MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Innovative Approaches for Gene Therapy Long-Term Follow-Up Leveraging Registries and Platform Trials

May 6, 2025

Learn more at www.mrctcenter.org

CC (closed captioning) enabled

The Multi-Regional Clinical Trials Center of BWH and Harvard

MRCT Center

- We are a research and policy center focused on addressing the conduct, oversight, ethics, and regulatory environment for clinical trials around the world.
- We engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.

Disclaimer

- The opinions contained are those of the authors and presenters and are not intended to represent the position of Brigham and Women's Hospital or Harvard University.
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- We have no personal conflicts of interest relevant to this discussion.
- We are recording this meeting and plan to make the recording publicly available on our website.

Long-Term Follow-Up for Gene Therapies (GTs)

- GTs are generally designed to achieve health effects through permanent or long-acting changes in the body.
- The U.S. Food and Drug Administration (FDA) and other health authorities recommend long-term safety monitoring of recipients of certain types of GTs—those with a risk of delayed adverse events.
    - LTFU extends the assessment period for clinical trial participants and may also be important for recipients of approved GTs.
- As these LTFU studies can last years (5, 15, even up to a lifetime), they pose significant scientific, operational, and logistical challenges.

Innovative approaches to LTFU: Panelists and Moderator

Avery McIntosh, PhD
Director of Biostatistics, Internal Medicine and Infectious Disease, Pfizer

Barbara A. Konkle, MD
Professor Emeritus University of Washington; hematologist at Washington Center for Bleeding Disorders; Medical Director of the Bleeding Disorders Laboratory at Bloodworks Nw

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Carolyn Chapman, PhD, MS
Lead Investigator, BWH
Member of Faculty, HMS
MRCT Center

Practical and Statistical Considerations for the Long-Term Follow Up of Gene Therapy Trial Participants

Avery McIntosh, PhD

Director of Biostatistics, Internal Medicine and Infectious Disease, Pfizer

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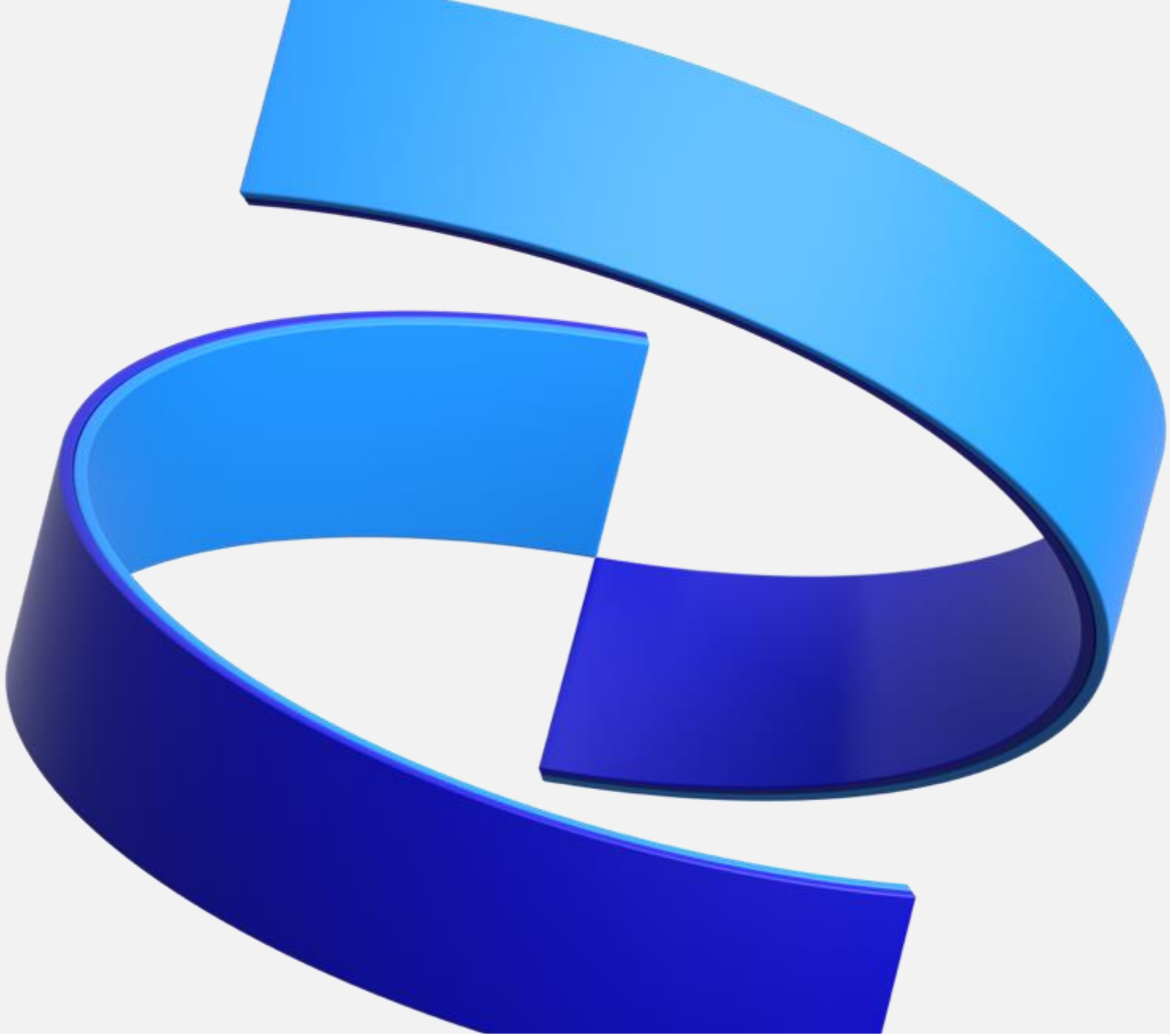
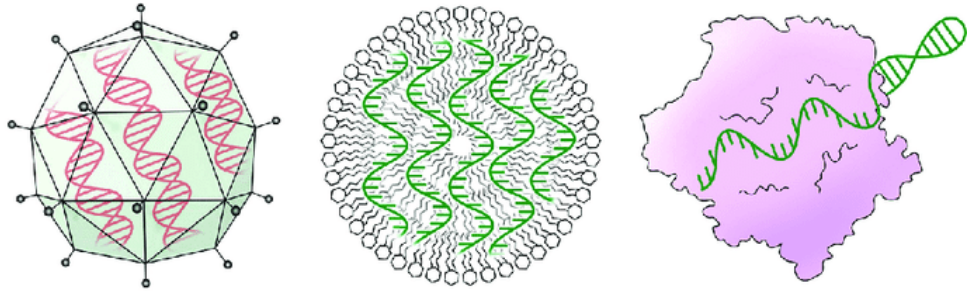
6 May 2025



Quick Primer on Gene therapies



"*Gene therapy is a technique that modifies a person's genes to treat or cure disease*." –FDA

Approach	Virus	Nanoparticle	Enzyme complex
Example	Adeno-associated virus (AAV) packaged with DNA encoding Cas9 & sgRNA	Liposomes encapsulating mRNA & sgRNA	Ribonucleoprotein (RNP) complex of Cas9 protein and sgRNA
Size	20 nm	50-500 nm	12 nm
Advantages	Extremely effective; prior use with classic gene therapy	Straightforward to prepare; low immunogenicity	Short lifetime and lower risk of off-target cutting

https://www.researchgate.net/publication/320339544_The_Promise_and_Challenge_of_In_Vivo_Delivery_for_Genome_Therapeutics

- Major differences between cell/gene therapies and traditional pharmaceutical products (LMW/ other biologics):
  - GTx are (so far) one-time administrations
  - Source of safety signals is manifold: delivery mechanism, transgene insert, promoter, over/under expression
  - ADME is a fundamentally different concept (biodistribution/shedding)
  - CMC is major challenging for GTx
  - Traditional study phases 1,2,3 often will not apply
  - Dose finding is often constrained
  - Often orphan, pediatric diseases, novel endpoints

FDA
Center for Biologics Evaluation and Research

Long Term Follow-Up (LTFU) for Gene Therapy

Why do GTx trials need long term follow-up?

- The long term safety profile of GTx products is still uncertain
- Long term data is required to fully assess benefit-risk profile
- Want to quantify the length of efficacy: 5,10 years? Lifetime?
- Assess adverse events due to the vectors:
  - Viral reactivation, immune reactions, off-target effects (e.g., dorsal root ganglion damage)
  - Risk of cancer from activating oncogenes if there is integration into the genome
  - Off-target edits from gene editing
- Collect data on long term biodistribution and viral shedding

Challenges

- FDA / EMA require sponsors to enroll patients administered a GTx product into LTFU study
- 5 – 15 years of follow-up
- Unprecedented length of engagement w/ patients: risk of loss to follow-up and lack of protocol adherence

Innovative solutions

- Platform trials / Master protocols
- Robust Bayesian hierarchical models (EXNEX) for borrowing safety information across gene therapy modalities
- Time-to-event models for adverse events
- Using existing patient registries
- Decentralized trials and use of electronic devices for data capture

Health Authority Guidances: LTFU

- Potential risks from integration activity of vector/genome editing
  - Insertional mutagenesis
  - Consequences from prolonged expression
  - Latency (i.e., reactivation from latency)
  - Persistent infection (replication competent vector)
- All subjects in clinical studies and post marketing approval should be monitored
    - 15 years for integrating vectors/ genome editing products
    - 5 years for AAV vectors (replication incompetent)
- LTFU does not need to be as detailed as safety monitoring for initial trial
        - Survival, SAEs, delayed onset safety effects (heme, immune, neuro, onc)

Long Term Follow-Up After Administration of Human Gene Therapy Products

Guidance for Industry

European Medicines Agency

GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

MedComm Open Access

PERSPECTIVE | Open Access

Advanced therapy medicinal products in China: Regulation and development

Jiaqi Lu, Longchang Xu, Wei Wei, Wu He

First published: 26 April 2023 | https://doi.org/10.1002/mco2.251

What is a Platform Trial?

