# ASGCT and FDA Liaison Meeting

1-4 PM Eastern Time
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# Innovative Clinical Study Design for Gene and Cell Therapies

Jake Elkins, MD
Head, Clinical Sciences
Sarepta Therapeutics

# Problem Statement:

- **Genetically-targeted therapies hold great promise for many serious diseases of high unmet need.**
- **Clinical development of these therapies, however, often face a unique combination of challenges:**
  - *Rare/ultra-rare disease prevalence – compounded by:*
    - *Genetic heterogeneity, may require separate gene-targeting constructs*
    - *Phenotypic heterogeneity/broad clinical spectrum of disease*
    - *Serologic exclusions based on vector immunogenicity for gene therapies*
    - *Potential for manufacturing process changes after FIH but prior to approval*
- ***These challenges can result in severe limitations in eligible patient numbers that require innovative solutions to trial design, analysis, and evaluation of success, in order to achieve therapeutic progress for these diverse groups of patients.***

- ***We suggest utilizing three innovations—combined endpoints; blind-start study design with comparison to pre-treatment baseline; and greater standardization around the use of gene-expression biomarkers and/or intermediate clinical endpoints to enable accelerated approval when appropriate.***

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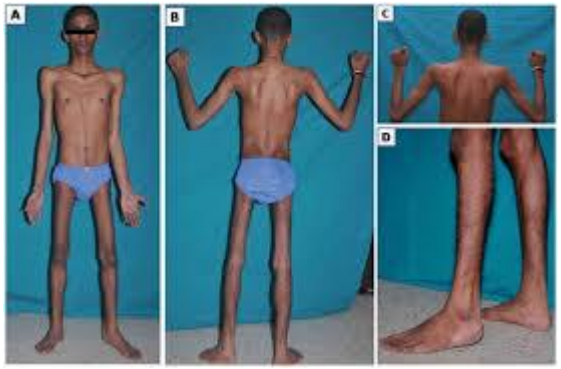
# Example: Limb-Girdle Muscular Dystrophy

- Rare, monogenic disorders characterized by progressive muscle loss, leading variably to loss of ambulation/ upper extremity paresis, cardiopulmonary insufficiency, and early mortality
- No current disease-modifying therapies
- Over 30 different genetic subtypes involving different myocyte proteins, many targetable with current gene therapy constructs capable of full native protein restoration
- Some genetic subtypes ultra-rare
    - Younger ambulatory patients within these subtypes, who may benefit the most from early intervention, may have global prevalence < ~ 20 patients identifiable for clinical trials, resulting in clinical trials with less < 10 subjects possible

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# Impact on Clinical Trial Design:

Traditional Design Process

1. Identify primary endpoint to measure therapeutic hypothesis
2. Define clinically-meaningful effect size
3. Estimate sample-size to achieve power >80% with alpha of 0.05
4. Conduct parallel group study with randomization to balance groups

Sample-size Limited Design Process

1. Trial size fixed by patient population size rather than power calculations
   - Use of $P<0.05$ typically no longer appropriate as success criterion.
   - Ranking of endpoints may further increase risk of false negatives
   - Greater need to rely on “totality of data” to interpret trial outcome
2. Randomization of small samples cannot be assumed to balance measured/unmeasured confounders
   - High risk of confounding for between group comparisons
   - Greater need to aggregate data from multiple sources (external controls/change from baseline trajectory/within-study controls) to make efficacy inferences

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# Innovation 1: Use of combined endpoints to increase study power

