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Reassessing the acceptability of risk of death associated with gene therapy for Duchenne muscular dystrophy: A qualitative study to inform updating a quantitative instrument

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Introduction

Background:

In 2017/2018, Parent Project Muscular Dystrophy (PPMD) & RTI International conducted a study on risk tolerance for gene therapy (GT) for Duchenne muscular dystrophy (Duchenne). We assessed maximum acceptable risk (MAR) of death in U.S.-based adults with Duchenne and parents [1, 2].

Duchenne is a progressive, life-limiting condition. GTs currently under trial could be disease modifying, but not curative. GT trials over the past 5 years have reported serious adverse events, been subject to clinical holds, and resulted in one death in late 2021 [3, 4].

Given advances in GT, new approved treatments, and a lack of data from individuals in the United Kingdom, we initiated a follow-up study with Duchenne UK and PPMD.

Our prior study did not include clinicians. Clinician attitudes are important given their critical role on clinical trial teams, and ultimately in shared decision making for approved therapies.

Objective:

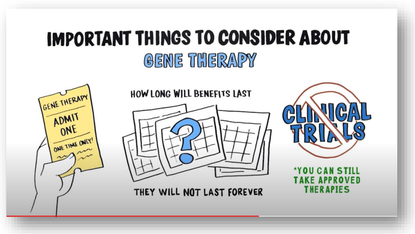
Use results from mixed-methods research with adults and parents in the U.K. and clinicians in the U.K. and U.S. to ensure suitability and inform critical revisions to our 2017/2018 MAR instrument

Methods

- Brief survey and three focus groups conducted via Zoom:
  - 2 with adults in the UK who have children with Duchenne
  - 1 with adults in the UK with Duchenne
- Brief survey and clinician interviews conducted via Zoom:
  - Clinicians with experience caring for individuals with Duchenne in the U.K. or in the U.S.
- Experienced researchers employed semi-structured guides. Data were coded using a matrix-based approach.
- Non-research engagement with the multidisciplinary advisory committee and GT experts regarding the state of science
  - Expert Advisory Committee members: Representatives from Audentes/Astellas Gene Therapies, Pfizer, REGENXBIO, Sarepta Therapeutics, Solid Biosciences, Vertex Pharmaceuticals; clinician experts; adults with Duchenne; parent caregivers
- Results were used to inform additions and changes to the 2018 version of the instrument. Changes were critically evaluated to determine importance.

Prior (2018) Survey

- Assessed MAR for death from gene therapy
- Benefit described as “help people’s muscles, lungs, and hearts work better for a longer amount of time”
- Cause of death described as “serious immune reaction”
- Duration of benefit described as uncertain, up to 10 years
- Limited to one-time use
- Survey teaching section was augmented using a white board video



Threshold example item, 2018 survey:
Your doctor tells you about the risk of gene therapy. 1 out of 2,000 people with Duchenne will die from using gene therapy. The person will die within a week after using it. The other 1,999 people will not die from gene therapy.

Results

Parents and adults with Duchenne (n=16)

- Of 12 parent participants, 10 had ambulatory children and 2 non-ambulatory. Parents reported that 6 children had participated in a clinical trial (1 in a GT trial).
- Of 4 adult participants, all were non-ambulatory. Three adults had participated in a clinical trial (0 in a GT trial.)
- Parent respondents reported at least “some” understanding of GT, while adults reported less understanding (Figure 1).
- Most anticipated a medium or large amount of benefit from GT in the next 10 years. None expected a cure (Figure 2).
- Most expected slowing/stopping progression of muscle, cardiac, and pulmonary decline.
  - These benefits were considered highly meaningful.
- Respondents described considerable uncertainty about GT risks and benefits.
- Most indicated that some risk for GT-associated death would be acceptable given the progressive nature of Duchenne.
- For some respondents, particularly adults with Duchenne, the risk of death was not the worst outcome; instead, additional disability or loss of existing, highly-valued skills were worse.
  - Some reflected concern about taking any new treatment based on unwillingness to threaten current status.
- When prompted on potential limitations of GT, most respondents expressed concern about the uncertain and limited benefit duration and one-time dosing.
- Some respondents expressed optimism that scientists would overcome current limitations of GT.

Figure 1. Which best describes your understanding of gene therapy?