- Complex and nonstandard study designs have grown in acceptance in recent years

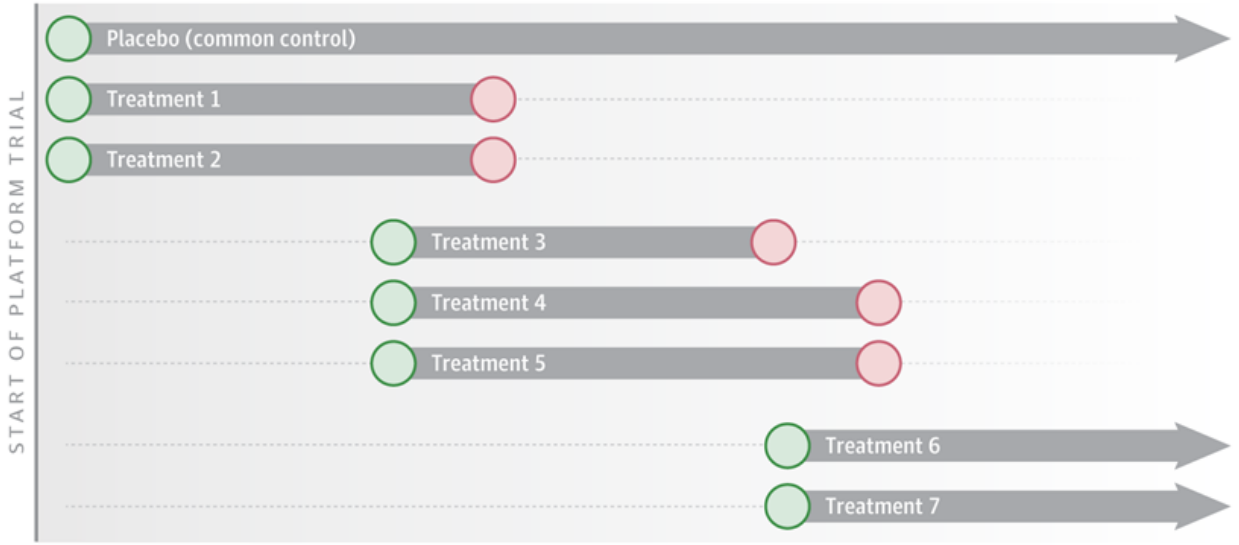
- Platform trials are the most flexible of the proposed designs, with patient groups or drug arms allowed to enter and exit the study in a predefined manner

- In the past these were used mostly oncology trials, but have recently expanded. Example: *the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia* (**REMAP-CAP**), that investigated hydrocortisone vs no hydrocortisone for patients with severe COVID-19

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock, Janet, and Lisa M. LaVange. "Master protocols to study multiple therapies, multiple diseases, or both." *New England Journal of Medicine* 377.1 (2017): 62-70.



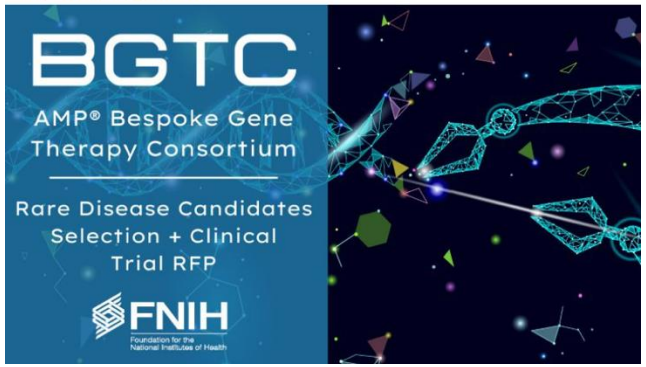
Park, Jay JH, et al. "How to Use and Interpret the Results of a Platform Trial: Users' Guide to the Medical Literature." *JAMA* 327.1 (2022): 67-74.

Bespoke Gene Therapy Consortium (BGTC)

Envision 4-6 test cases

Foundation for the National Institutes of Health
5,740 followers
1d • Edited •

AMP® BGTC is pleased to announce it has selected 14 rare disease candidates. In addition, a new RFP has been issued for clinical trial proposals directed to one of these 14 bespoke indications. Read the full selection announcement here: https://lnkd.in/gguU_whr



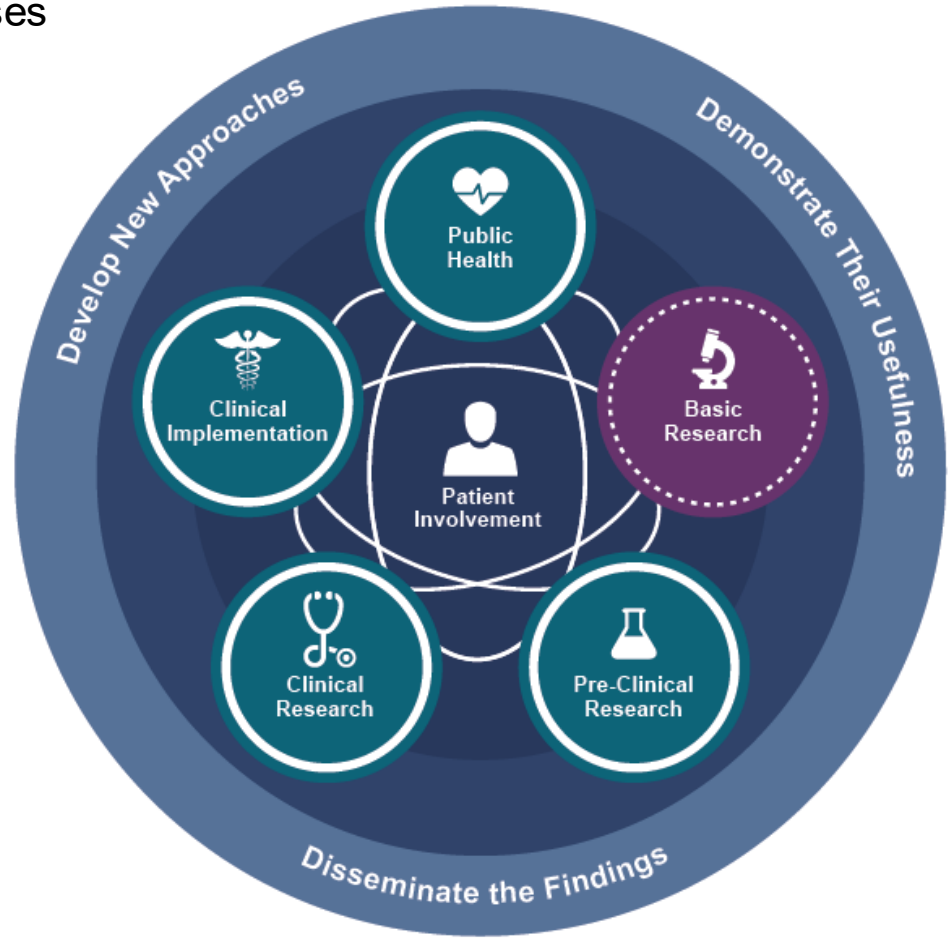
BGTC Goals

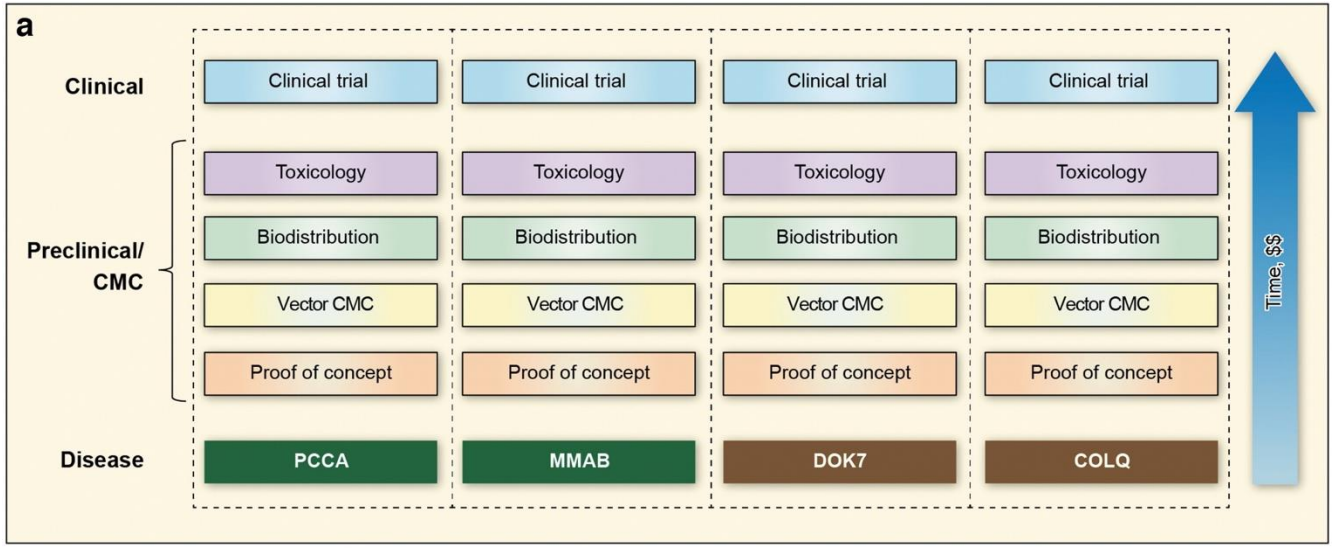
- Make adeno-associated virus technology more accessible to a broader range of diseases
  - Optimized AAV vector production protocols
  - Improvements in AAV target gene expression
- Streamline preclinical and product testing
  - Harmonized and validated sets of manufacturing and pre-clinical testing requirements
- Facilitate scientific and regulatory advances that will ultimately benefit the entire field
  - Standardized regulatory submission package templates
- Bring gene therapies to all affected populations sooner
  - Clinical development manual to help advance all future AAV gene therapies for rare diseases

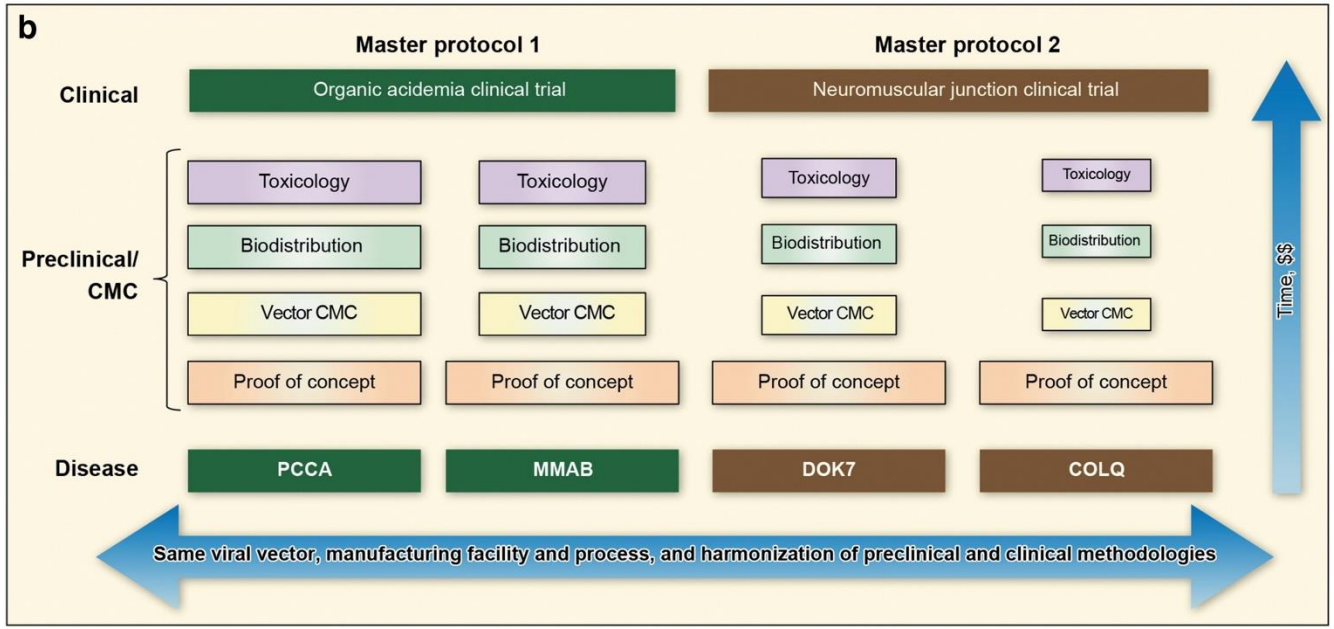
The Two Critical Pathways of BGTC Research