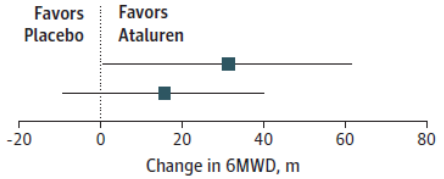
- Assessment of efficacy in clinical trials generally relies on selection of a single primary endpoint that “is capable of providing the most clinically relevant evidence” (ICH E9)
  - Existing FDA guidance on use of multiple endpoints is primarily focused on control of Type 1 error/sequential testing of multiple endpoints, as opposed to maximizing power under conditions of sample size restriction
- Global assessment of treatment effect can be obtained by aggregating data across multiple individual efficacy endpoints (either as a subject level composite or analysis across endpoints)
  - If there is some treatment effect on several prespecified endpoints, the aggregated endpoint will generally have a better effect-to-variance ratio than an individual endpoint – resulting in increased statistical power
  - Limitation of technique is generally related to interpretation when combining endpoints across different scales. When test of aggregated endpoint is positive, no direct conclusions can be made on the individual component endpoints.
- *In settings where sample size is limiting, gain in statistical power from endpoint aggregation outweighs price of less detailed inference of the individual endpoints*

# Innovation 1: Use of Combined Endpoints - Example

Figure 1. Conventional End Point–Specific Analysis

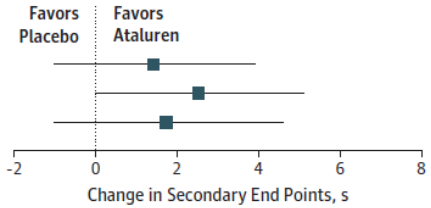
A 6MWD

| Study | Estimate (95% CI) |
|---|---|
| NCT00592553 | 31.3 (0.9 to 61.7) |
| NCT01826487 | 15.4 (-9.2 to 40.0) |




B NCT00592553

| Outcome | Estimate (95% CI) |
|---|---|
| 10-m Walk or run | 1.4 (-1.0 to 3.7) |
| 4-Stair climb | 2.4 (0.0 to 4.8) |
| 4-Stair descend | 1.6 (-1.0 to 4.2) |




C NCT01826487

| Outcome | Estimate (95% CI) |
|---|---|
| 10-m Walk or run | 1.2 (-0.4 to 2.7) |
| 4-Stair climb | 1.8 (0.1 to 3.6) |
| 4-Stair descend | 1.8 (0.0 to 3.7) |

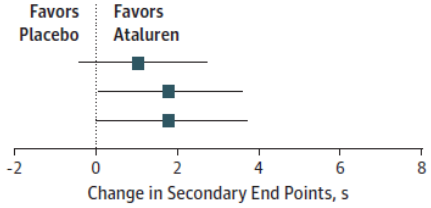
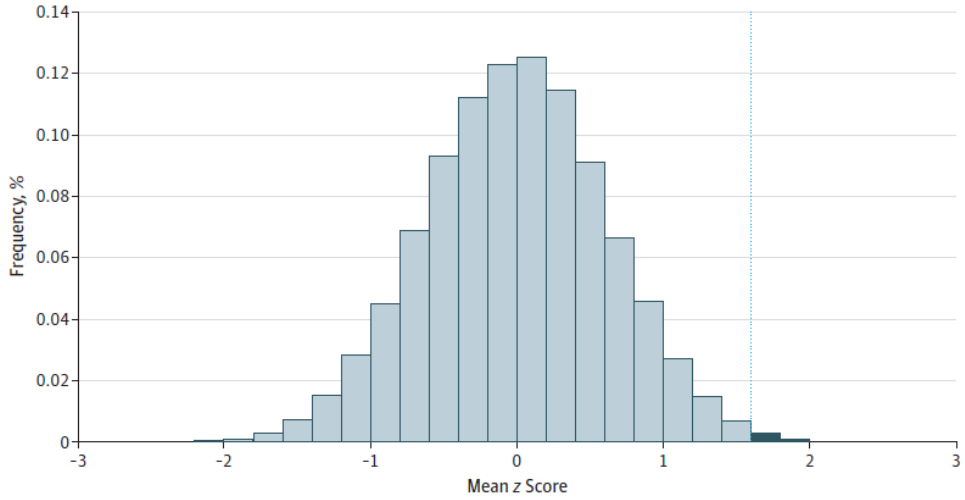



Figure 2. The Distribution of Simulated Mean Observed *z* Score Assuming No Treatment Effect




***Li et.al, Assessment of Treatment Effects with Multiple Outcomes in 2 Clinical Trials of Patients with Muscular Dystrophy, JAMA Network Open, 2020***

