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The Changing Landscape of Clinical Trials for Mitochondrial Diseases: 2011 to Present

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Abstract

We reviewed the status of interventional clinical trials for primary mitochondrial diseases. Using national and international search engines, we found 48 randomized controlled trials (RCTs) registered as of May 15, 2019. Consilience between lay and professional mitochondrial disease communities to engage in RCTs has increased, as has progress in developing new disease and treatment biomarkers and potential therapies. The continued advancement of general knowledge of mitochondrial biology has fostered appreciation for the fundamental role mitochondria play in the etiopathology of other rare and common illnesses, emphasizing the therapeutic potential of mitochondrially-targeted small molecules for an increasing spectrum of human diseases.

1. The original problem.

In 2011 we reviewed the status of interventional clinical trials for primary mitochondrial diseases (PMDs), noting the intellectual chasm between nonclinical research on mitochondrial biology generally and the paucity (and failure) of randomized controlled trials (RCTs) for PMDs (Stacpoole, 2011). At that time, using PubMed as the search engine, we found only 10 RCTs that focused on PMDs in which a molecular genetic diagnosis was an inclusion criterion. All were single-center trials that evaluated either a small molecule xenobiotic or one or more naturally occurring products. None reported funding support from pharmaceutical or biotechnology sources. At least one of these trials ended prematurely, in large part because of reluctance by the affected lay community to participate in a placebo-controlled trial that might temporarily stop them from using nutritional supplements, believing that would jeopardize their clinical status. Most importantly, none of the trials led to Food and Drug Administration (FDA) approval of the intervention.

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This analysis raised several questions. Why, given the long and robust history of research in mitochondrial biology and disease, had the modern era made such paucity progress in translating scientific discoveries into effective treatments? Indeed, although PMDs are among the commonest group of human genetic illnesses (Wallace, 2018), there are no FDA-approved treatments for any PMD.

Why was there evidence of such pushback from the lay community to engage in RCTs? Here, the likely answer is grounded in the historical reliance on questionable medical advice. Recognizing the essentiality of numerous vitamins and cofactors in enabling mitochondrial metabolic reactions and energy production, the medical community evolved various nutritional “cocktails” to treat PMD patients, justified primarily on the rationale that such naturally occurring substances should not be harmful and might be therapeutic. Consequently, both the scientific and lay communities became addicted to these concoctions, none of which has endured the ethical or scientific rigor of an RCT. Thus, affected patients and families faced an emotional dilemma when trying to navigate the straits of placebo-controlled clinical trials, in which participation could require modification or temporary withdrawal of their cocktail.

Finally, given the diversity of PMDs and magnitude of the affected population, what accounted for the slow entry of the drug industry into this huge market? From a historical perspective, large pharmaceutical companies saw little financial return from investing in individual rare diseases, with small patient markets. This calculus changed completely with passage of the Orphan Drug Act (ODA) of 1983 (Haffner, et al. 2002). By this law, congress defined a rare disease as one that occurs in < 200,000 patients in the U.S. The ODA provided incentives associated with the designation of a so-called “orphan drug,” including a 50% tax credit for clinical research and testing expenses; a waiver of use fees by the sponsor; and seven years of marketing exclusivity upon FDA approval of a specific orphan drug for a specific indication. As a result, since 1983, the FDA has approved over 600 orphan drug indications from over 450 distinct drug “products,” defined as drugs having the same active ingredient and formulation (Lanthier, 2017). An early industry entry for PMDs was a start-up company, Edison Pharmaceuticals, focused on the synthesis and clinical testing of a coenzyme Q₁₀ analog, EPI-743 (Enns, et al. 2012).

2. How the problem is being addressed.

From the above it is clear that progress in developing treatments for PMDs depends on many factors. These include attitudinal changes by the scientific, industry and lay communities regarding the importance of RCTs in advancing new therapies; an expansion of funding opportunities for conducting FDA-compliant clinical trials that could lead to new drug applications and approvals; validation of primary efficacy endpoints used in RCTs; regulatory flexibility in evaluating data from PMD trials; and expansion of the pharmaceutical repertoire of potential therapeutics.

