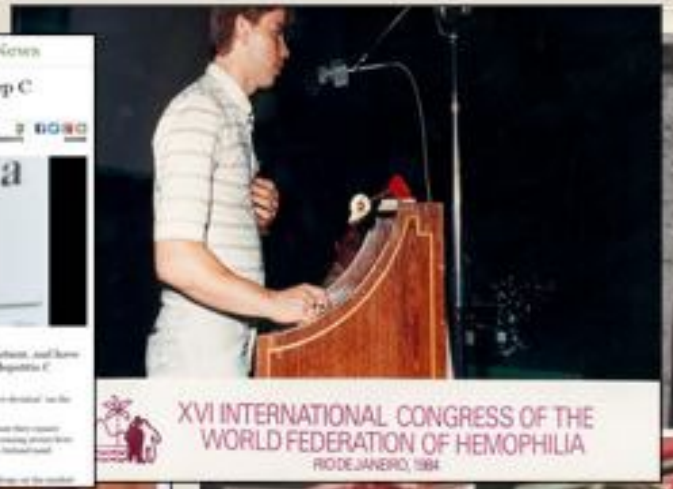
Before gene therapy

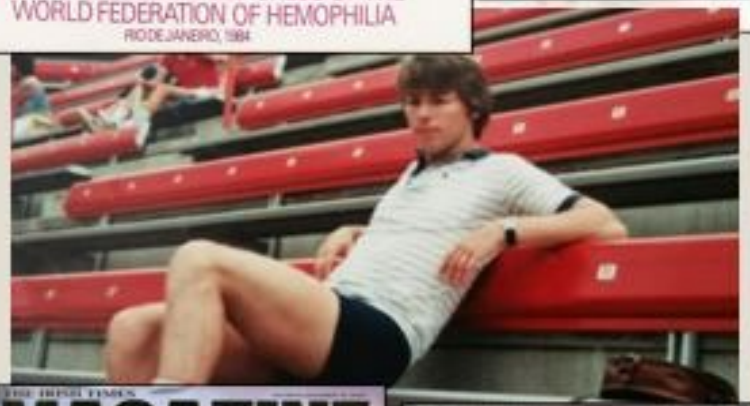
- Treatment with EHL FIX
- Prophylaxis every 10 days
- Venous access not great
- ABR: 0–1
- Knee replacement (2018)
- Preexisting joint damage with degree of chronic pain