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# Innovation 2: A novel Blind Start study design comparing pre/post treatment effects

- Mucopolysaccharidosis VII (MPS VII or Sly syndrome) is an ultra-rare lysosomal disorder.  Vestroindase alpha (Mepsevii) is a recombinant enzyme replacement therapy developed for disease modification
- Development program restricted to 23 patients total based on rarity of condition
- Pivotal Design: N=12 were randomized to 1 of 4 blinded groups, each crossing over to active treatment in a blinded fashion at different timepoints with efficacy analysis comparing the last assessment before crossover to after 24 weeks of treatment.

# Delayed start design to minimize bias for analysis of within subject change from baseline

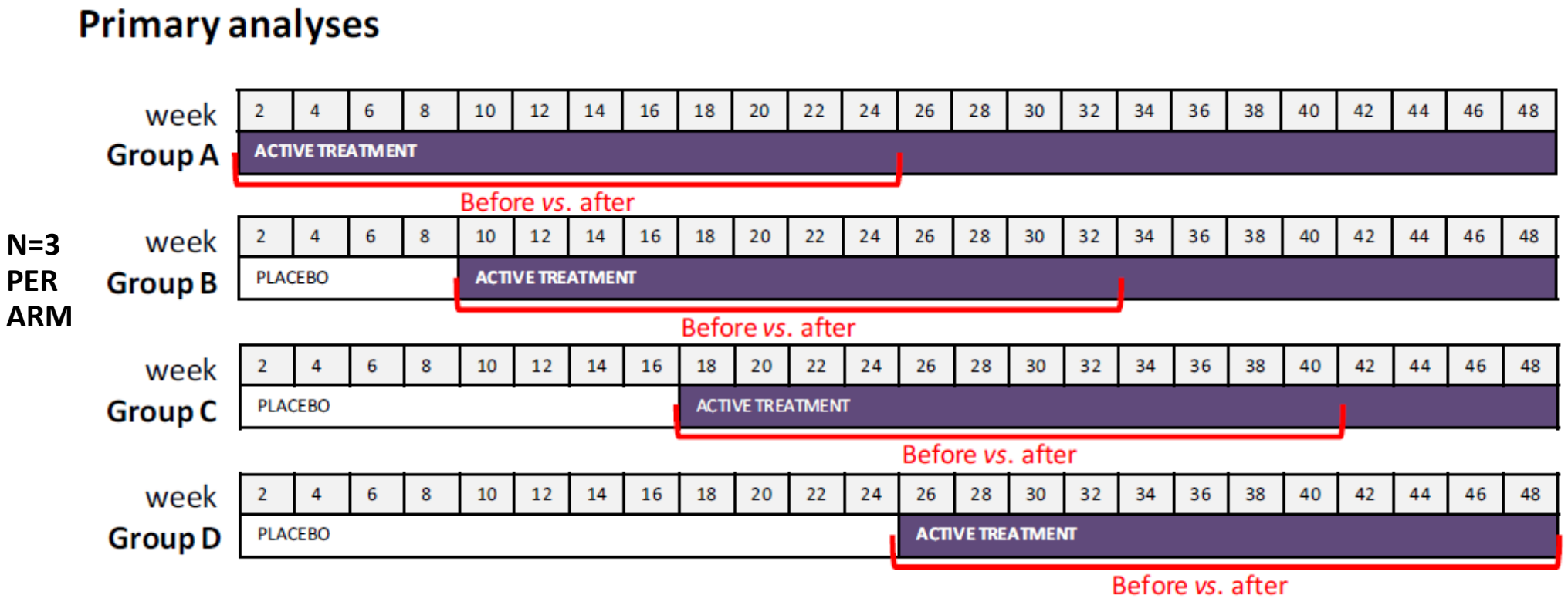


**Fig. 1.** Blind Start study design.

- All subjects contribute to estimate of treatment effect
- Use of blinding to adjust efficacy assessment for placebo effect/expectation bias and better approximate efficacy estimates from parallel group designs