2.1. The changing clinical trials landscape

How has patient-oriented research on PMDs evolved since 2011? We reviewed published data from PubMed, clinicaltrials.gov and the clinical trials registries of the WHO

International Clinical Trials Registry Platform, the European Union, the Japanese National Institute of Public Health, and the International Standard Registered Clinical/social sTudy Number from February 11, 2011 through May 15, 2019 for information on the following search terms: mitochondria; mitochondrial diseases; clinical trials (mainly open label, nonrandomized); RCTs (mainly specifying a general disease phenotype, e.g., mitochondrial myopathy, rather than a genetically discrete group) and RCTs in primary (aka genetic) mitochondrial diseases. Fig. 1 summarizes the differences in publication citations, according to specific categories. A major inflection point differentiates the number of clinical trials identified between the time periods. There is a 2-fold increase in RCTs for PMDs between 2011 and 2019, using only the PubMed search engine, and an almost 5-fold increase in RCTs for PMDs between 2011 and 2019, when including international registries. Using the expanded search engine list, we analyzed RCTs according to disease category. We divided RCTs into two domains: trials focused on treatment of syndromic complications of PMDs, such as myopathies, lactic acidosis or Leigh syndrome that are characteristic of multiple, discrete genetic etiologies (so-called “syndromic” mitochondrial diseases) and RCTs conducted in PMD patients of a specifically defined genotype, such as Leber’s Hereditary Optic Neuropathy (LHON) or pyruvate dehydrogenase complex (PDC) deficiency (Table 1). Most of the 35 unspecified RCTs defined “mitochondrial diseases/disorders” broadly. In contrast, the 48 RCTs in “genetic” mitochondrial diseases included patients with either a single gene locus mutation (e.g. Friedrich’s Ataxia, Barth Syndrome) or functionally closely related mutations (e.g. PDC deficiency, Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) deficiency). Supplemental Table 1 provides additional descriptive information of these 83 trials, including specific interventions, primary endpoints, funding sources and activity status.

Of particular interest was that most of the RCTs listed in Table 1 and Supplemental Table 1 were mid-to-late phase trials. Of the 89 RCTs reported, half were Phase II and 29 percent were Phase III trials. Note this exceeds the total number reported in Table 1 because some studies included two separate trial phases that were counted individually. Collectively, these RCTs investigated 47 small molecule xenobiotics, 26 nutritional interventions and 10 other therapeutics (Table 2).

Table 3 categorizes the primary outcome measures for Phase II and III RCTs for mitochondrial diseases. Given the clinical phenotype of nearly all PMDs includes abnormalities in neurological function or neuroimaging or both, it is interesting that such features were used as an outcome measure in only one RCT, a study of Friedrich’s Ataxia and the use of MIN-102. Visual acuity testing or other ophthalmological endpoints were frequent primary outcome measures in LHON trials. Various outcome measures were applied in 15 trials that related to exercise physiology or endurance metrics, including the 6-minute walk test and bicycle ergometric and respiratory function indices. However, specific, quantifiable biochemical outcome measures were used in only three RCTs. Rating scales (e.g. Newcastle Pediatric Mitochondrial Disease scale) or disease-specific (e.g., an Observer Reported Outcome survey for PDC deficiency) served as primary outcome measures for nine trials. We could not determine how many of the specified primary outcome measures had been independently validated for the particular mitochondrial disorder to which they were applied in these trials.

In our original 2011 survey, all 10 single-center RCTs in PMDs originated in North America or western Europe. Today, using our expanded list of search engines, the RCT landscape for mitochondrial diseases is global, with multicenter trials having become the norm (Fig. 2). Europe and N. America remain the major hubs for such trials, but every continent is now represented as a participant in such studies.

