MASAC Document #282
(Replaces Document #277)

MASAC RECOMMENDATIONS ON HEMOPHILIA TREATMENT CENTER PREPAREDNESS FOR DELIVERING GENE THERAPY FOR HEMOPHILIA

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on September 22, 2023, and endorsed by the NHF Board of Directors on October 27, 2023.

INTRODUCTION

Successful gene therapy will require broad-based, multi-stakeholder participation to define patient eligibility, educate health care providers, educate persons with hemophilia (PWH) and families, and develop shared decision-making tools to facilitate discussions between providers and PWH considering gene therapy. In addition, multi-stakeholder preparation is required to develop clinical protocols for eligibility screening, administration, and follow-up of gene therapy, and to identify ways to remove barriers to access and achieve excellence in clinical delivery to maximize health outcomes. This guideline is focused on hemophilia treatment center (HTC) preparedness for commercial gene therapies for hemophilia.

CLINICAL DELIVERY OF GENE THERAPY FOR HEMOPHILIA

Site Preparedness - Dosing Centers and Follow-Up Centers

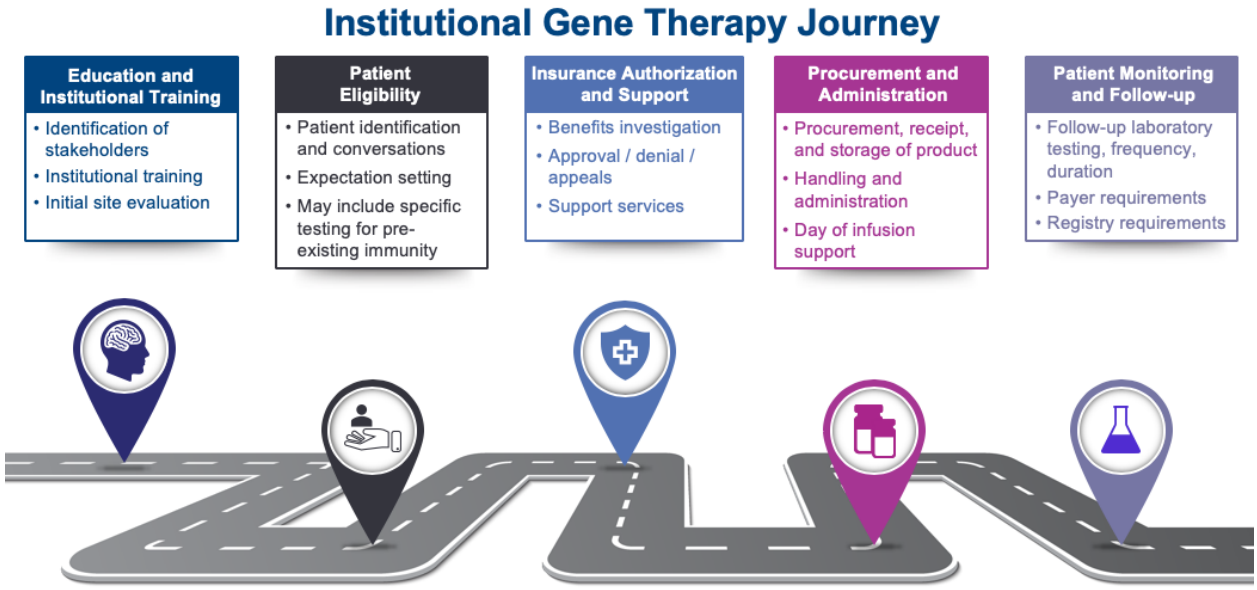
Site readiness requires close collaboration between economic stakeholders, clinicians, and institutional Biological Safety, Infection Control and Pharmacy and Therapeutics Committees. Each HTC should use this document as a guide to prepare their own standard operating procedures, workflows, and follow-up plans which include equitable access and treatment for all.