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# Recommendations: Combination endpoints and Blind Start study design

1. Existing Rare Diseases[1] guidance could be strengthened through addressing development situations characterized by sample size restriction:
    - Include how and when the agency deems it appropriate to incorporate comparison of pre- and post-treatment disease course into evaluation of efficacy to complement use of external or concurrent controls.
    - Acknowledge the shortcomings of randomization with small sample sizes and clarify methods for aggregating data across concurrent and historical controls and pre-treatment disease trajectory.
2. Draft guidance on Demonstrating Substantial Evidence of Effectiveness[2] and/or Multiple Endpoints in Clinical Trials[3] would benefit from expanded discussion of the methods the agency finds acceptable for assessing the totality of evidence from well controlled trials (including considering the consistency of data across multiple clinical and biologic endpoints) to establish efficacy.
    - Existing guidance mentions potential to use p-values > 0.05 as a success criterion, but not clear how this would be implemented or justified
    - Totality of evidence from multiple endpoints, which can be combined with stat methods to quantify the chance of occurrence under the null hypothesis of no treatment effect.

[1] Human Gene Therapy for Rare Diseases, https://www.fda.gov/media/113807/download

[2] Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry, https://www.fda.gov/media/133660/download

[3] Multiple Endpoints in Clinical Trials Guidance for Industry, https://www.fda.gov/media/102657/download

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# Innovation 3: Integration of gene-expression biomarkers into clinical trial design of gene therapies for Accelerated Approval

- Current law establishes an accelerated approval pathway in some disease conditions based on using a "surrogate endpoint that is reasonably likely to predict clinical benefit…taking into account the availability or lack of alternative treatments."
- In practice, there remains a high degree of subjectivity in determining the conditions under which a surrogate endpoint is considered "reasonably likely to predict clinical benefit" and applied through the accelerated approval pathway. Clarity from the Agency would be helpful on the data needed for a gene therapy with a projected durable effect before approval through the accelerated approval pathway, and the data needed to assess durability after product approval.
- Given the development challenges of genetically-targeted therapies, greater clarity on integration of gene-expression biomarkers is one of the most important priorities to enable the development of new treatments to reach patients in need.

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# Use of Biomarkers, Surrogate Endpoints, Intermediate Clinical Endpoints for Accelerated Approval

- Facilitates patient access by getting products approved sooner than it would take for full approval, with post-approval confirmation of clinical benefit based on clinical endpoints that may take longer (sometimes years) to evaluate.
- For gene therapy: "**We're going to be looking at accelerated approval endpoints for earlier approval on questions of efficacy with more vigorous long term follow up**." - *Former FDA Commissioner Scott Gottlieb at the Jan 2018 World Economic Forum*
- "Accelerated approval pathway may offer a faster route to approval for new treatments, including potentially curative benefits in significant, unmet medical needs. But the pathway also offers additional authorities for FDA to require post market follow-up studies. **Since many of the risks associated with gene therapy products relate to questions about the product's durability and potential for rare instances of off-target effects, it may not be feasible to conduct pre-market trials that address all these theoretical risks in any reasonably sized study**. - *Peter Marks and Scott Gottlieb Joint FDA Statement, January 15, 2019*
- Tecartus, approved in July 2020, is the first and only accelerated approval for a gene therapy product and leverages an intermediate clinical endpoint
- FDA's Guidance on Human Gene Therapy for Hemophilia[1] includes recommendation for use of accelerated approval leveraging factor activity. **ASGCT recommends also using shorter term ABR as an intermediate clinical endpoint sufficient to support accelerated approval, with longer term ABR provided post approval.**

[1] Human Gene Therapy for Hemophilia, https://www.fda.gov/media/113799/download

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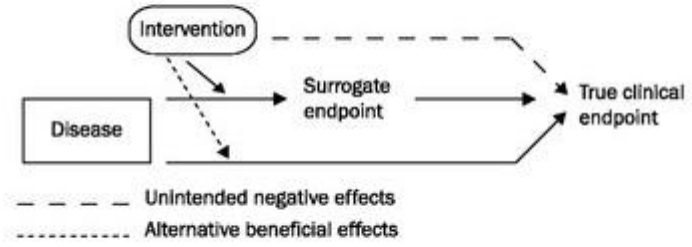
# Gene therapies frequently enable a more direct assessment of causality in the evaluation of surrogate endpoints