2.2. Funding of trials for mitochondrial diseases

Industry involvement in research and development of potential new therapies and funding of clinical trials for rare diseases has surged since passage of the ODA. Currently, sales of orphan drugs targeting rare diseases is approximately \$151 billion and is projected to exceed \$260 billion by 2024 (Doughman, 2019). The financial and proprietary benefits to rare disease drug sponsors originally provided in the ODA have undoubtedly contributed to this growth of industry involvement. However, there have been significant other developments regarding the approval and post-approval environment for orphan drugs. While the FDA requires pivotal trials of any intervention adhere to high standards of ethical and scientific rigor, it also recognizes the unique challenges of clinical trials for rare diseases, including small numbers of patients and their geographical disbursement, the paucity or lack of alternative therapies and the often dire nature of the disease in question, emphasizing efficiency in the drug evaluation and approval process.

As a result, the FDA may opt to exert a level of regulatory flexibility in evaluating potential therapies for rare disorders, including relaxing the conventional level of proof of effectiveness from the results of late-phase RCTs (Murphy, et al. 2012; Sasinowski, et al. 2015). The FDA also grants Breakthrough Therapy Designation for drugs intended to treat a serious condition for which preliminary clinical evidence indicates the drug may demonstrate a substantial improvement over available therapies, if any exist (Lanthier, 2017). Approximately 60% of Breakthrough Therapies are indicated for rare diseases, which, to date, exclude PMDs. In addition, the FDA grants Priority Review Designation to drugs that treat a serious condition and, if approved, “would provide a significant improvement in safety or effectiveness” (Lanthier, 2017), telescoping the regulatory review process from over a year to approximately 6 months. As a further industry incentive to accelerate both development and approval of drugs for rare disorders, Congress passed in 2007 the Priority Review Voucher program (Ridley, et al. 2006) that was extended in 2012 to include rare pediatric diseases. Under the program, the sponsor receives a voucher for priority review for a different drug. Thus, two drugs receive priority review for each voucher: the drug assigned the original voucher for a rare pediatric disease and a voucher for another drug for another indication, providing earlier entry into the drug approval process and commercial marketing than for those pharmaceuticals from competing companies. Alternatively, the company may choose to sell its voucher to another company that, in turn, can use it to move a drug (for any indication) in its clinical pipeline to the front of the regulatory review queue. Clearly, depending on projected sales, early approval can be worth up to hundreds of millions of dollars to the voucher holder (Ridley and Regnier, 2016). Not surprisingly, since 2015, 15 priority review vouchers have been sold for over \$100 million each (<http://priorityreviewvoucher.org>).

It is difficult to imagine funding opportunities more incentivizing to industry for rare disease drug development than the Priority Voucher Program. However, what of the independent academic investigator who attempts to develop an off-the-shelf orphan small molecule for a rare disorder? A few NIH institutes, particularly the National Institutes for Child Health and Development (NICHD) and Neurological Disorders and Stroke (NINDS) have supported investigator-initiated early to late phase RCTs for mitochondrial diseases through R01, Program Project, Small Business Innovation and Research (SBIR) and Small Business Technology Transfer (STTR) funding mechanisms. Another traditional funding source for rare disease Phases I-III RCTs is the FDA's OOPD.

In our view, there are several over-arching limitations to developing successful investigator-initiated RCTs. The first is the funding ceiling imposed by the various federal grants (Table 4). To meet FDA regulatory standards, the drug intervention (and placebo, if one is used), must be manufactured and undergo extensive testing under current Good Manufacturing Practices (cGMP). cGMP conditions required by FDA and federal law impose extremely strict regiments of control, validation, procedure and documentation on both drug production and supporting laboratory activities on sponsors (an academic investigator or a company) that develop and manufacture pharmaceuticals for human consumption and commercial distribution. Therefore, if an academic investigator is aiming to develop an orphan drug to the eventual point of a New Drug Application (NDA) and, ultimately, FDA approval, compliance with cGMP regulations should be met throughout the process of clinical testing. However, most academic investigators are naive to the intricacies and cost of cGMP regulations, which usually includes the need to outsource manufacturing and testing to cGMP-compliant companies. Undertaking these processes can cost at least several hundreds of thousands of dollars and absorb an inordinate amount of federal grant funds.