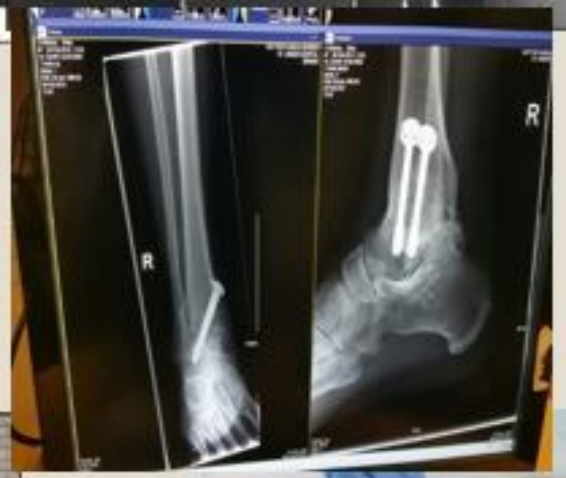
Rationale

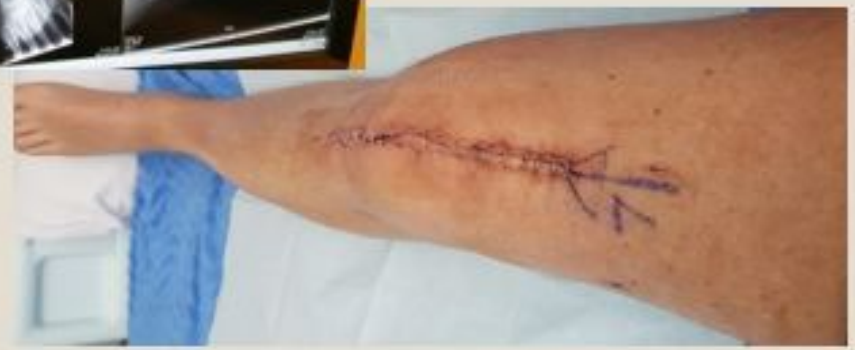
- Hoped for factor expression between 20% and 60%
- Decrease in chronic pain in joints
- No requirement for constant IV infusions
- Degree of mental freedom
- Wanted to try life without severe haemophilia
- Eligible for 1 trial
- My age at time of infusion
- I wanted to lead

Photos, Brian O'Mahony









Hospital Recovery

My Outcomes to Date

- Good factor expression (circa 50%)
  - I had hoped for 20% to 60%
- Some variability in FIX expression after year 1
  - Remained close to or within low normal range
- No requirement for steroids
- Chronic pain decreased in target joints
  - GT and time since surgery
- ABR 0 after 24 months
- Treatment required only for a biopsy, steroid injection (to 100%)
- No treatment required, despite 2 traumas

My Outcomes to Date

- Schedule of visits in first 3 months was challenging but not unexpected
- No treatment-related adverse events apart from iron deficiency (weekly blood draws)
- Fitter and healthier due to GT, lifestyle, and decrease in constant travel
- No treatment remorse

My Outcomes to Date

- Definite degree of mental freedom: having to plan treatments around activities/travel
- Freedom from regular intravenous infusions; freed up some hard drive space in my brain
- Veins recovered
- No loss of “identity”
- “Freedom” from haemophilia less for me, given my roles with IHS/EHC/WFH

CBER Perspective on the Critical Role of Patients in Advancing Gene Therapy Treatments for Rare Diseases