Platform Vector Gene Therapy (PaVe-GT)

Basic Questions of PaVe-GT: can efficiency of GTx development be increased by using a standardized platform process: same capsid and manufacturing, for four distinct diseases



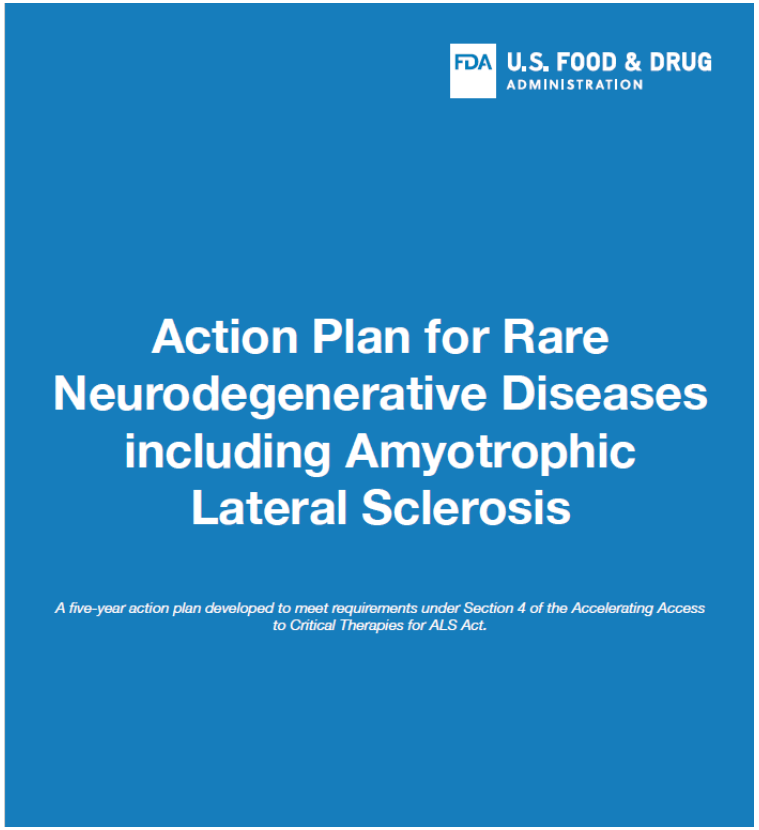




Recent FDA Initiatives Support this Approach to Safety

Cell and Gene Therapies Safety Project
FDA will review its experience with applications for ALS and rare neurodegenerative disorder treatments to identify cross-application safety signals, with a focus on factors such as the specific type of product (e.g., gene therapy, cell therapy, vector), route of administration, and study population (e.g., age, disease severity, clinical manifestations). FDA will use this safety information to inform the design of subsequent clinical trials for the use of cell and gene therapies to treat ALS and other neurodegenerative diseases.

Explore the Use of Fit-for-Purpose[13] Digital Health Technologies[14]
FDA will encourage exploring the use of digital health technologies to potentially improve understanding of the disease and increase access to investigational drugs through more accessible clinical trials. Using digital health technologies may enhance use of decentralized trial approaches that can increase trial participation and reduce the burden of trial participation on individuals with ALS and their caregivers. For example, digital health technologies may reduce the need for travel to study sites. These technologies may also be used to increase ability to monitor and assess drug response by providing a more comprehensive assessment of the rate of decline in the range of functional capabilities affected by ALS.



Why Have a Platform Safety Approach in LTFU?

- Rationale: the safety profile, including immediate and long-term toxicity and AAV integration/carcinogenesis potential should have some similarities, either across vector serotypes/cassettes (e.g., AAV9), or even across the entire class (all AAV), or perhaps within a given therapeutic area (e.g., heme, CNS, cardiac)

Scientific	Commercial/ geographies	Indication expansion	Reduce cycle times	Increase PoS for future submissions
Pooling standardized data (same assays, durations, aligned schedules of assessments for biopsies/ samples), both short term and long term, will enable **major** unanswered questions in GTx to be addressed	A more robust safety package for follow-on geographies can increase probability of success for HTA assessments and access	Health authorities may have fewer concerns about expansion into adjacent populations (older, younger, heavier, different phenotype) if there's robust and identifiable safety profile	Follow from left column: increased confidence in safety profile across a class can reduce or eliminate the clinical evidence needed for indication expansion	A more robust safety package for new products in a class could inform benefit-risk assessment during reg. review and increase probability of approval in a new but adjacent indication or modality

Benefits of Platform Trials for LTFU

Scientific	Pooling standardized data can address major unanswered safety questions (e.g., same assays, durations, aligned schedules of assessments for biopsies / samples)
Patient Access	A robust safety package for follow-on geographies can enhance HTA dossiers for successful reimbursement / access
Efficiency	Increased regulator confidence in safety across a therapeutic class can reduce the clinical evidence needed for adjacent populations (e.g., older, younger, different phenotype)
Pharmacologic	Clinical pharmacology models of exposure, persistence, and other dynamic parameters can be informed by longer term human data pooled across appropriate classes
Future Development	Robust safety for new products in a class (e.g., gene editing) could inform benefit-risk and increase likelihood of approval in new but adjacent indications / modality

Comparing Apples to Apples

ARTICLE

Standardized Data Structures in Rare Diseases: CDISC User Guides for Duchenne Muscular Dystrophy and Huntington's Disease

Ariana P. Mullin[1], Diane Corey[1], Emily C. Turner[1], Richard Liwski[1], Daniel Olson[1], Jackson Burton[1], Sudhir Sivakumaran[1], Lynn D. Hudson[1], Klaus Romero[1], Diane T. Stephenson[1] and Jane Larkindale[1,*]

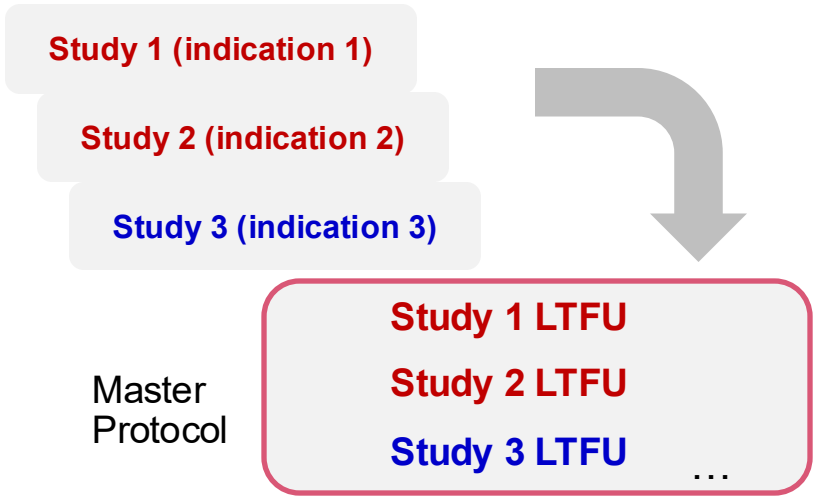
The principle of standardization to increase efficiency is well described in the rare disease space

We need to be able to compare biosamples from identical assays, collected in an identical manner, during an identical time course (schedule of assessments)

CDISC/ C-PATH efforts in this spirit are instructional

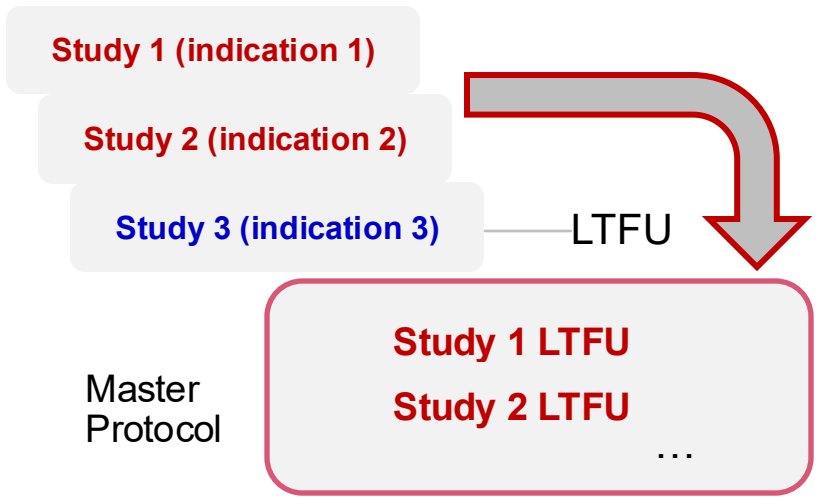
Types of Platform Studies

Scope	Multiple therapies in heterogeneous populations; explicitly assumes safety may be heterogeneous
Duration	Open ended, with study populations entering and exiting as available/ complete
Number of groups	Any number of studies with only treated subjects
Assessment of safety signals	May or may not be transferrable from one population/ modality to the next
Schedule of assessments	Could be individually tailored by study, standardized across studies, or shared core SoA with appendices for given diseases
Sponsor support	Could be single sponsor, or cross-industry consortium



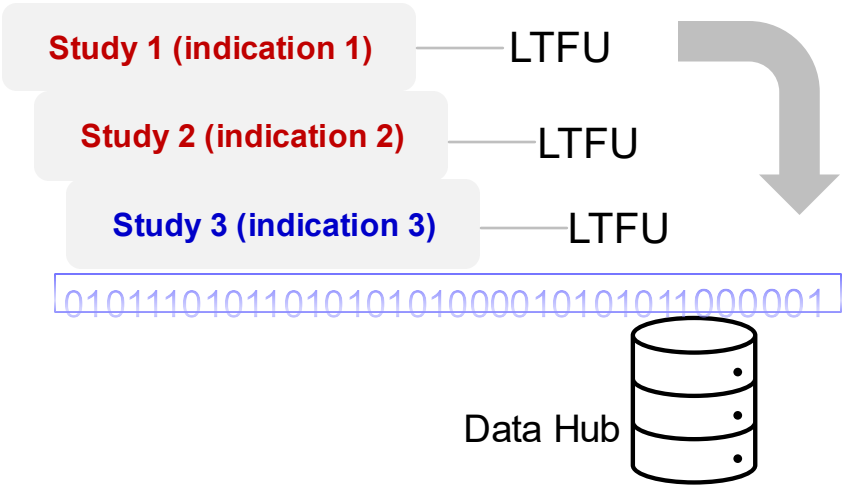
Case 1: Pool multiple LTFU GTx studies

- Can harmonize SoAs, CRFs across studies, modalities/ constructs, indication classes
- Opportunities for alignment at a high level



Case 2: Pool *select* LTFU GTx studies

- Can harmonize SoAs, CRFs across studies within an indication class
- Could have multiple platforms per indication



Case 3: Pool data from LTFU studies in a hub

- Eliminates total harmonization of assessments, but opportunities for data pooling still possible with workarounds, limitations

CRF = Case report form; GT = Gene therapy; LTFU = Long-term follow up; SoA = Schedule of assessment.