HTC sites delivering a dose of gene therapy, hereafter referred to as Gene therapy Dosing Centers, should achieve the required approvals from their Biologic Safety and/or Infection Control Committees, demonstrate the availability of the necessary facilities and equipment for reconstitution of viral vector therapies, and identify a suitable clinical infusion site. Only Centers at or affiliated with HTCs who meet all the criteria should be Dosing Centers. It is imperative for the manufacturers of each approved drug to develop the appropriate training tools, institutional site preparedness checklists and for the HTCs to ensure dissemination of the information within the institutional administration and across their clinical staff. HTCs or hematologists seeing post gene therapy patients for follow-up, hereafter referred to as Follow-

up Centers, should demonstrate suitable follow-up policies and close collaboration with Dosing Centers, particularly within their respective region.

The “Roadmap” for institutional preparedness should address the following 5 areas (see Appendix A for full Roadmap Checklist):

I. Education and Institutional Training
II. Patient Eligibility
III. Insurance Authorization and Support
IV. Procurement and Administration
V. Patient Monitoring and Follow-up



I. Education and Institutional Training

Key stakeholders (physicians, advance practice providers, nurses, case managers, social workers, psychologists, pharmacy staff, and financial administrators) should receive tailored education about gene therapy based on their role. This care should be provided in a manner that respects the individuals culturally, linguistically, background, literacy, gender identifiers, age, economic restrictions, and ability status.

There should be specific education modules that must be completed prior to participation in a clinical gene therapy program. Suggested sources of modules are shown below. Training should be documented, and records maintained at the Center. Procedures should be in place for onboarding new staff and at least annual re-education.

Standard Provider education should include:

1. Gene therapy basics including preclinical data
    a. Dosing center roles

    b. Follow-up center roles
2. Safety and efficacy data and subsequent durability from clinical trials
3. Patient eligibility
4. Important aspects to include in patient conversations and shared-decision making – addressing unconscious bias and limitations of current products
5. Transitioning patients from on-demand or prophylaxis to gene therapy
6. Dosing
7. Administration procedure
8. Management of infusion reactions/anaphylaxis
9. Staffing requirements for day of infusion
10. Follow-up requirements
11. Psychosocial support – inclusive of cultural humility and the importance of diversity, equity, and inclusion.
    a. Performing a psychosocial evaluation for patients to ensure logistical and emotional well-being, before and after gene therapy
12. Bleed and surgery management post-infusion
13. Product handling regulations
14. Laboratory monitoring (one stage assay vis a vie chromogenic assay)

Standard Pharmacy education should include:

1. Gene therapy basics
2. Safety and efficacy data from clinical trials
3. Dosing
4. Procurement, receipt, and storage of product
5. Consideration of redundancy of storage systems given cost of drug
6. Handling and preparation of product
7. Compounding requirements
8. Infusion requirements
9. Administration procedure
10. Staffing requirements for day of infusion
11. Day of Infusion support
12. Management of infusions reactions

Education may be completed through a combination of specific drug training through manufacturer support, along with more general training from institutional based programs and/or online modules from nationally or internationally recognized expert groups. The Table below includes some of the available educational resources.

International Society on Thrombosis and Hemostasis	Gene Therapy in Haemophilia: An ISTH Education Initiative	Multiyear roadmap for capacity building around gene therapy education	genetherapy.isth.org
World Federation of Haemophilia	Gene Therapy for Haemophilia	• Evolution of haemophilia therapy • Basics of gene therapy • Gene therapy for haemophilia	elearning.wfh.org/resource/gene-therapy-for-hemophilia
National Bleeding Disorders Foundation	Future Therapies	• Consumer education • Glossary of terms • Frequently asked questions • Resources	www.hemophilia.org/Bleeding-Disorders/Future-Therapies
European Haemophilia Consortium	EHConversations: Gene Therapy Series	• What is gene therapy? • How does a clinical trial in gene therapy for haemophilia work? • Safety and gene therapy • Gene therapy: A patient's perspective	www.ehc.eu/ehconversations-gene-therapy-series
Medscape	Clinical Advances in Gene Therapy for Haemophilia	• Science of gene therapy • Clinical trial results • Potential clinical application	www.medscape.org/sites/advances/gene-therapy-hemophilia
American Society of Gene and Cell Therapy	Education	• Gene therapy 101 • Disease treatments	www.asgct.org/education
American Society of Hematology	Education		www.hematology.org
IHTC Partners Program	Education	• Gene therapy for providers 101 • Gene therapy for providers 201 • Gene therapy for providers 301 • Gene therapy for patients and families 101	www.partnersprn.org/online

II. Patient Eligibility

Eligibility for a commercial gene therapy product will be in accordance with the product labeling, and the patient's own health status in discussion with their doctor.