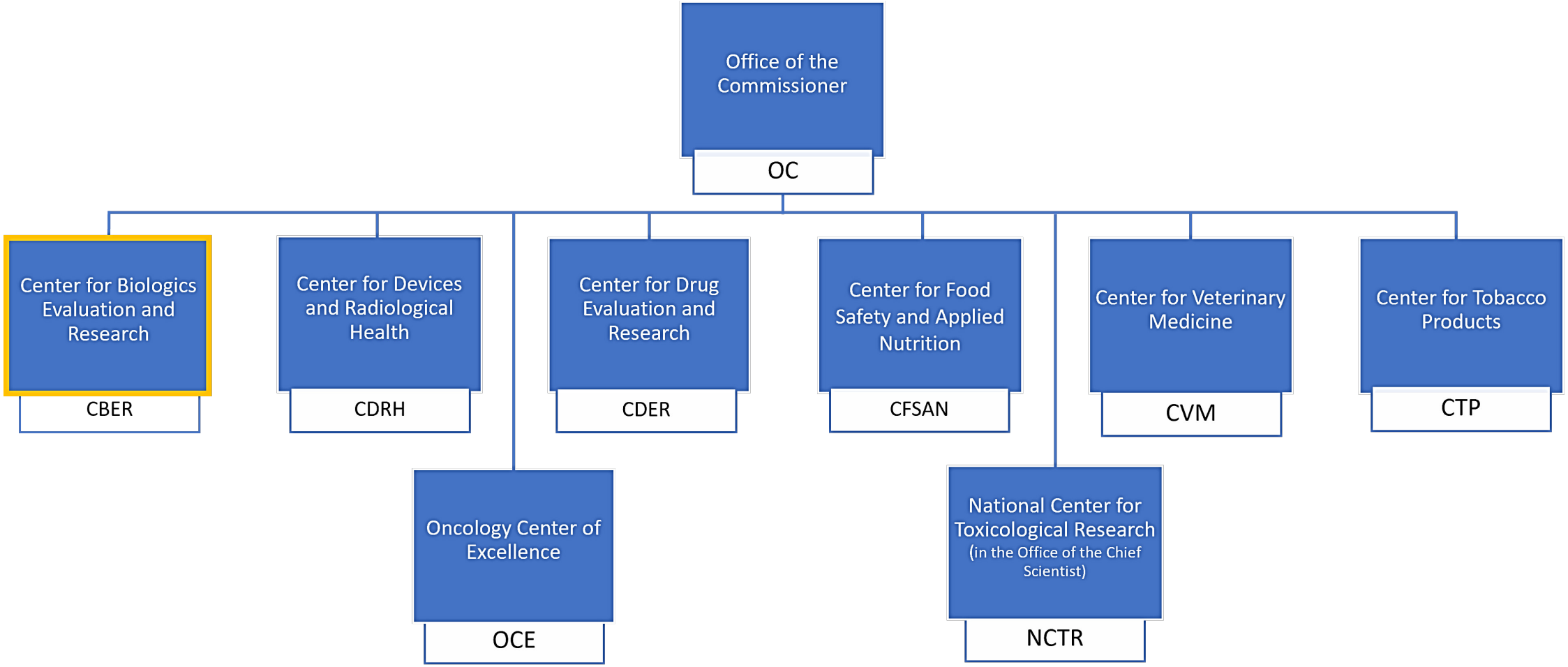
CAPT Julienne Vaillancourt, RPh, MPH

Rare Disease Liaison

Center for Biologics Evaluation and Research

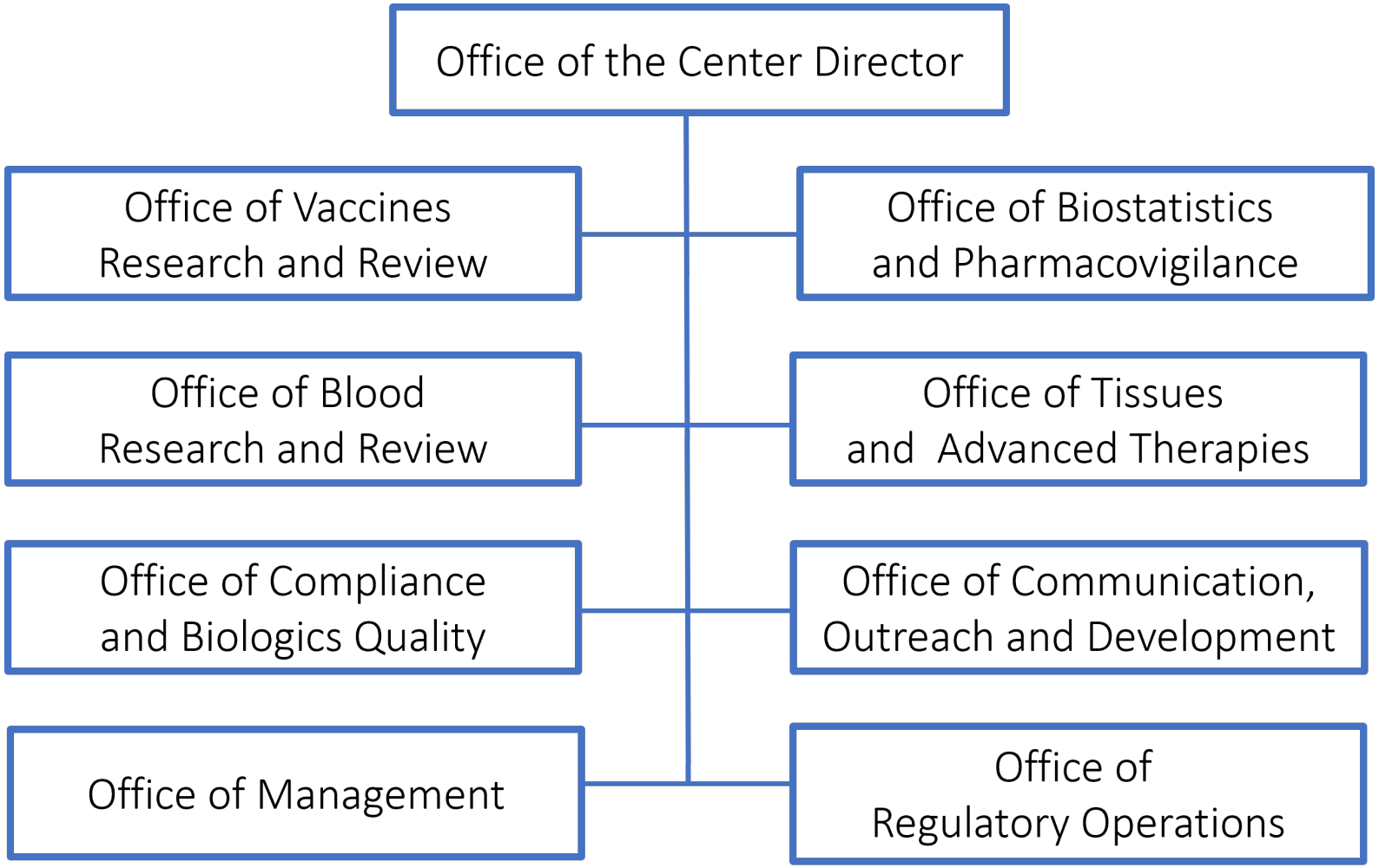
Office of the Director

CBER is one of several centers at FDA



Center for Biologics Evaluation and Research (CBER)

Peter Marks, PhD, MD, Director
Celia Witten, PhD, MD, Deputy Director



CBER is committed to facilitating and advancing the development and timely approval of safe and effective biologics to improve the lives of children and adults with rare diseases.

CBER Collaborates with Rare Disease Partners Across FDA to Support Many Activities

- Patient Engagement