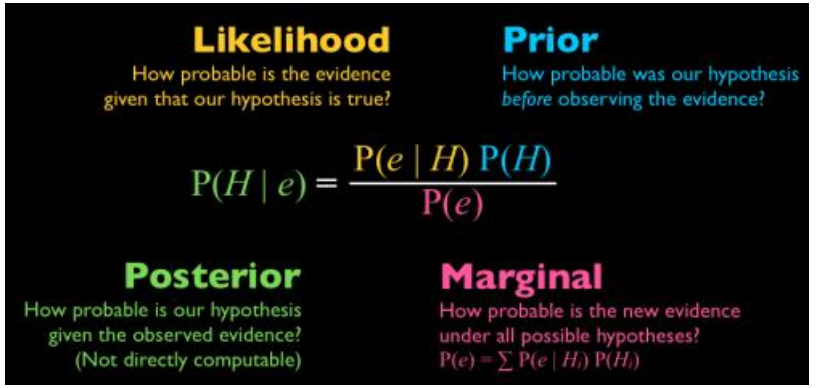
How /Why to Pool AE Rates Across a Class for GTx

- The European Commission's guideline on summary product characteristics (SmPC) classifies AEs in five frequency categories:
  - very rare (< 0.01%)
  - rare (< 0.1%)
  - uncommon (< 1%)
  - common (< 10%)
  - very common (≥ 10%)

- Accurate estimation of anything but "very common" and "common" is infeasible for LTFU trials that may have < 100 subjects

- The answer to this limitation is in statistical tools that "borrow strength" from similar categories within a cluster

Bayesian Hierarchical Modeling (BHM)



- Hierarchical statistical models are appropriate when there is more than one level of structure or hierarchy in the data
- Strong scientific rationale to support the hypothesis that classes of gene therapy products have similar adverse event profiles:
  - Mechanism of action
  - Route of administration
  - Vector
- **For a platform trial containing related sub-studies, we should borrow information on adverse event rates (where appropriate)**
- Bayesian modeling is well-suited to hierarchical models because prior knowledge can inform the degree of information borrowing and MCMC methods can fit complex models

Neuenschwander, B., Wandel, S., Roychoudhury, S., & Bailey, S. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharmaceutical statistics*, *15*(2), 123-134.

EXNEX

MAIN PAPER

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1730

Published online 18 December 2015 in Wiley Online Library

Robust exchangeability designs for early phase clinical trials with multiple strata

Beat Neuenschwander,[a]* Simon Wandel,[a] Satrajit Roychoudhury,[b] and Stuart Bailey[c]

- In BHMs, sharing is determined by how much data was collected in each trial
  - Trials with less data borrow more strongly from the other trials

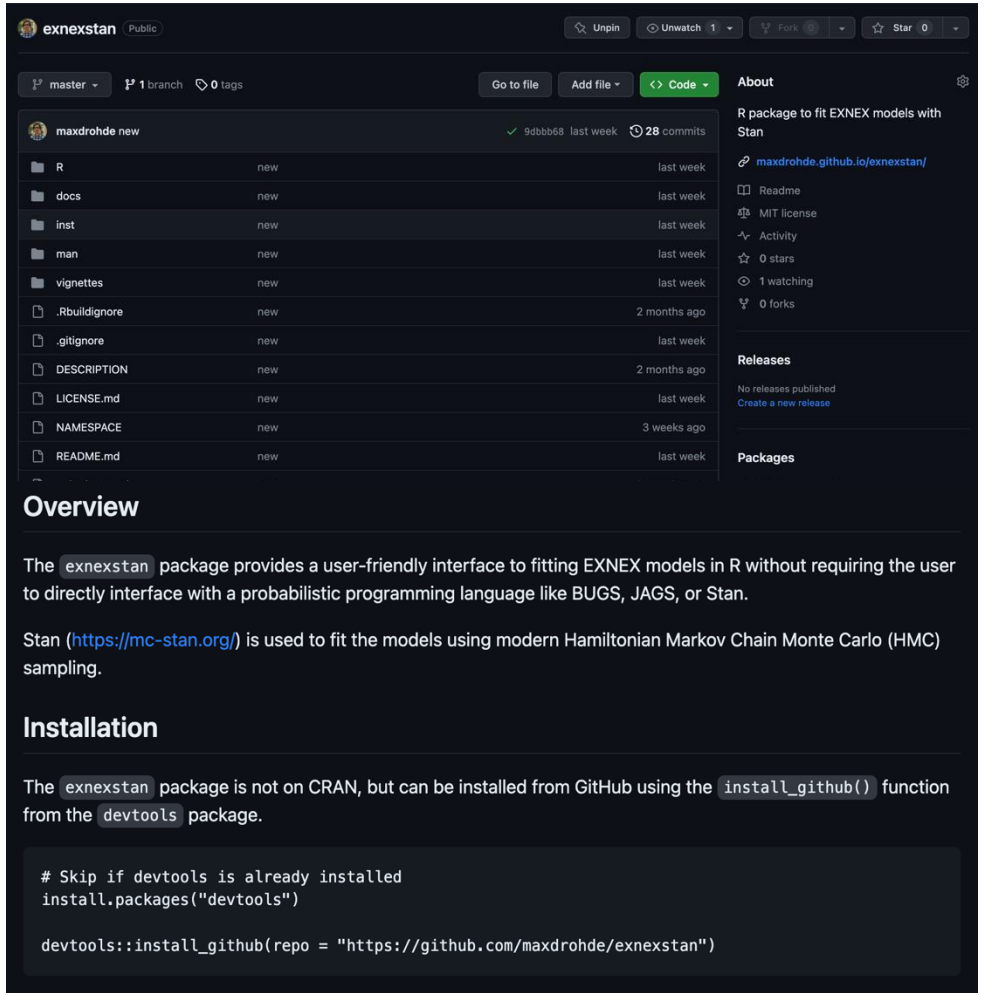
- Bayesian hierarchical models:
  - Perform well when the trials are "exchangeable" (i.e., cluster around a common rate)
  - Perform poorly if any of the trials has an extreme event rate compared to the others

- **EXNEX** ("Exchangeable/Non-Exchangeable") is an extension of BHMs that is more robust to outlier clusters
  - Mixture model where each trial is "exchangeable" with the others in platform with probability p_j or not exchangeable with *any* with probability (1- p_j)

Neuenschwander, B., Wandel, S., Roychoudhury, S., & Bailey, S. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharmaceutical statistics*, *15*(2), 123-134.

Fitting EXNEX models with the *exnexstan* R package

GitHub page



R package vignettes

exnexstan: Binary data and package overview

Code

AUTHOR
Maximilian Rohde

PUBLISHED
July 25, 2023

Background

The exnexstan package implements the EXNEX model for binary data introduced in "Robust exchangeability designs for early phase clinical trials with multiple strata" by Neuenschwander et al. (2015) (https://onlinelibrary.wiley.com/doi/10.1002/pst.1730) using Stan. The cmdstanr package is used to interface R with the Stan probabilistic programming language that fits the models using Markov Chain Monte Carlo (MCMC)[1].

EXNEX models are an extension of Bayesian hierarchical models (BHMs). Bayesian hierarchical models are commonly used to analyze data from related studies, such as strata in a basket trial, since the partial pooling resulting from BHMs is often a good compromise between complete stratification and complete pooling. However, BHMs can perform poorly if some strata are not exchangeable with the other strata.

EXNEX is a mixture model that allows for each strata the possibility of being exchangeable (with probability p_j) with the other strata, or nonexchangeable with the other strata (with probability (1 - p_j)). This increases the robustness of the model to certain strata being not exchangeable with the others. More than two exchangeability groups may be specified in the model, although they can be difficult to fit depending on the amount of data available. Currently, exnexstan only supports a single exchangeability group.

