What would help or hinder patient participation in mitochondrial disease clinical trials?

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As clinical trials gear up with the aim of attaining the first FDA-approved treatments for mitochondrial disease, a new study reports for the first time what patients and families say would motivate them for or against participating in such research trials.

Based in malfunctions in mitochondria, the tiny structures within cells that act as biological batteries, mitochondrial disease is a highly variable collection of energy deficiency disorders that can affect nearly any and all organs and systems—at any age. Scientists have discovered approximately 300 different gene disorders that collectively contribute to the broad class of primary mitochondrial disease.

"The inherent complexity of mitochondrial disease gave rise to our central finding: the need to understand patients' perspectives in identifying their most prevalent and disabling symptoms," said study leader Marni J. Falk, MD, executive director of the Mitochondrial Medicine Frontier Program at Children's Hospital of Philadelphia (CHOP). "We can now incorporate these key insights as we design clinical trials, to measure clinical outcomes that are meaningful to patients and families."

Falk and colleagues published their findings online May 17 in *PLOS ONE.*

"When we asked patients to specify how many health problems they had, they reported an average of 16 major clinical symptoms, and some had as many as 35," said Falk. The most frequent reported symptoms were muscle weakness, chronic fatigue, exercise intolerance, gastrointestinal issues and balance problems, with parents of pediatric patients also concerned with developmental delay.

One surprising finding was that more severely affected patients—those at higher risk of stroke, kidney failure and death—were not necessarily more tolerant of risk in clinical trials than patients with less severe disease. "In the medical literature, mitochondrial disease is often portrayed as uniformly devastating," said Falk. "But in day-to-day life, a patients' experience may be quite variable, even when living with a severe, chronic condition. So patients and families may be more interested in finding therapies that improve their resilience in coping with a chronic disease and ability to function in their daily lives."

The researchers conducted online electronic surveys in two patient cohorts. The single-center discovery cohort comprised mitochondrial disease patients at CHOP, evenly divided between children and adults, with 30 respondents out of 67 invited. An independent replication cohort consisted of patients with primary mitochondrial disease from an NIH-supported national contact registry, the Rare Disease Clinical Research Network, with 290 respondents out of 1,119 invited.

When asked to rate factors that would likely motivate them to participate in a clinical trial, patients preferred a study drug that could be self-administered, such as pills, vitamins, antioxidants, and natural or plant-derived compounds. They also preferred daily treatment, guaranteed access to the treatment during and after the study, short travel distances to the study site, and participation in late-stage (phase 3) clinical trials.

Factors that would make patients less likely to participate were taking a

new study drug not previously studied in people, having to discontinue their current medications, experiencing disease progression, needing to undergo daily phlebotomy, requiring intravenous infusions and requiring patient payment for trial participation. There was no difference in trial preferences reported between the adult and pediatric patient groups.

"When we ask the Food and Drug Administration what they require to determine if a tested drug is successful in a clinical trial, we can summarize their benchmark as being able to demonstrate improved patient survival, feeling and function," said Falk. "Endpoint data such as laboratory values or biomarkers are important, but not particularly meaningful as a primary outcome measure to the FDA or to patients' sense of well-being."

The study showed that patients are not intuitively invested in important elements of robust research study design such as including a placebo control, blinding everyone to which therapy is being given and randomizing patients to treatment or placebo. However, researchers and the FDA recognize that such methodologic factors are key elements in objectively finding effective treatments.

Falk added that "these study results tell researchers and clinicians that we have more work to do in terms of patient education—we need to effectively explain how to best design rigorous, effective clinical trials, while at the same time responding to patient priorities and needs. One important factor in both patient education and meeting patient needs, she added, is forming strong partnerships among researchers, patients and patient advocacy organizations.

"Clinical trials are still a new experience for many patients with mitochondrial disease," said Falk, who notes that until now, a patient's only option has been to rely on empiric "cocktails" of unstandardized and untested vitamins and supplements. "While such approaches may

well hold therapeutic value, a properly designed clinical trial is needed to ultimately identify safe and effective therapies, to optimize doses, and to learn which of each mitochondrial disease patient's symptoms are improved with each treatment," she added.

Finally, said Falk, the findings on patient preferences and motivations in mitochondrial medicine may be relevant to patients with other rare complex disorders. "Understanding and applying patient preferences to trial design and outcome selection are essential to achieve successful therapies for all of the rare, complex diseases that are now readily recognized due to advances in genetic diagnostics. Precision diagnosis is essential, but no longer sufficient. Patients rightfully hope and expect that this knowledge will be translated into precision therapies that improve the aspects of their disease they view as most essential to their overall well-being."

More information: Zarazuela Zolkipli-Cunningham et al, Mitochondrial disease patient motivations and barriers to participate in clinical trials, *PLOS ONE* (2018). DOI: 10.1371/journal.pone.0197513

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