- Training for Reviewers
- Stakeholder Outreach
- Review
- Cross-Cutting Issues
- Guidance Development
- FDA Rare Disease Day
- Special Projects

CBER Collaborates with External Stakeholders to Advance Development of Products for Rare Diseases

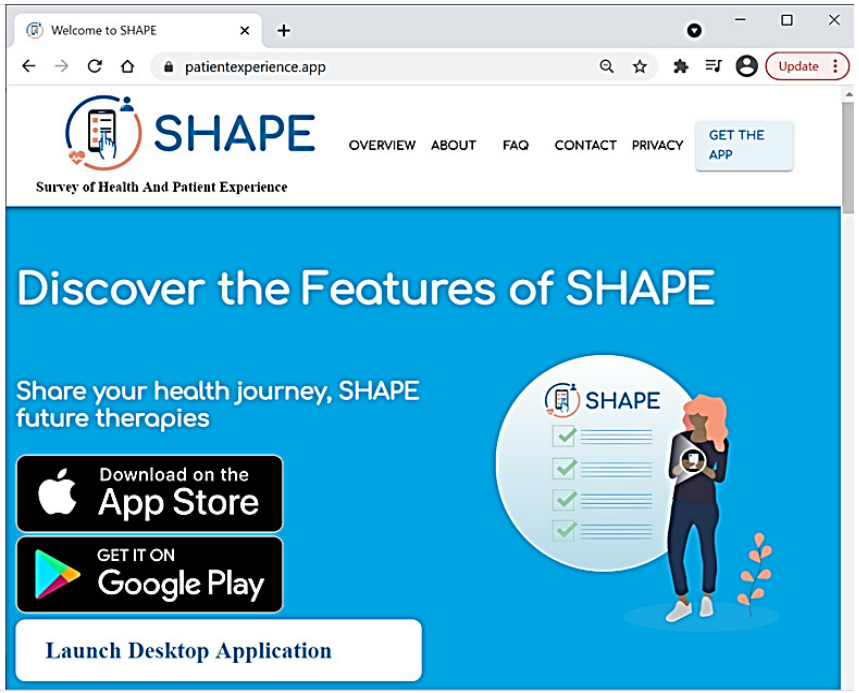
Accelerating Medicines Partnership® Bespoke Gene Therapy Consortium (AMP® BGTC)

Streamlining Adeno-Associated Virus (AAV) manufacturing and regulatory frameworks to increase accessibility of gene therapies for rare diseases

This public-private partnership between NIH, the Foundation for NIH, FDA/CBER and several public and private organizations was launched in October 2021.