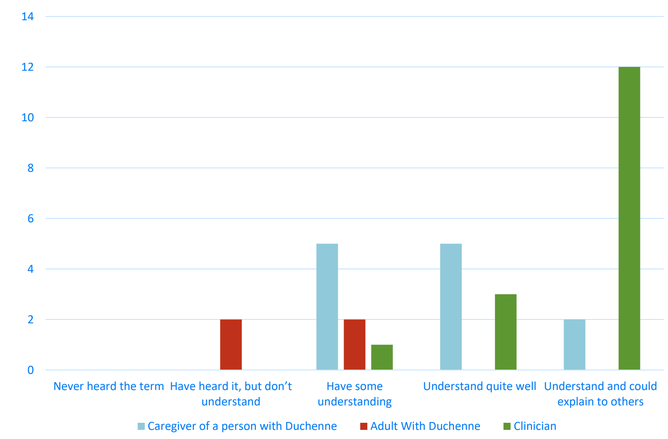
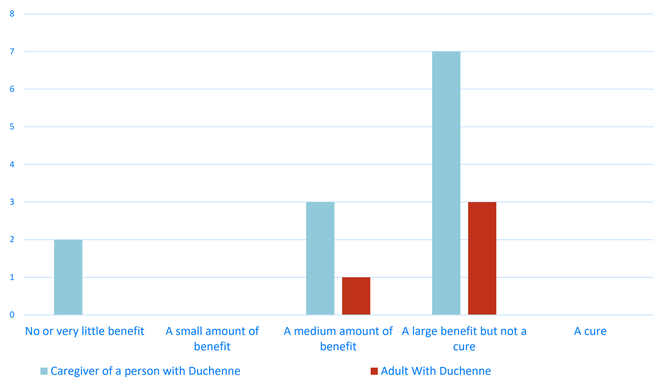


Figure 2. Based on your current understanding of gene therapy, which best shows your expectation about the benefits that people with Duchenne may get from gene therapy in the next 10 years?



Clinicians (n=16)

- All respondents were part of a trial team for one or more Duchenne clinical trials.
- 5 have experience in a Duchenne GT trial.
- Most self-rated their understanding of GT as “understand and could explain to others”, as shown in Table 1.
- Expected benefits of GT varied, spanning modest to curative.
- Expected duration of benefits ranged from 1 year to lifelong.
- Many described concern that patients and families had inappropriately high expectation of GT benefits.
- Clinicians referenced organ failure as the greatest risk of GT.
  - Most risks were anticipated to be mild to moderate, with a low risk for severe adverse events, including death.
- Most indicated acceptability of some GT-associated risk of death given the progressive nature of Duchenne.
- Clinicians reported that potential benefits would need to outweigh risks (so severe risks would not be acceptable for minor benefits).
- Some clinicians noted that patient/family tolerance for risk was most important in treatment decision making.

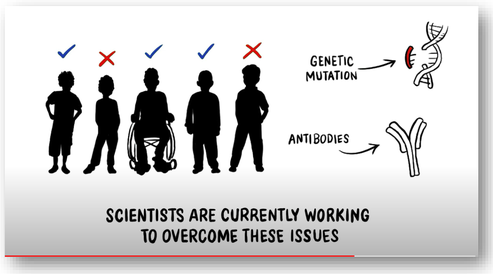
Instrument modifications

Based on these results, we added new measures as potential predictors of MAR:

- Knowledge of gene therapy
- Optimism regarding new therapy development

As exploratory domains, we added respondent-reported novel items on:

- Uncertainty
- Satisfaction with current treatment
- Potential for getting worse when trying a new therapy
- Comparison of risks: kidney failure requiring lifelong dialysis vs death



Updated Whiteboard video available at https://youtu.be/F_6Jmmuv8dE

We implemented several state-of-science updates, including current limitations in eligibility and describing organ failure as cause of death.

Revised threshold example item:
Your doctor tells you about the risk of gene therapy. 1 out of 2,000 people with Duchenne will die from using gene therapy because of organ failure (such as kidney or liver failure). People who experience organ failure from using gene therapy are treated in the hospital and will die within one month after receiving the therapy. The other 1,999 people will not die from gene therapy.

Discussion

- Our expert engagement and qualitative data indicate that our 2017/2018 survey remains relevant and suitable for use in the U.S. and U.K. after updates to current state-of-science. Updates are important given advances in research and clinical management.
- Mixed-methods research with clinicians, parents and adults with Duchenne resulted in additions to the instrument.
- In late 2022 we will begin recruitment to assess current MAR for GT in the U.S. and the U.K.
- Future research should assess MAR for GT among clinicians.

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