<u>Recommendations for discussing gene therapy with potentially eligible individuals</u>

The decision to undergo gene therapy is complex and MASAC recommends a series of conversations over time using shared decision-making tools that synthesize the scientific evidence of benefits and risks of available treatment options and elicit patient preferences and goals. Shared decision-making tools may facilitate informed decision-making for commercially available gene therapy and other novel therapies.

Important elements include:

- Plain language document that patients can understand and take with them
- define/explain the decision to be made,
- present options,
- discuss benefits/risks/costs/potential for redosing,
- elicit/clarify patient's values/preferences,
- discuss patient's ability/self-efficacy,

- discuss the health professionals' knowledge/recommendations, with cultural awareness of the patient's perspective
- check/clarify the patient's understanding and expectations for the therapy,
- make or explicitly defer the decision,
- and arrange follow-up.

The discussion should provide the important elements of safety and efficacy for the individual to make an informed decision related to gene therapy. Particular attention should be made to discuss current gaps in knowledge regarding safety, efficacy, and durability on a recurring basis.

Key elements include:

- Potential ranges of efficacy and implications for participation in activities/invasive procedures
- Expected duration of response/lack of response and uncertainty for return to previous therapies
- Role of AAV antibodies positivity on outcomes
- Hepatitis and chronic liver disease history
- Expectations for the screening processes and day of infusion
- Required follow-up laboratory testing and clinic visits (short and long-term) and implications for non-adherence
- Restrictions on alcohol consumption
- Recommendations for effective contraception and family planning
- Restrictions on concomitant medications
- Post-dose contact precautions
- Potential side effects and their management, including side effects related to immunosuppression
- Psychosocial impact
- Recommendations for social support (culturally informed)
- Cost/insurance coverage/approvals needed

III. Insurance Authorization and Support

Each HTC should have a protocol in place to guide insurance authorization processes. The authorization team should receive training about the unique aspects of benefits investigation, approval/denial/appeals, and support services for commercial gene therapy products.

The authorization team should work closely with the clinical team to ensure that all the relevant clinical and quality of life information is available to support the prior authorization.

HTCs should utilize manufacturer programs to facilitate insurance coverage and patient financial assistance when indicated and investigate other financial assistance when the programs meet their limits.

IV. Procurement, Receipt, and Storage of the Gene Therapy Product

Each Dosing Center will need their standard operating procedures (**Appendix A**) regarding procurement, receipt, and storage of the gene therapy product. In order to be a Dosing Center, sites should demonstrate the required receiving, storage, and pharmacy capacities in addition to center required approvals required per center.

Procurement

Each Dosing Center will need to determine if they will purchase the product.

Each Dosing Center will have equitable policies and procedures in place for processing patient enrollment forms for gene therapy and writing the initial prescription.

Receipt

Each Dosing Center will have policies and procedures in place for receipt of the gene therapy product. This includes but is not limited to ultra-cold chain handling and storage, space for thawed product when applicable, and biosafety protocols. Policies and procedures will be approved by appropriate regulatory groups at each institution (Biosafety/Infection Control, Pharmacy and Therapeutics Committee).

Administration

Each Dosing Center will have policies and procedures in place for scheduling patients for the day of infusion, providing day of infusion expectations and timeline for the patient, ensuring appropriate pharmacy, nursing and physician oversight and any translation services needed on the day of infusion.

Each Dosing Center will have a protocol for preparation and administration of the product as well as protocol for response to anaphylaxis and other adverse reactions.

Infusion day orders will be in place including nursing communications for IV placement and monitoring, pre-medications, gene therapy medication order and infusion instructions, and anaphylaxis orders.