SBIRs and STTRs are partnerships between academia and a (domestic) small business interested in eventually licensing intellectual property (IP) and commercializing the orphan product. Consequently, the academic investigator receives only a fraction of the total SBIR or STTR award, depending on the phase, and neither grant is sufficient to completely fund FDA-compliant Phase II-III clinical trials. The FDA's OPD program has been another major funding resource for rare disease clinical trials. Unfortunately, its traditional annual budget ceiling of \$400 thousand for total costs of a project includes indirect costs that can seriously deplete available funds for actually conducting an RCT, particularly if multiple institutions are involved. However, this year, OOPD is beta-testing a new Request for Applications for rare disease clinical trials (RFA-FD-20-001) in which \$500 thousand (or more if appropriately justified) per year for up to 4 years in direct cost dollars alone may be sought for conducting a late-phase RCT, while also providing commensurate levels of indirect costs to applicant institutions. Such awards are very similar to a typical NIH R01, in terms of the amount and distribution of funds; it remains to be determined whether this welcome change in OOPD's funding approach will be sustained.

3. The future.

The National Organization for Rare Disorders (NORD) has a simple, but compelling, logo of an emerging human figure moving "out of the darkness into the light," implying hope for

the treatment of patients with rare diseases. In our estimation, such hope in developing FDA-approved therapies for patients with PMDs has brightened considerably over the past eight years. Many mid-to-late phase RCTs have been completed or are in progress, mostly underwritten by industry in partnership with academic researchers, making for a truly global effort in moving potential new treatments forward.

Nevertheless, there are several traditional and new challenges in navigating the clinical trials landscape for mitochondrial diseases, including:

1. *Genetic and phenotypic heterogeneity of PMDs.* Variability in clinical presentation and course are unequivocal realities of PMDs, including among patients harboring the same genetic mutation. Such diversity may have multiple underlying causes, but stochastic distribution of a pathological mtDNA mutation by means of heteroplasmy, variable penetrance of a mtDNA mutation or lyonization of an X-linked gene can greatly modify the phenotype of a monogenetic mitochondrial disease, apart from a host of environmental and epigenetic influences. While some of these factors pose challenges to the design of and recruitment to any clinical trial, they are major potential variables in developing an RCT of a PMD. Absent the time and resources to recruit patients with a genetically discrete PMD and a near-homogenous phenotype, there are alternative strategies to developing scientifically sound RCTs for mitochondrial diseases. First is to orient the trial around a syndromatic manifestation common to more than one PMD, as exemplified in the studies listed in Table 1. Second is to develop a primary efficacy endpoint sufficiently robust as to account for phenotypic diversity, as in the development of the Observer Reported Outcome survey for the Phase III trial of PDC deficiency. However, the scalability of such a tool requires considerable interaction with the particular community that is therapeutically targeted, so as to include items that reflect clinical complications most common to the particular PMD.
2. *Developing validated clinical endpoints.* In some cases, biochemical or imaging markers may be useful to track the effects of therapeutic interventions on disease course and outcome. However, we believe that validated techniques that quantify a subject's overall functionality, encompassing more the totality of patients' abilities to cope with their disease burden may better reflect their overall response to treatment. These are not quality of life assessments, which at least some regulatory divisions of the FDA do not accept as primary outcome measures for pivotal trials. Instead, simple, short surveys, such as the Karnofsky/Lansky scale (Lansky, et al. 1987) or a recently developed scale for children with PDC deficiency (Stacpoole, et al. 2018) provide a fairly global assessment of a treatment's efficacy and safety and can be administered daily by a patient, caregiver or healthcare researcher, thereby providing within a few minutes considerable quantifiable data while minimizing recall.
3. *Appreciating the requirements and costs of FDA-compliant RCTs.* For investigator-initiated trials, federal support is necessary but, at least currently, is insufficient to absorb the costs of cGMP manufacturing, testing and distribution