- Traditional interventions often have unanswered questions about surrogates:

1. Relationship of surrogate to clinical outcome
2. Effect of intervention on outcome that is unrelated to the surrogate

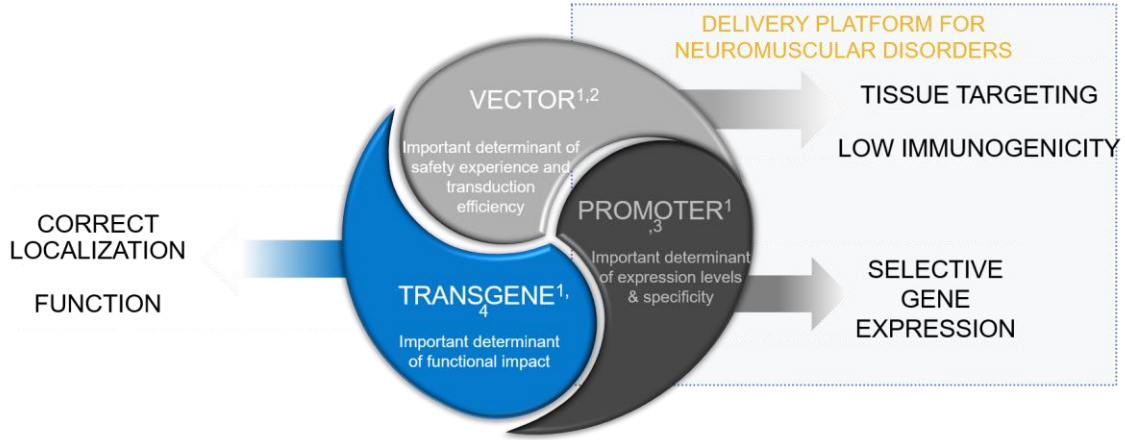
**Additional Reasons For The Unreliability Of Proposed Surrogates: Disease Processes Having Multiple Causal Pathways And Interventions Having Mechanisms Of Action Independent Of The Disease Process**




**SOURCE:** T.R. Fleming and D.L. DeMets, "Surrogate End Points in Clinical Trials: Are We Being Misled?" *Annals of Internal Medicine* 125, no. 7 (1996): 605–613.

- Genetically-targeted therapies address these issues around causality based on the strong biological data establishing that:

1. Effects of therapy are mediated through protein expression.
2. Protein expressed is causally related to clinical outcome by human genetic data



# Integration of gene-expression biomarkers into clinical trial design of gene therapies

- Key criteria for evaluating gene-expression as surrogate endpoint reasonably likely to predict clinical benefit
  1. Construct is designed to restore the native protein
  2. Gene expression is documented in the relevant tissue and intracellular location at levels expected to be clinically meaningful
  3. Gene expression is documented to result in functional protein as defined by downstream interactions and localization
- Definitive correlation of gene expression with clinical outcomes is long-term goal but should not be pre-requisite for initial acceptance of a surrogate endpoint in serious diseases of high unmet need
  - Functional outcomes can often require years of follow-up for definitive evidence of treatment effect and durability, which can obviate goal to "provide patients with serious diseases more rapid access to promising therapies."