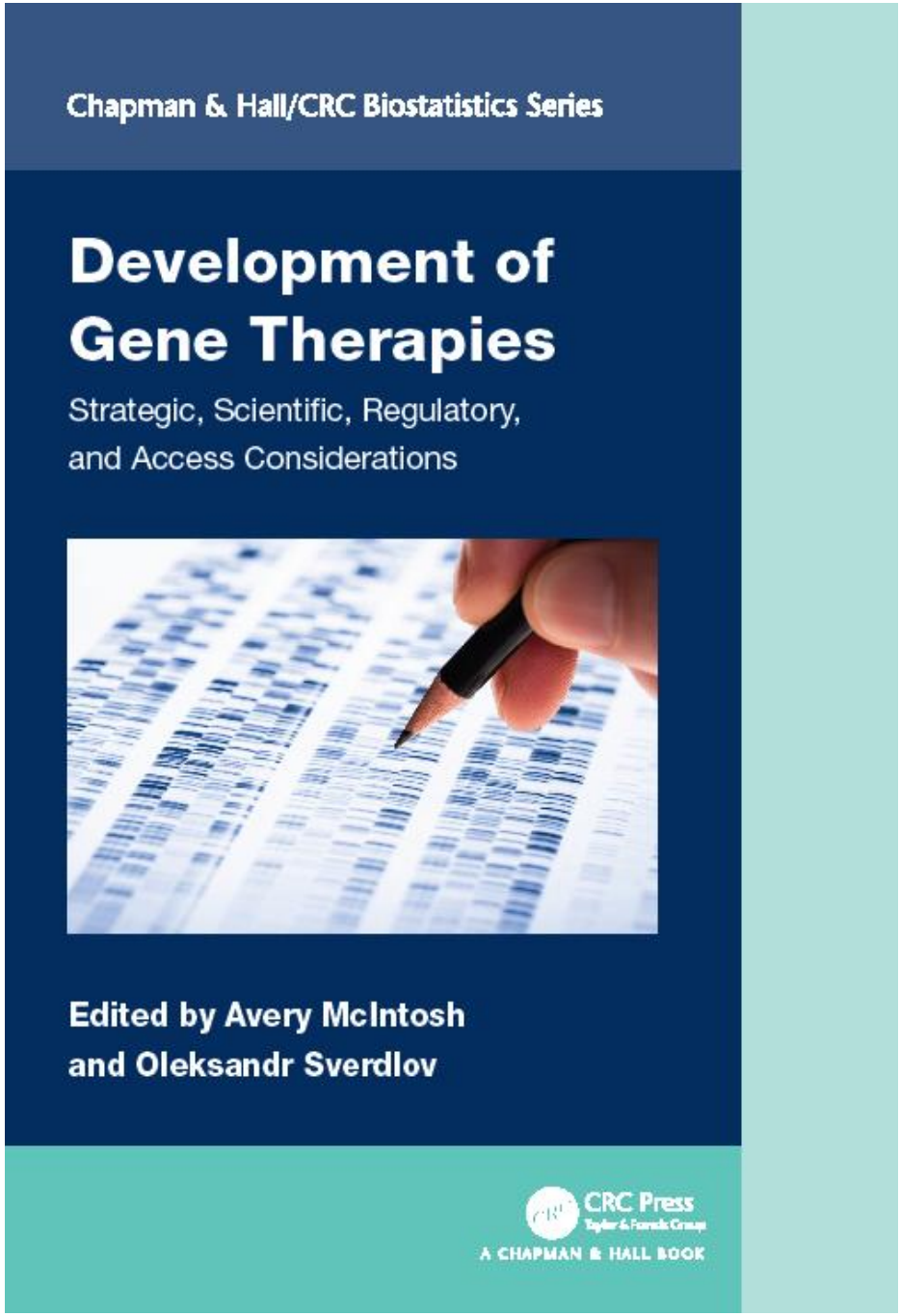
We write out the model in mathematical notation below. For clarity, we use the names for the prior values as given in the code.

$$
\begin{aligned}
Z_j &\sim \text{Bernoulli}(p_j) && \text{(Indicator variable of EX vs NEX)} \\
\theta_j &\sim \text{Normal}(\text{mean} = \mu_{Z_j}, \text{sd} = \tau_{Z_j}) && \text{(Response probability on log-odds scale)} \\
\mu_0 &= \texttt{nex\_prior\_mean} && \text{(NEX mean)} \\
\tau_0 &= \texttt{nex\_prior\_sd} && \text{(NEX standard deviation)}
\end{aligned}
$$

More on Gene Therapy Drug Development

Available from https://www.routledge.com and other booksellers

19 chapters from experts in industry and academia, with a focus on strategic and operational considerations from multi-stakeholder perspectives



Some recent publications on GTx trial design & analysis:

Clinical Pharmacology & Therapeutics

Clinical Pharmacology & Therapeutics

World Federation of Hemophilia (WFH)'s Gene Therapy Registry (GTR)

Barbara A. Konkle, MD
Professor Emeritus
University of Washington;
hematologist at Washington Center for Bleeding Disorders;
Medical Director of the Bleeding Disorders Laboratory at Bloodworks NW

WFH Gene Therapy Registry

Barbara A. Konkle, M.D.

Washington Center for Bleeding Disorders
Professor Emeritus, Hematology Oncology
University of Washington
Seattle, WA USA

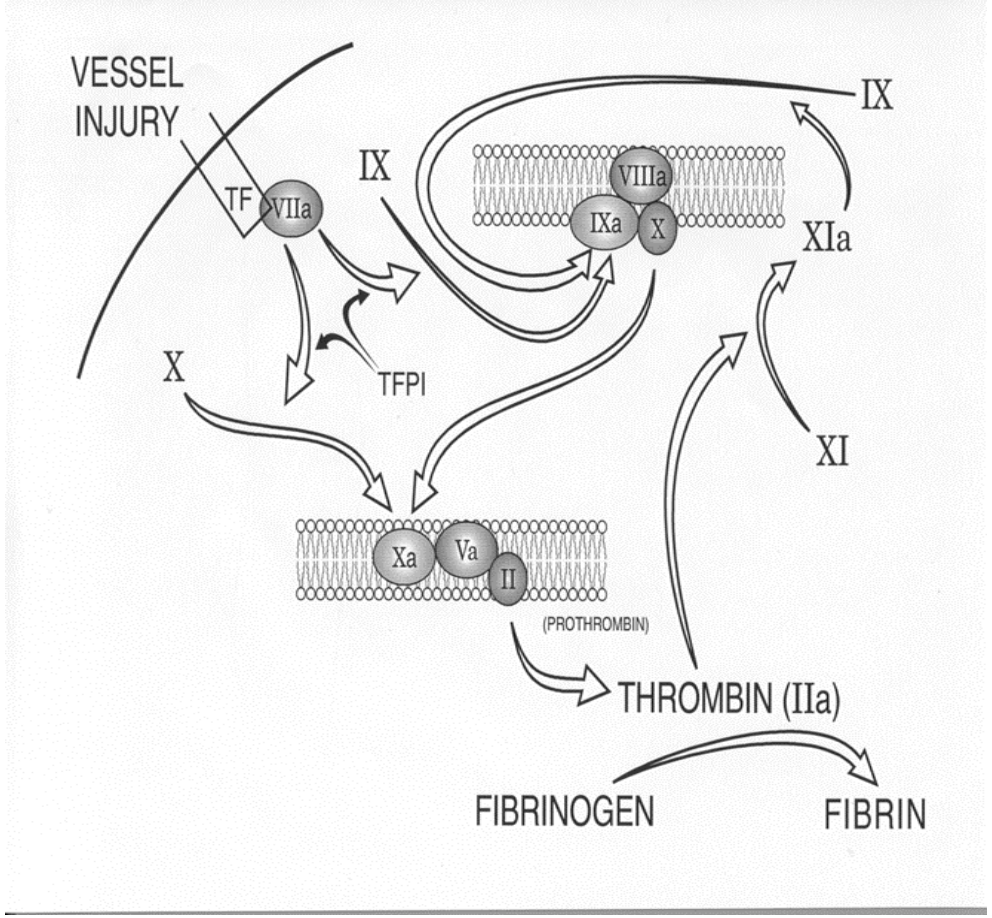
Member, Board of Directors, World Federation of Hemophilia
Co-Chair, GTR Steering and Scientific Advisory Committees

GTR
WFH GENE THERAPY REGISTRY

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Hemophilia

- Results from deficiency of FVIII (A) or FIX (B)
- *F8* and *F9* genes on X chromosome
- Worldwide > 1/5000 males with hemophilia born per year
- Affected females also with bleeding although severe disease rare
- Spontaneous and trauma-induced hemorrhage
  - –Life-threatening and disabling
- Wide range of therapeutic values
  - –Good target for gene therapy



Iorio et al, Ann Int Med 2019;171:540, Peyvandi F et al, Lancet 2016;388:187, den Uijl IEM, et al. *Haemophilia*. 2011;17:41; Soucie JM, et al. *Blood Adv*. 2018;2:2136.

World Federation of Hemophilia

- A non-profit organization founded in 1963
- Focused on hemophilia and other bleeding disorders
- 152 national member organizations
- Works collaboratively with providers and scientists
- Among programs, education and research and data collections
- Data collections include World Bleeding Disorder Registry and Gene Therapy Registry

GTR Objectives

Primary Objective

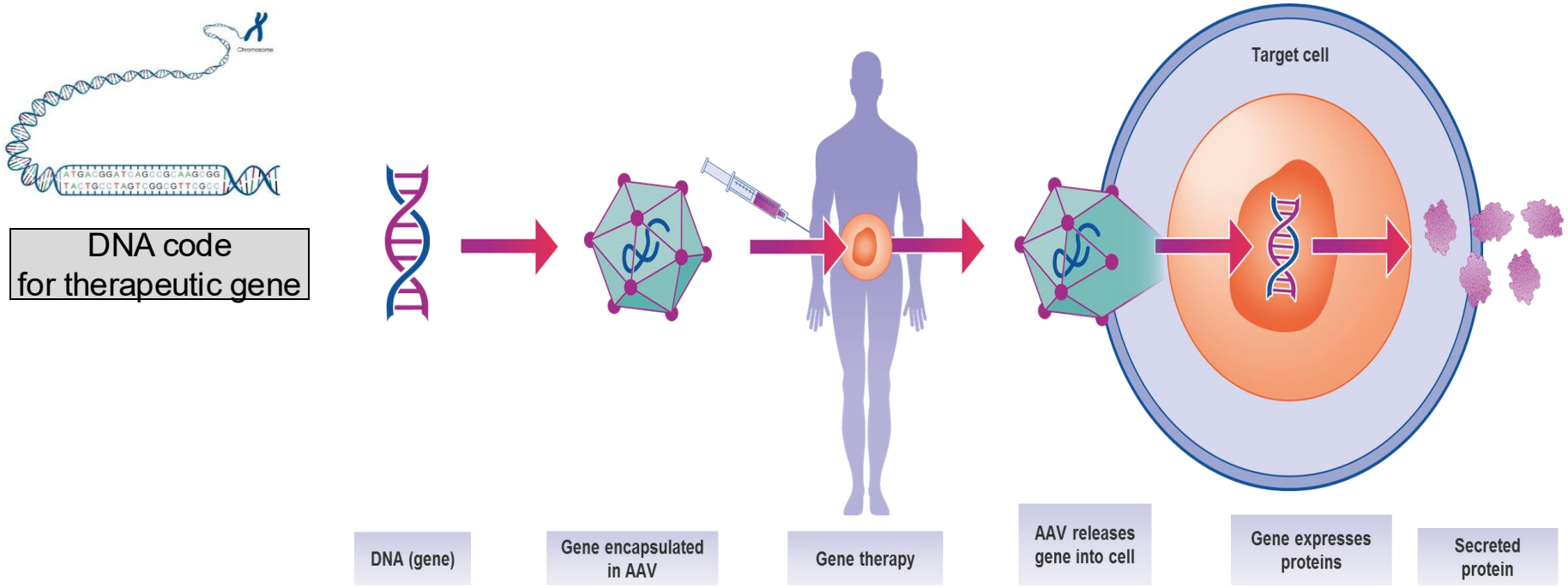
- to determine the long-term safety of factor VIII and factor IX gene therapies in patients with hemophilia

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.

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;18:3074-3077.