Each Dosing Center will have a protocol in place for day of infusion monitoring (duration of monitoring, what to monitor for, when to notify physician/advance practice provider, response to infusion reactions). A physician or advanced practice provider should be immediately available during the infusion and in the monitoring phase to evaluate and respond to any infusion reactions.

V. Patient Monitoring and Follow-up

Each Dosing Center and Follow-up Center should have policies and procedures in place for individualized short-term and long-term monitoring and adverse event reporting **(Appendix B).** As part of the initial gene therapy discussions, patients should receive education regarding the importance of adherence to monitoring and this education should be reinforced throughout the course of follow-up.

When applicable, Dosing Centers should provide Follow-up Centers a summary of the gene therapy treatment and plan for transition of monitoring.

Monitoring protocols should be set for the following post-infusion time periods:

1 day to 1 week
1 week to 1 year
>1 year

Protocols should include recommendations for frequency of follow-up calls, follow-up visits (in person and video), laboratory testing, imaging, liver biopsies, and management of immunosuppression. Remote monitoring with telephone calls and where available and appropriate, utilization of telemedicine and remote laboratory sites and mobile nursing should be considered to decrease patient burden.

Policies and procedures should be in place for patient follow-up tracking and interventions when patients are not adherent with follow-up.

Policies and procedures should be in place for clinical review of lab results as well as communication of results and documentation in the medical record.

Individual bleed management plans should be written in plain language the same as the protocols so that every patient can read and understand. The average person living in the US reads at about a 6-7th grade level so all health information should be written at this level.

Longitudinal Data Collection

Site preparedness should include establishing surveillance and research collaborations for long-term monitoring with the CDC, American Thrombosis and Hemostasis Network (ATHN), World Federation of Hemophilia (WFH), and other gene therapy company required registries. MASAC encourages that all individuals receiving gene therapy participate in post-marketing registries. Post marketing surveillance to gather critical post-therapy evidence of safety and durable efficacy will be critical (https://pubmed.ncbi.nlm.nih.gov/32495492/). Some data will come from open-label extensions of ongoing phase III and future phase IV clinical trials; however, much of the burden will be on registry studies to amass long-term data on a large cohort of patients. The WFH has established the WFH Gene Therapy Registry (https://pubmed.ncbi.nlm.nih.gov/32462720/) which will also include data shared from the gene therapy module of the ATHN Transcends study. The accumulation of patient exposure captured in longitudinal registries is the most robust means of revealing unexpected or rare events associated with this new technology class. Detecting low incident or delayed safety events, particularly in small treatment cohorts of a rare disease, necessitates that each patient who receives gene therapy be followed over the long term, preferably their lifetime (https://pubmed.ncbi.nlm.nih.gov/32495492/). A core outcome set incorporating the essential elements to be collected has been finalized (https://pubmed.ncbi.nlm.nih.gov/33463024/).

Appendix A-Example of Site Preparedness Checklist

- **Education of PWH and Staff**
    - Shared decision making that incorporates gene therapy among existing therapies
        - Inclusive of cultural humility and DEI (making decisions with diverse populations)
    - Potential benefits and risks
        - Fully informed from clinical trial data
- **Biologic**
    - Institutional preparedness for product handling and administration, and required institutional approvals
        - infection control committee review
        - nursing handling and infusion
        - patient and staff precautions
    - Pharmacy preparedness
        - Product receipt, handling, storage
        - Reconstitution – thaw time and containment needs
- **Infrastructure and Staff**
    - Clinical pharmacist available and trained for product handling
    - Trained skilled nursing for infusion
    - Physicians available during infusion
    - Safe area for infusion
        - Appropriate containment
        - Suitable to respond to infusion reactions
        - Plan for infusion modification if needed
            - Infusion rate change, supportive therapeutics
- **Pre-infusion screening**
    - Liver health
    - Neutralizing antibody assay (companion device central lab send out)
    - Obtain baseline transaminase results at planned post-infusion monitoring site
    - Reimbursement approvals, authorization for drug acquisition
- **Day of Infusion Plan**
    - Coordination of product receipt, reconstitution, infusion, and immediate post-infusion monitoring
    - Patient instructions on peri-infusion and post-infusion treatment plan, including factor management plan
- **Post-infusion monitoring**
    - Schedule of assays – transaminases and factor levels and liver health measures
    - Establish immunomodulation plan and appropriate prescriptions
    - Communication plan between patient, lab and follow up center
- **Long-term monitoring**
    - Data collection plan for safety and efficacy endpoints
    - Data sharing plan – across HTCs, national and global registries