of investigational drugs, especially for Phase II and III RCTs. Thus, absent major institutional support, the investigator/sponsor must establish partnerships with philanthropic organizations and/or industry to conduct such trials. Accordingly, it becomes incumbent on the investigator/sponsor to become educated about the relevant cGMP and other regulatory requirements in order to generate trial data suitable for submission to FDA for an NDA. Such knowledge is hard to find in academic health centers, except informally through ad hoc interactions with seasoned faculty experienced in conducting such trials. The NIH-funded North American Mitochondrial Disease Consortium (NAMDC) has as a major goal helping to foster new treatment for PMDs and sponsors a fellowship program for new mitochondrial disease investigators. We suggest it may be useful for NAMDC, in coordination with the United Mitochondrial Disease Foundation (UMDF), to create a structured, on-line educational experience for fellows (and, for that matter, more senior clinical investigators) contemplating a career in drug development and clinical trials, with input from companies already engaged in conducting FDA-compliant research and development of new therapies. Such didactics could also be complemented by an on-site mini-sabbatical or “clinical trials clerkship” offered by a company to provide hands-on experience, including attending meetings between the company and FDA in discussing new or on-going trials.

4. *Maintaining buy-in by the lay community.* The motivations and barriers for patients to participate in clinical trials (Zolkipli-Cunningham, et al. 2018) are not unique to those with mitochondrial diseases. They include the availability, ease of administration and affordability of study drugs, proximity to clinical trial sites, continuing disease burden and maintenance or cessation of mitochondrial “cocktails.” The annual meetings of NORD, the UMDF and the Society for Inherited Metabolic Disorders are excellent venues to attract patients and families interested in becoming aware of, and participating in, clinical trials. Indeed, the FDA encourages engagement by the representative lay community in both the development and implementation of RCTs (<https://www.regulations.gov>; <http://kppt.com>).
5. *Widening the therapeutic window for acquired mitochondrial diseases.* The over 200,000 citations for “mitochondria” in our analysis (Fig. 1) encompass an ever-growing number of disorders in which mitochondrial dysfunction figures importantly in disease pathogenesis. This fact is not surprising, given the varied roles mitochondria play in maintaining cellular and organismal homeostasis. Thus, it is logical to assume that therapeutics aimed at treating a particular PMD could have therapeutic potential in other rare or common diseases not directly caused by a loss-of-function mutation in nuclear or mitochondrial DNA that encodes a mitochondrial protein. One example is the orphan drug dichloroacetate (DCA), currently being studied in children with PDC deficiency, but also investigated in early phase trials for diabetes (Stacpoole, et al. 1978), congestive heart failure (Bersin, et al. 1994), pulmonary arterial hypertension (Michelakis, et al. 2017) and cancer (Michelakis, et al. 2010; Dunbar, et al. 2014; Chu, 2015).

Another example is elamipretide (Bendavia), a synthetic tetrapeptide targeting the mitochondrial inner membrane that is undergoing trials in adults with mitochondrial myopathy (Supp Table 1) and in patients with heart failure (Daubert, et al. 2017). Conversely, certain FDA-approved drugs for non-mitochondrial conditions that affect mitochondrial function may be future candidates for treating PMDs, such as phenylbutazone, an FDA-approved drug for certain urea cycle disorders that may have utility in patients with PDC deficiency (Ferriero, et al. 2013).