AAV-Mediated Gene Therapy:
Regulatory Approved Approach in Hemophilia



ssDNA virus, 2 genes-rep and cap, 20nm, non-pathogenic upon human or animal infection

>200 human trials using AAV – based gene therapy have been conducted in the past 30 years

Image: National Human Genome Research Institute's Talking glossary
(http://www.genome.gov/glossary/) http://www.abedia.com/wiley/vectors.php

GTR Data Set & Data Collection

Core Data Set

- Steering Committee monthly teleconferences: iterative process; published in JTH as an ISTH SSC publication (2020)
- Focus on critical questions published in JTH from the ISTH Working Group on Gene Therapy (2024)

Data will be collected at:

- Baseline / Vector infusion
- Follow-up visits

  Month 3, 6, 9, 12, 18, 24

  Annually thereafter

Sections included:

Demographics & Diagnosis

Medical/Clinical History

Gene Therapy Infusion Details

Safety Data

Efficacy Data

Patient Reported Outcome Measures

Mortality

Konkle BA et al 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;18:3074-3077.
Miesbach et al, Recommendations for a minimum data set for monitoring gene therapy in hemophilia: communication from the ISTH SSC Working Group on Gene Therapy. *J Thromb Haemost* 2024;22:1510-1515.

GTR Core Data Set - Safety

- Serious Adverse Events
- Unexpected Adverse Events
- Adverse Events of Special interest
  - FVIII inhibitors
  - FIX inhibitors
  - Thromboembolic events
  - Autoimmune disorders
  - Malignancies
  - Liver disease
  - Sensory paresthesias
  - Infusion / hypersensitivity reaction
  - Hepatitis B (new or reactivation)
  - Hepatitis C (new or reactivation)
  - Serious complications due to immunosuppression
  - Other

Konkle BA et al. *J Thromb Haemost*. 2020;18:3074-3077

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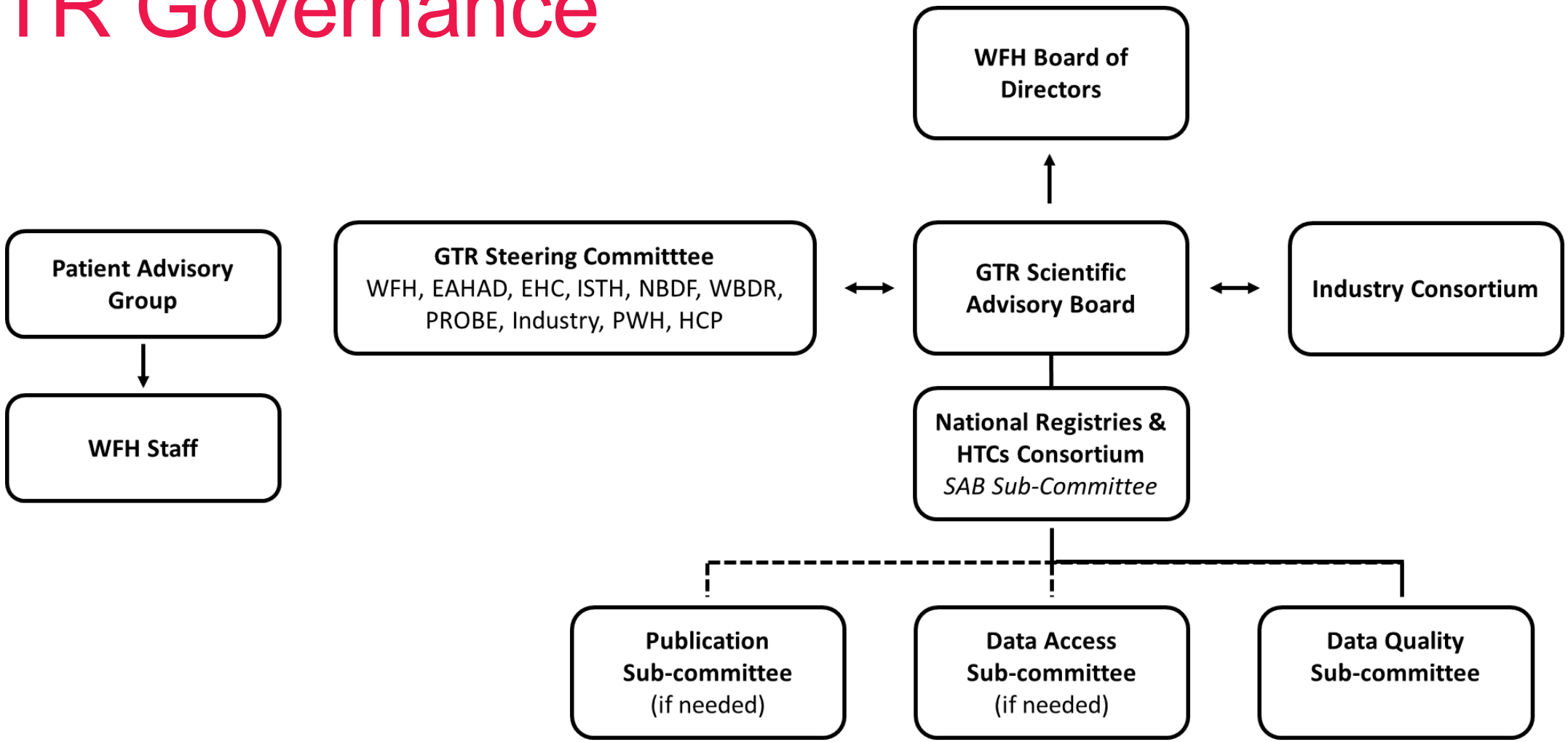
GTR Governance



GTR
WFH GENE THERAPY REGISTRY

GTR and Regulatory Authorities

Protocol and core data set informed by EMA Scientific Advice (November 2019) and FDA comments

EMA Qualification – received a strong letter of support received in September 2023

> "The CHMP supports the WFH GTR as the worldwide registry for consolidating all international data on individuals with hemophilia who receive gene therapy and encourages collaboration of hemophilia treatment centres and national registries worldwide. It is expected that utilising the WFH GTR for post approval safety or efficacy studies of gene therapies will be of particular value and its use as planned data source for mandated Phase IV studies for new hemophilia treatments is recommended."[1]

Data collection could fulfill post-marketing regulatory requirements while also informing the provider/scientific and patient communities

Decreased provider effort

[1] European Medicines Agency. 2023. Letter of Support for World Federation of Hemophilia (WFH) Gene Therapy Registry (GTR). Accessed 23 October 2023. (https://www.ema.europa.eu/en/documents/leaflet/letter-support-world-federation-hemophilia-wfh-gene-therapy-registry-gtr_en.pdf)

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Timeline in Development of Gene Therapies

- WFH GTR database can be adapted for future therapies

Figure adapted from Bulaklak & Gersbach, Nat Commun 2020;11:5820

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Participation in the GTR

Data will be captured in the registry in one of 2 ways:

- Through data transfer from existing national hemophilia registries
- Directly via participating HTCs

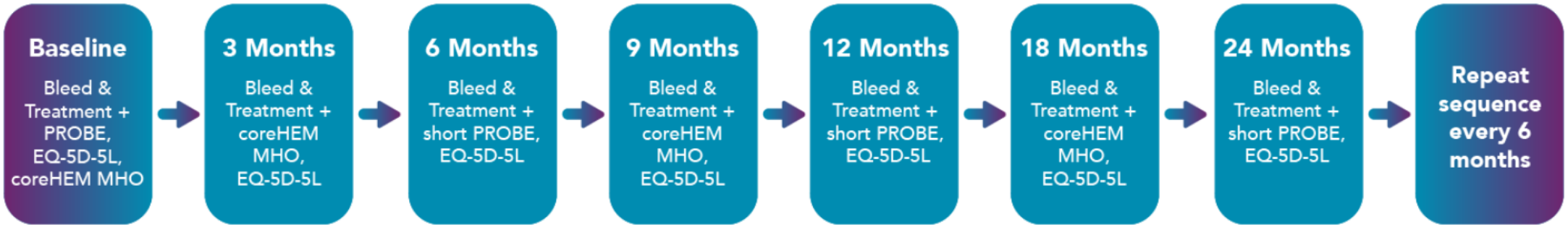
Minimum data elements to be entered defined

Capture both post-regulatory approval and clinical trial participants

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; 18:3074-3077.

myGTR

- For HTCs participating in the GTR directly
- Based on feedback received from WFH GTR Steering Committee and patient group.
- Simple, text or email-based alert @ 6-month intervals.
  - Bleeds experienced
  - Treatment received
  - Patient Reported Outcome tool (alternate between: PROBE, EQ5D5L, coreHEM Mental Health Outlook (when available))



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THANK YOU!

Barbara A. Konkle, M.D.
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Overview of CIBMTR's Approach to Gene Therapy Long-Term Follow Up

Amy Moskop, MD, MS
Assistant Professor, Medical College of Wisconsin and Scientific Director of Gene Therapy,
Center for International Blood and Marrow Transplant Research (CIBMTR)

Overview of CIBMTR's Approach to Gene Therapy Long Term Follow Up

Amy Moskop, MD, MS

Scientific Director of Gene Therapy

Scientific Director of Morbidity, Recovery and Survivorship – Cellular Therapy

CIBMTR, Medical College of Wisconsin

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Innovative Approaches for Gene Therapy Long-Term Follow-Up | Leveraging Registries and Platform Trials | The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard | May 6, 2025

Outline

- CIBMTR Registry
- Gene Therapy Industry Landscape and Registry Approach
- Long-Term Follow Up for Gene Therapies
  - Post Approval Safety Studies
- Industry Collaboration Considerations
- Research Community Considerations
- ePRO
- Conclusion