Ref: Pipe et al., HAEMOPHILIA, 2022

Appendix B-Example of Follow-up Tracking Form

Baseline (21)	2xBaseline (42)	AEOSI	>ULN

	Local Labs		Central Labs					
Visit Name	**Local FVIII One-Stage**	**Tacro**	**Central FVIII One-Stage**	**Central FVIII Chromo**	**ALT**	**AST**	**GGT**	**LDH**
Screening			<1.0	<3	16	11	20	137
Baseline			<1.0	<3	21	11	24	139
Day 1	Dosing Day		Not tested, per protocol					
Day 4					16			136
Day 8			Not tested	Not tested	14	13	23	147
Week 2			2.5	<3	18	12	21	159
Week 3								
Week 4	STOPPED PROPHY HERE		1	<3	16	13	19	146
Week 5	light gray is remote visit		1.6	<3	19	15	21	163
Week 6			3.7	<3	20	15	22	148
Week 7			4.8	<3	28	17	24	138
Week 8			5.7	3.1	22	12	21	158
Week 9			4.3	<3	24	15	23	128
Week 10			5.4	<3	38	20	26	148
Week 11			Cancelled	Cancelled	43	21	26	138
	Started 30 mg BID steroids here (example of how this could be added then tracked)							
Week 12			2.6	<3	35	13	38	145
Week 13			4.3	<3	30	13	47	155
	This type of highlighting signified a AE							
Week 14			5.5	<3	30	9	51	158
	Tapered steroids to 20 mg BID (example)							
Week 15			6.6	3.7	26	11	44	175
Week 16			7.3	3	36	12	49	190
Week 17			5.5	3.5	42	14	52	196
	Tapered steroids to 15 mg BID (example)							
	Started Tacro 2 mg BID (example)							
Week 18		8.6	6.1	3.8	41	16	55	220
		7.7	NA					
Week 19		5.7	8.4	3.8	53	15	55	199
Week 20			6.3	4.3	47	14	59	203
Week 21		6.7	7.3	4.6	42	13	69	227

	Tacro 3 mg BID							
Week 22		17.9	7.5	4.6	41	13	67	194
	Tacro 2.5 mg BID							
Week 23			5.7	4.8	43	14	73	225
Week 24		8.2	5.3	4	40	12	77	238
Week 25			UNAVAIL	UNAVAIL	44	13	71	222
Week 26			8.1	4.8	37	15	63	250
Week 27		7.9	42.4	40.5	53	17	74	270
Week 28		14.8	5.8	3.5	55	18	73	267
	Tacro 3 mg in AM and 2.5 mg in PM							
Week 29		9.2	7.7	4.1	43	15	69	239
	Tacro 3 mg BID							
Week 30		7.3	8.7	5.3	55	22	69	288
Week 31		8.3	7.1	5	48	15	69	258
	Tacro 3.5 mg BID							
Week 32		12.9	5.4	3.5	45	16	62	252
Week 33		10	8.4	5.9	52	17	84	268
Week 34			9.6	4.9	53	19	79	268
Week 35		15.3	6.1	3.4	51	18	85	298
	Procedure (example)							
	AE (example)							
Week 36		10.2	11.8	6.7	41	19	63	242
		11.4						
Week 38			7.4	5.5	48	22	60	246
		9.2						
Week 40		8.3	7.2	4.6	37	18	53	218
Week 42			11.9	5.8	36	22	39	219
		9.5						
Week 44			12.3	5.8	31	28	29	251
		14.4						
Week 46		11.3	Pending		33	30	23	241
Week 48			5.6	4.1	19	21	19	214
Week 50		9.7	6	4.1	18	19	18	187
Week 52		11.6	3.7	<3	14	17	16	168

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