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# **Case Study: Tecartus** (CAR-T Cell Therapy) for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma (MCL)

| Trial Design | Efficacy | Durability | Unmet Medical Need |
|---|---|---|---|
| Single-arm, open-label, N=60 with refractory or relapsed MCL who were followed for at least 6 months after their first objective disease response. | Single Phase 3 study with supporting data provided from 3 ongoing phase 1/2 studies<br><br>First **accelerated approval** for a gene therapy; relied on an **intermediate clinical endpoint** (ORR and CR) | **<u>According to FDA Review Documents –</u>**<br><br>**Durability of efficacy** based on 6-months follow-up after objective response rate (ORR) achieved **to be further evaluated post-approval in the confirmatory study** with a minimum of 18-month follow-up. “The six-month ORR and CR [complete response] rates are intermediate clinical endpoints that are reasonably likely to predict a clinical benefit…” | Several available therapy options at the time of approval. |

# **Case Study:** Hemophilia

- Existing FDA guidance[1] on gene-expression biomarkers as surrogates in hemophilia identifies three areas of concern about use of factor activity levels as surrogates in gene therapy programs to support accelerated approval:
    1. Discrepant results in factor assays after GT treatment vs. recombinant or plasma-derived treatment
    2. Lack of molecular characterization of protein translated *in-vivo*
    3. Uncertain impact of genetically-engineered modifications to increase factor activity
- Recommendation proposed by FDA: Provide evidence, specific for each GT, that factor levels correlate with clinical outcomes through long-term clinical observation.
- Important distinction between concerns regarding assays and protein characterization that are addressable through technical assessment as compared to concerns (e.g. modifications to the native protein) that may require additional clinical data validation.
- More generally, requests for long-term clinical data vs. technical/biological data to validate gene-expression as a surrogate endpoint create uncertainty about how to support an accelerated approval without first conducting traditional clinical efficacy trials.

[1]Human Gene Therapy for Hemophilia https://www.fda.gov/media/113799/download

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# Recommendations: Accelerated Approval

**ASGCT provides recommendations to increase regulatory predictability and certainty.**

1) Demonstration that a gene therapy can restore a functional version of a native protein that is known to be causative for the target disease should be considered a surrogate endpoint that is reasonably likely to predict clinical benefit.
   - **Guidance[1] should be expanded to standardize and clarify how such measures of gene expression as surrogate endpoints can support accelerated approval.**
2) Shorter term improvement in clinical benefit should be considered sufficient to leverage as an intermediate clinical endpoint to support accelerated approval.
   - **Guidance should be expanded to articulate the use of intermediate clinical endpoints with continued clinical assessment post approval**
3) We recommend that FDA **adopt the use of tools such as modeling and simulation, and Bayesian Statistics in supporting the understanding of durability leveraging shorter term data**, while continued clinical assessments can continue in the post approval setting (e.g. while a therapy may spare loss of life early in a condition (such as SMA), approval should be provided long before durability is established)
4) **Incorporate patient voice** into the determination of unmet need, or unrealized unmet need into benefit/risk decision making to support decision to accelerate approval. Greater clarity is needed overall on how to demonstrate a "meaningful advantage over other therapies" in the context of accelerated approval.

[1]Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, https://www.fda.gov/media/120267/download

# Utilizing gene-expression biomarkers

Manufacturing

- It is common for manufacturing process changes to occur between the initiation of a gene-therapy clinical development program and the commercial launch. In many development programs, the preclinical comparability of the manufacturing processes is well-characterized, and gene expression biomarkers establish similar expression in relevant target organs between product batches in clinical trials.
- Use of gene-expression biomarkers can be used to bridge data across changes in manufacturing processes after initiation of clinical development

Clinical data

- Personalized medicine approaches for these diseases require multiple variations of a therapy that are mutation specific. In these cases, it may not be feasible to repeat clinical efficacy studies for each variation of the therapy, and greater clarity is needed from the agency on how to bridge data across these variants to facilitate the development of personalized medicine approaches for rare, genetically-heterogeneous disorders.
- Use of biomarker surrogates is especially important in cases when a single rare disease phenotype is caused by multiple genetic mutations.

# Recommendations: Utilizing gene-expression biomarkers

- We recommend that FDA provide parameters for how sponsors may use gene expression biomarkers obtained with the different manufacturing processes along with pre-clinical comparability data to support approval or licensure.

- We recommend the agency develop a guidance document to provide clarity from the agency regarding how to bridge clinical and CMC data across variants of rare, genetically-heterogeneous disorders as described in Section 529A of the FFDCA.

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# Thank you