CIBMTR Center Network Agreements

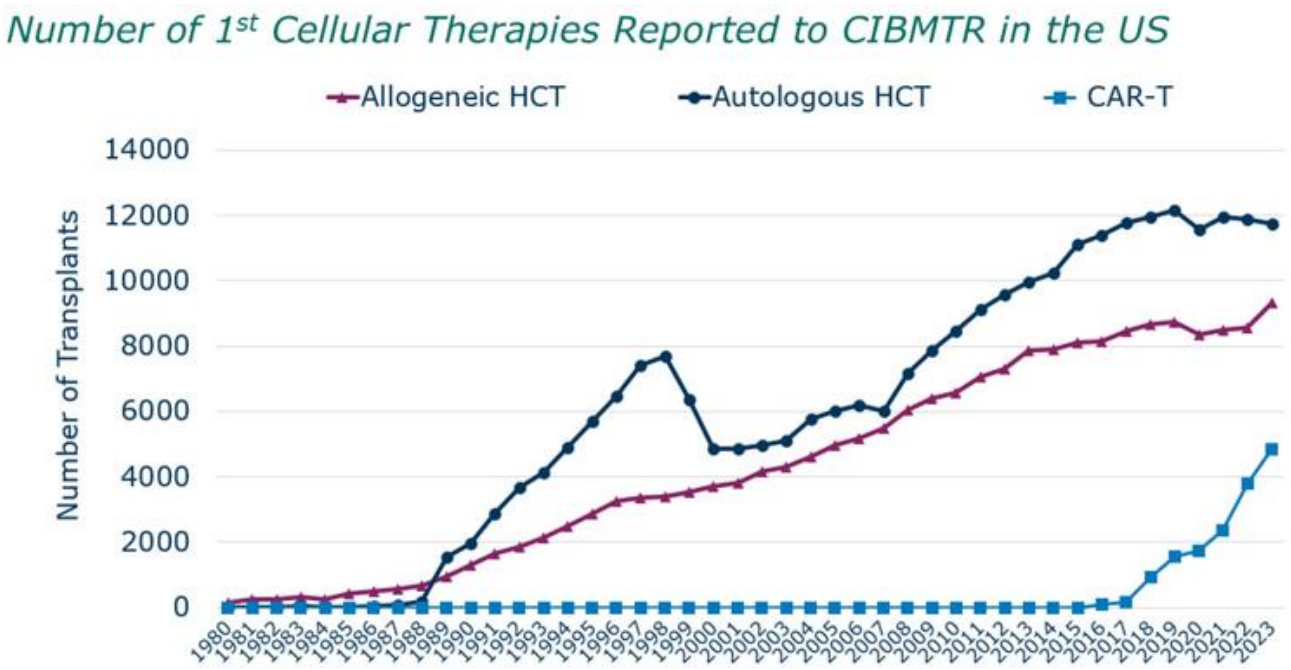
Master agreements for data transmission and use

Includes all U.S. centers performing allogeneic transplantation as mandated by HRSA and under the SCTOD contract

Registry Protocols govern research data collection, consent and use

- Research Database Protocol (RDP) describes broad research data use
    - Patients consent to participation in database activities, including linking to other sources
    - Consent is obtained by the treatment center and reported to CIBMTR RDP consent governs use of PRO and Sample data
    - Supplemental ICFs can be collected with the standard ICF if necessary, e.g. CMS CED studies
- PRO Data Collection Protocol governs collection of PRO data
    - ePRO system includes consent capabilities
    - Data is stored in the Research Database and is governed by the RDB protocol
- Sample Collection Protocol governs collection of samples

CIBMTR's Registry



- CIBMTR has been a part of the cellular therapy community for over 50 years
- Data has been used effectively to advance the field
- Data has been noted by the FDA as a source of high-quality RWD
- LTFU questions can be effectively addressed through a large multi-center observational outcomes registry
  - Secondary source of clinical and non-clinical data
- Reuse of infrastructure represents a cost-effective approach

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FDA Approved Gene Therapy Products

8/17/22

ZYNTEGLO (betibeglogene autotemcel)
bluebird bio, Inc.

- Treatment of adult and pediatric patients with transfusion dependent B-thalassemia (TDT)

9/16/22

SKYSONA (elivaldogene autotemcel)
bluebird bio, Inc.

- Boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD)
  - Asymptomatic or mildly symptomatic (NFS $\leq$ 1) with gad enhancement and Loes score of 0.5-9

12/8/23

LYFGENIA
bluebird bio, Inc.

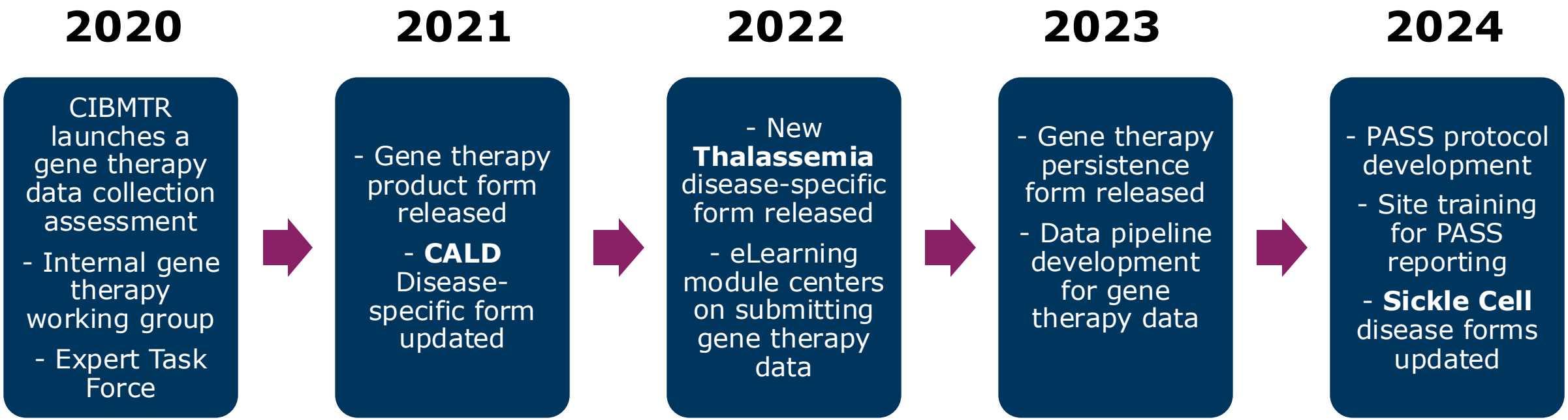
- Treatment of patients with SCD in ages $\geq$12 years with recurrent VOCs

1/16/24

CASGEVY
Vertex Pharmaceuticals Incorporated

- Treatment of patients with SCD in ages $\geq$12 years with recurrent VOCs
- Treatment of patients with transfusion dependent B-thalassemia (TDT)

Gene Therapy Registry Approach



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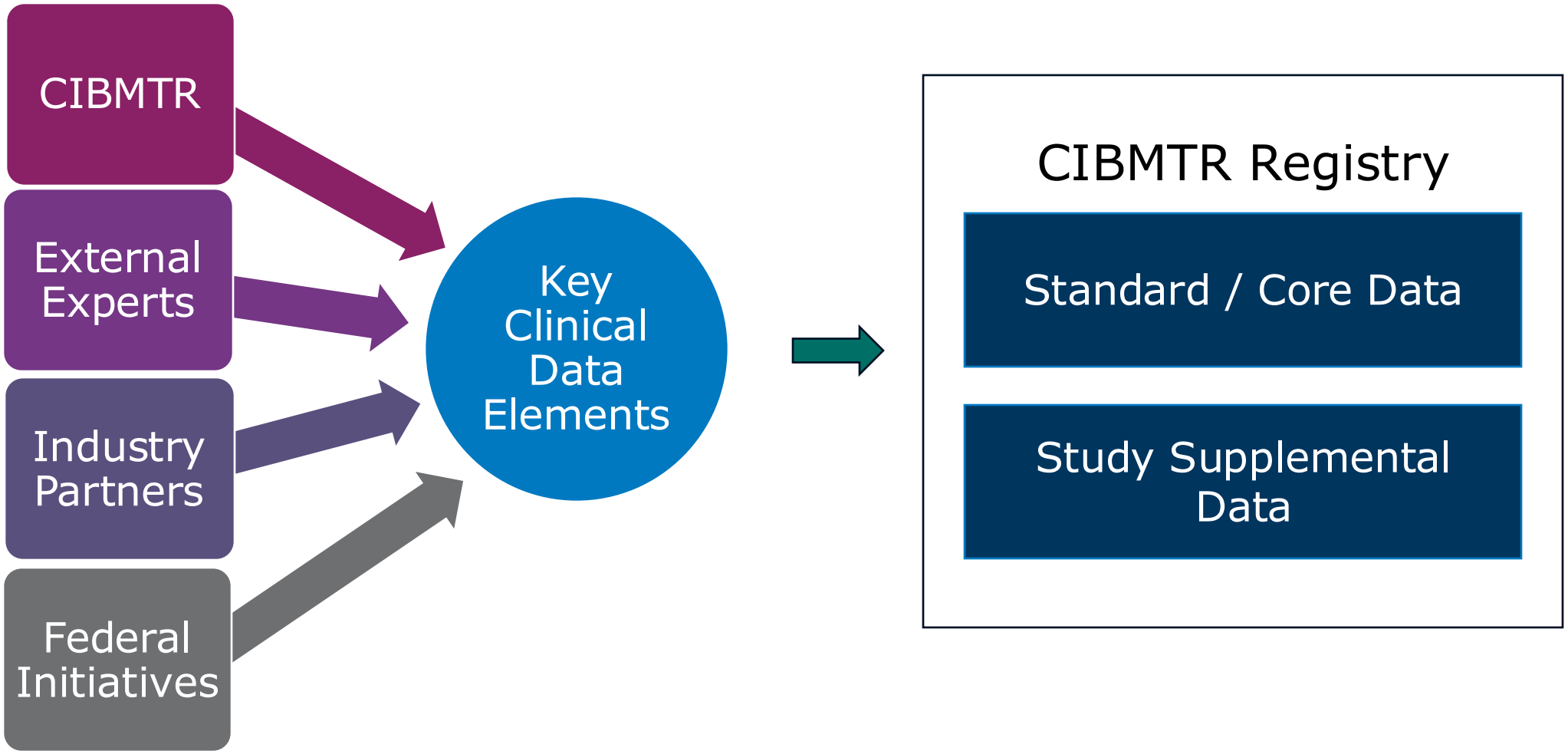
Key Clinical Data Element Identification



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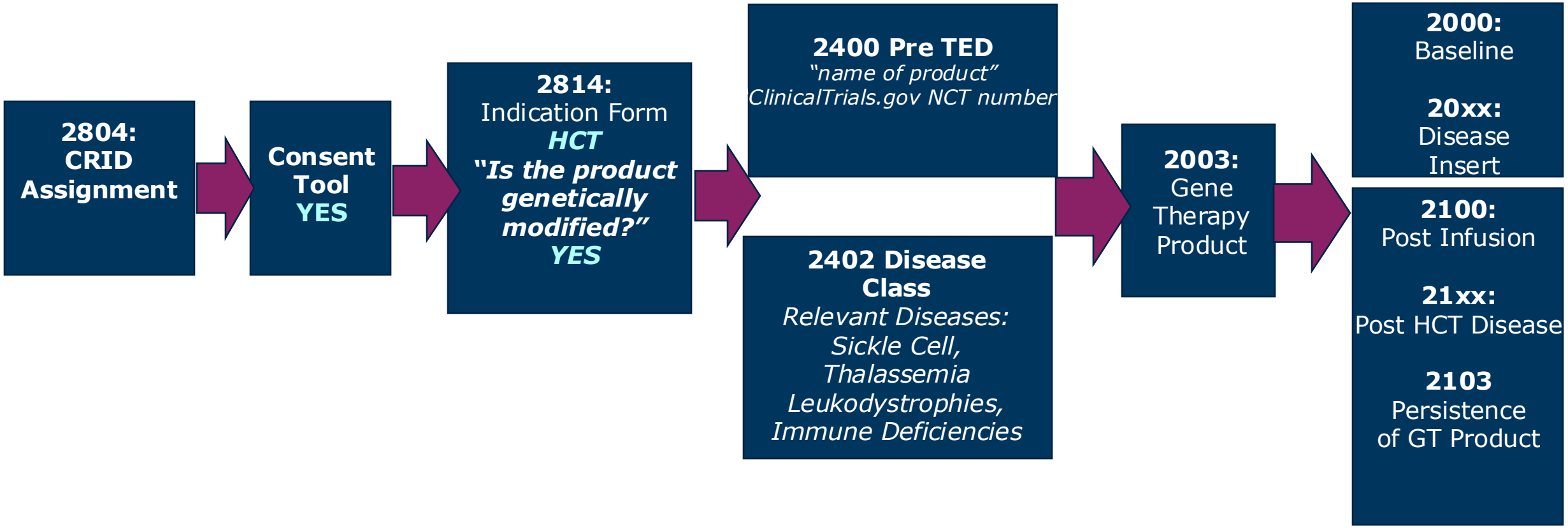
Gene Therapy Forms Journey