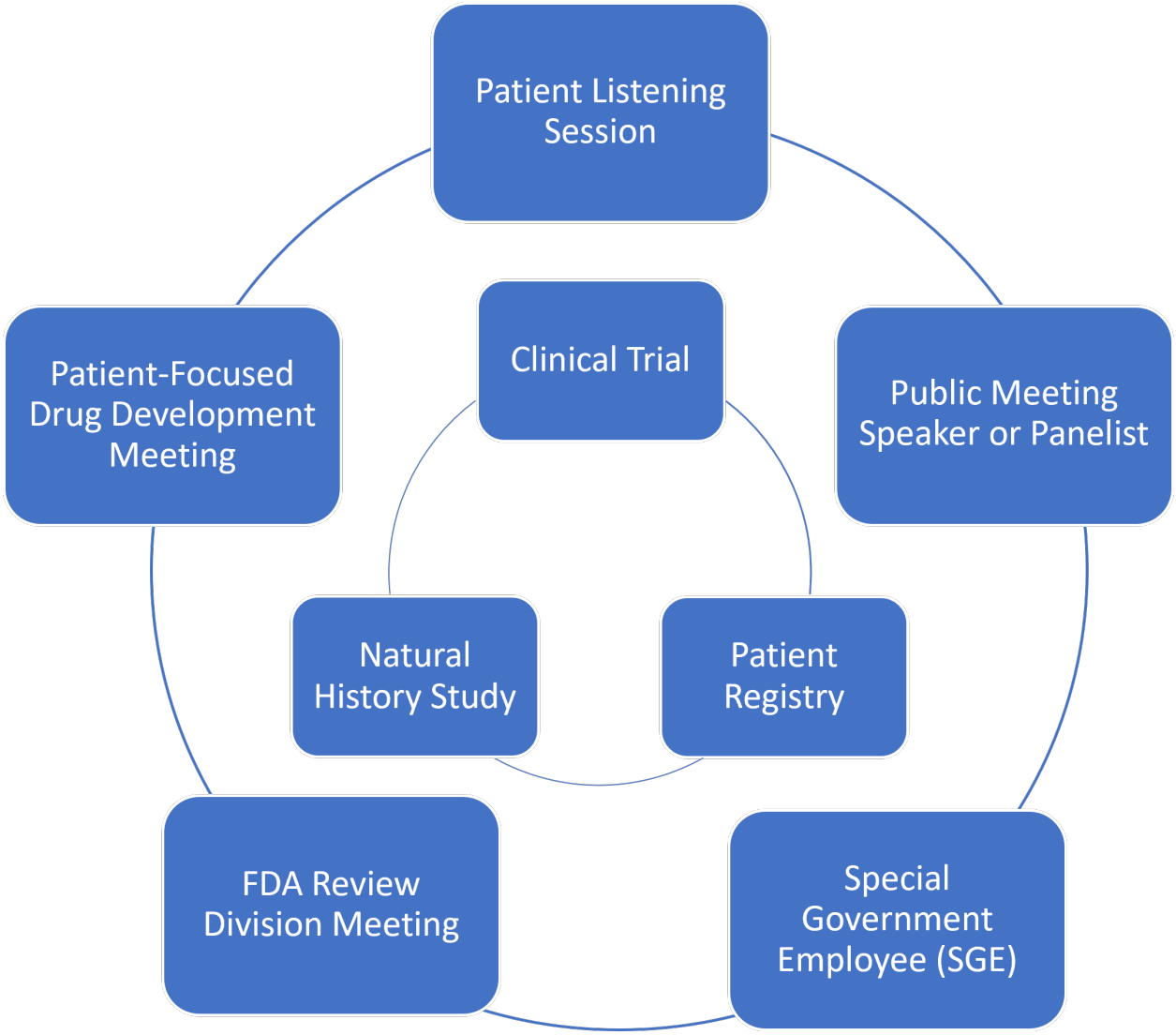
Natural History Of METachromatic Leukodystrophy (HOME) Study