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Slide provided courtesy of Tiffany Hunt, Data Ops Manager

Long Term Follow-up for Gene Therapy Recipients

- The Food and Drug Administration requires that manufacturers follow all recipients of genetically modified cell and gene therapy for at least 15 years post-infusion

- Potential Risks of Delayed Adverse Events following exposure to gene therapy products:
  - Integration activity of the GT product
    - Potential for disruption of human genes at the site of integration or activation of proto-oncogenes near integration site
    - Increase risk of malignancies (particularly insertional mutagenesis)
  - Genome editing activity: off target effects on genome
  - Prolonged exposure to the therapeutic protein leading to unregulated cell growth and malignancies
  - Reactivation from latency

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Post Approval Safety Study (PASS)

- Observational prospective clinical study
- Protocol defined longitudinal collection of outcomes data and analyses
- Primary outcome of newly diagnosed malignancies plus other safety and efficacy outcomes
- Voluntary center reporting to CIBMTR
- CIBMTR Registry infrastructure accommodates requirements of the PASS
- Use CIBMTR Master Agreements and network

Gene Therapy Post Approval Studies for LTFU

Project	Sponsor	Objective	Launch & Duration
Skysona LTFU (elivaldogene autotemcel)	**bluebird bio, Inc.**	Safety and efficacy outcomes (PASS) **Diseases: cALD** **n=120**	**Spring 2024** **15** years of follow up
Zynteglo LTFU (betibeglogene autotemcel)	**bluebird bio, Inc.**	Safety and efficacy outcomes (PASS) **Diseases: TDT** **n=150**	**Spring 2024** **15** years of follow up

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Industry Collaboration Considerations

- Supporting **regulatory** requirements, analytics as well as research questions
- Embargo of data and publishing critical results.
  - Impact on others in the research community
- Aggressive timelines and very specific requests.
- ***Outcomes of interest***
  - *Regulatory & safety driven*
  - *Business analytics*
- Routine study team changes throughout a LTFU project

Metrics of Success

- Industry funding supports **infrastructure expansion** needed to collect these outcomes.

- *However,* CIBMTR is NIH funded with a mission to support a **broad portfolio of research** and to provide investigators access to use of its Registry resource.

- An industry embargo of data is temporary and over time (no more than 2 years) the **data is available for broad use.**

- Within the embargo timeframe, CIBMTR has successfully facilitated **investigator led studies with industry support/representation**.

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Research Community Considerations

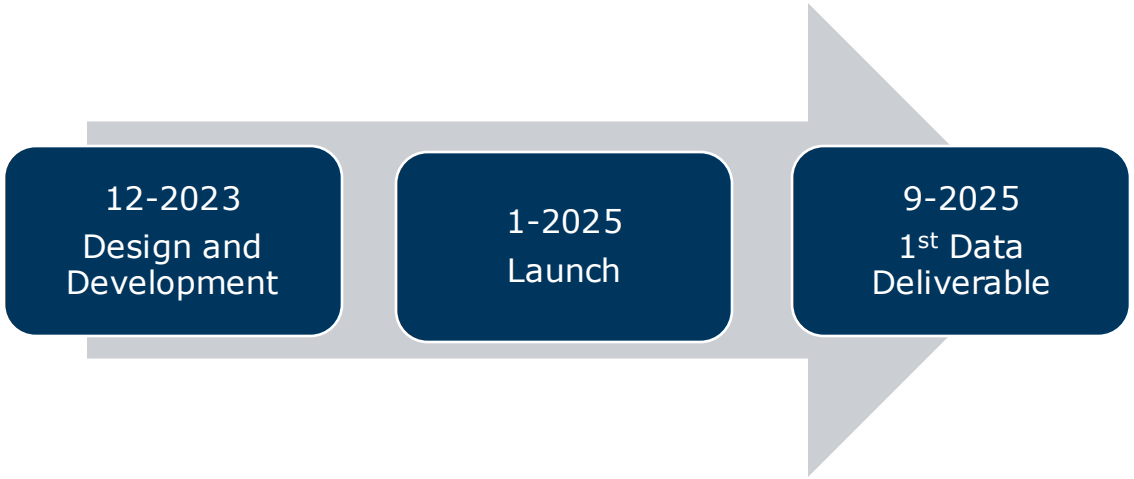
- Delay in access to data due to embargo
  - Mitigated by data maturity timeline within a Registry setting.
- Potential differences in what is considered most important to investigate
  - ACT council provides an opportunity to raise concerns and support community discussion
  - Appropriate involvement and attribution to non-industry researchers through working committee studies and within the industry program

Cell and Gene Therapy Access Model for Sickle Cell Disease Study
Centers for Medicare and Medicaid Innovation (CMMI)

Description: CIBMTR study supporting access to transformative sickle cell disease treatments

CIBMTR Role:

- Support CMMI Access Model SCD Data Requirements
- Develop innovative linking and data sharing approaches
- Expand ePRO data collection including pediatrics



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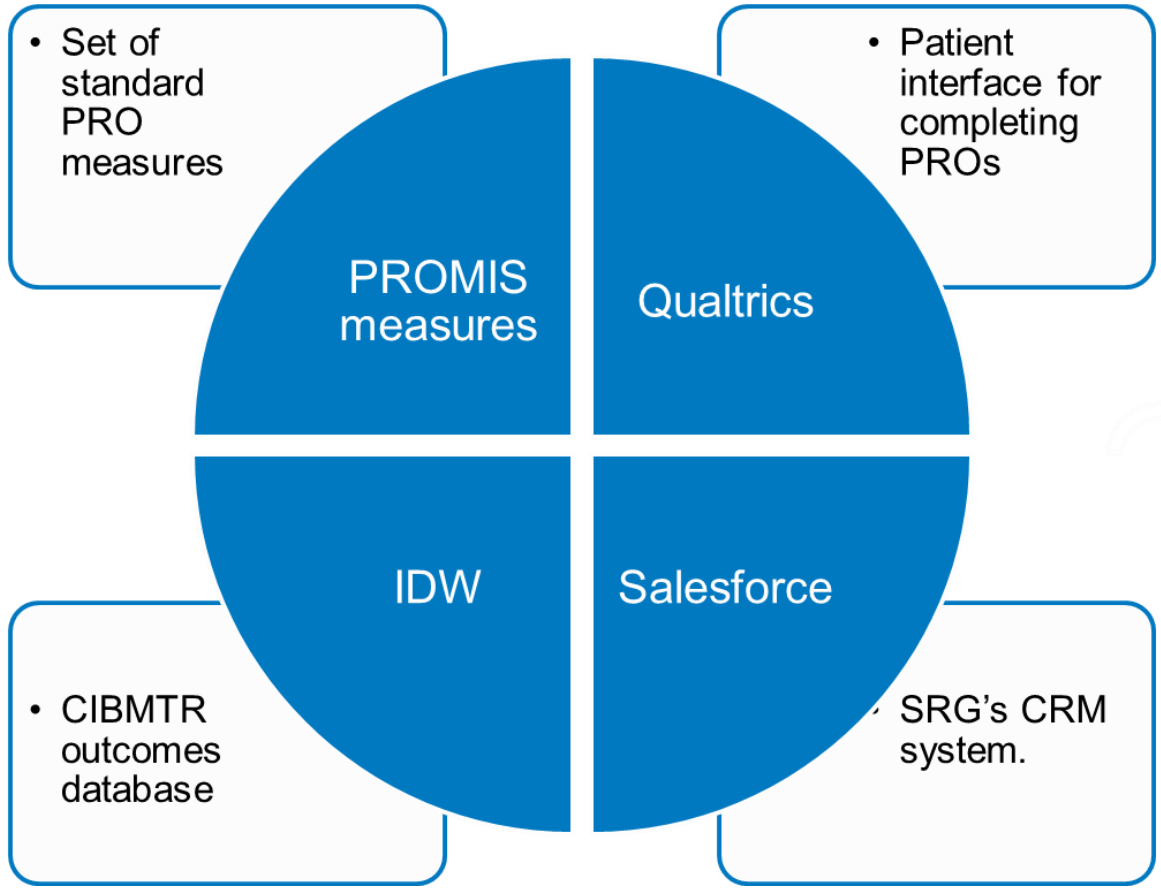
CIBMTR ePRO Data Collection

CIBMTR launched the ePRO system in 2018

Adult only, consent collected at survey launch

CIBMTR's Survey Research Group also supports non-electronic survey collection



Pediatric ePRO development

- Current CIBMTR ePRO supports adults only
- A pediatric expansion is ongoing with a planned, partial, launch in January 2025
- Can include pediatric specific measures
  - Malignant and non-malignant
  - Disease specific

Conclusion

- CIBMTR collects long term data on safety and efficacy following gene therapy to support variety of research initiatives

- CIBMTR offers infrastructure for data collection and aims to facilitate real world collaborative research efforts for long term follow up of recipients of gene therapy, including industry sponsored regulatory projects

- Opportunities for consortium collaboration to expand the opportunities for clinical research

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- Bluebird bio
- Vertex

- **Patients**
- **Participating centers**

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Q&A / Discussion

Thank You!

WEBINAR

Cell and Gene Therapies Project

Patient-Centered Long-Term Follow-Up for Gene Therapies

This webinar will explore patient-centered approaches for Gene Therapy (GT) Long-Term Follow-Up (LTFU) studies.

June 26, 2025 @ 1 pm ET

The registration link, our newsletter signup, and today's recording are (or will be) available on our website, ***mrctcenter.org***