Conducted by NORD and supported by CBER
HOME Study (https://rarediseases.org/mid-home-study)



Developed by IBM with CBER support.
Innovative data collection tool for patient-centered research.
Current use: HOME study

Patients Can Help Advance Development of Gene Therapies for Rare Diseases in Many Ways



Clinical Trials Support Medical Product Approval

- The sponsor of a clinical trial to be conducted in the United States must submit an Investigational New Drug (IND) application for FDA review.
- The IND contains the study protocol, information about the product, data from animal studies to support the clinical study, and more.
- If the proposed clinical study is allowed to proceed after initial FDA review, subsequent clinical studies may be conducted and reviewed by FDA under the same IND.
- Eventually the sponsor may submit a Biologics License Application (BLA) that includes clinical trial data to support the product's safety and effectiveness in the intended population, along with many other types of data for FDA review and possible marketing approval.

"FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects…"
21 CFR 312.22 (a)

Gene Therapy Clinical Trial Participation

- Volunteering to participate, or not, is **a big decision**
  - Ask questions and discuss concerns
  - Learn and understand to make the best decision for you/your loved one
- Participating in a gene therapy clinical trial for a rare disease is
  - A contribution to the knowledge base about use of the investigational gene therapy product to treat your rare disease
  - A gift of your time and more

Where to Learn More

- **FDA's "For Patients" webpage**
  - Gateway for information on engaging with FDA, clinical trials, approvals, and more.
  - https://www.fda.gov/patients
- **ClinicalTrials.gov**
  - Public database for clinical trials conducted around the world.
  - "For Patients and Families" – helpful links on how to search for a trial, glossary, and more.
  - http://ClinicalTrials.gov
- **MedlinePlus provides related trusted information from NIH**
  - https://medlineplus.gov/
- **NIH/NCATS Genetic and Rare Disease Information Center (GARD)**
  - Current, reliable, and easy-to-understand information about rare or genetic diseases in English or Spanish; also links to organizations, specialists, and more for each disease, if available.
  - https://rarediseases.info.nih.gov/
- **NIH/NCATS Toolkit for Patient-Focused Therapy Development**
  - https://ncats.nih.gov/toolkit
- **Rare Disease Patient Advocacy Organizations**
  - Example of a recent collaborative effort involving several organizations (EveryLife Foundation, BIO, National Health Council, PhRMA): Guide to Patient Involvement in Rare Disease Therapy Development
  - https://everylifefoundation.org/pfdd-compendium/

How to Contact Me

CAPT Julienne Vaillancourt, RPh, MPH
Rare Disease Liaison
Center for Biologics Evaluation and Research,
Office of the Director, Policy Staff

Julienne.Vaillancourt@fda.hhs.gov

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Thank you

Panel Discussion

Please type your questions into the Q&A box.

Stay Connected and Engaged

Helpful Resources:

- Visit CBER's website: www.fda.gov/vaccines-blood-biologics
- Sign up for our newsletter, "What's New @ CBER": www.public.govdelivery.com/accounts/USFDA/subscribers/new
- Follow us on Twitter: @FDACBER

#RegenMedEd

Thank you!

Webinar materials will be available in a few weeks on FDA.gov.

Stay tuned for OTAT's Annual Patient Engagement & Regenerative Medicine Workshop in May!

#RegenMedEd