6. *Facing the challenge of mitochondrial “cocktails.”* The safety and efficacy of various mixtures of vitamins and cofactors as therapy for any PMD remains unproven. It is a topic of major controversy in the mitochondrial disease research community (Camp, et al. 2013; Camp, et al. 2016), a profitable enterprise for manufacturers of the ingredients and a financial burden for affected families. Developing study designs sufficiently robust to investigate the safety and efficacy of various cocktail permutations is daunting, as is the crafting of applications for peer-reviewed, extramural funding. The National Center for Complementary and Integrative Health (NCCIH) is an NIH center that supports studies of natural products, including early phase trials, Phase II RCTs and Clinical Coordinating Centers for trials of natural products (<http://nccih.nih.gov/grants/funding/clinicaltrials#natural>). Thus, a potential funding mechanism exists through NCCIH that might be complimented by an R01 from the OOPD, affording a possible strategy that could be further strengthened if submitted under the auspices of NAMDC and the UMDF.
7. *Ensuring the costs of approved drugs are sustainable for patients and the nation.* Many orphan drugs cost thousands of dollars per month, which is unsustainable for the average individual, even if possessing health insurance (Jayasundara, et al. 2019). As summarized by Murphy and colleagues (Murphy, et al. 2012), “The high cost of these drugs within the United States has led to patients buying orphan drugs from abroad at a fraction of the US cost. In some cases, these are drugs that are FDA-approved and have been manufactured by a US-based company, exported, and sold elsewhere more cheaply. However, it is illegal for anyone but the manufacturer to reimport exported drugs, even if they comply with all FDA regulations (US Food and Drug Administration, 2009),” further rendering these costs unsustainable for patients and for the nation.

It is likely that the first FDA-approved drugs for PMDs will become approved within the next 5 years – a seminal achievement for both the lay and professional mitochondrial disease communities. It is, therefore, their joint responsibility to maintain vigilance over the cost of approved treatments and to advocate for their affordability. The alternative is to force patients to decrease compliance with these medications or to seek less expensive alternative treatments that may be of unproven safety and/or efficacy. A formal cost of illness analysis for PMDs has not been conducted (Angelis, et al. 2015); therefore, their socio-economic burden cannot be estimated with accuracy. Nevertheless, it is reasonable to expect that the unaffordability of approved drugs not only sustains a patient’s disease burden but also the financial toll on the individual and society. The prospect of unaffordable medications also

dampens patients' motivations for participating in future clinical trials. As a consequence, failure to ensure affordable, approved treatments yields only a pyrrhic victory for drug companies, patients and society.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

cGMP	current good manufacturing practices
DCA	dichloroacetate
FDA	Food and Drug Administration
ISRCTN	International Standard Registered Clinical/social sTudy Number Registry
LHON	Leber's Hereditary Optic Neuropathy
NCCIH	National Center for Complimentary and Integrative Health
NDA	New Drug Application
NICHD	National Institute of Child Health and Development
NINDS	National Institute of Neurological Disorders and Stroke
NMDC	North American Mitochondrial Disease Consortium
NORD	National Organization for Rare Disorders
ODA	Orphan Drug Act
OOPD	Office of Orphan Product Development, FDA
PDC	pyruvate dehydrogenase complex
PMD	primary mitochondrial disease
RCT	randomized controlled trial
SBIR	Small Business Innovation and Research
STTR	Small Business Technology Transfer
UMDF	United Mitochondrial Disease Foundation

VCLAD	very long chain acyl-CoA dehydrogenase
WHO	World Health Organization

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Fig. 1.

Evolution of interventional clinical trials for primary mitochondrial diseases, 2011- Present.

Red: citations in original study using only PubMed through February 11, 2011; blue: citations using PubMed through May 15, 2019; yellow: citations using all citations listed above through May 15, 2019.

Fig. 2.
Geography of Randomized Controlled Trials in Mitochondrial Diseases, 02/11/2011 – 05/15/2019. Data obtained from the expanded search engine list described in the text.

Table 1.Categories of Randomized Controlled Trials in Mitochondrial Diseases¹

Genetic Mitochondrial Diseases²		Syndromic Mitochondrial Diseases³	
Disease/Process	Number	Disease/Process	Number
Friedrich's Ataxia (FA)	30	Mitochondrial Diseases/Disorders	15
Leber's Hereditary Optic Neuropathy (LHON)	9	Mitochondrial Myopathies	11
m.3243A>G	6	Long-Chain Fatty Acid Oxidation Disorders	4
Barth Syndrome	1	Mitochondrial Cytopathies	2
Pyruvate Dehydrogenase Complex deficiency	1	Congenital Lactic Acidosis	1
Very Long-Chain Acyl-CoA Dehydrogenase deficiency	1	Mitochondrial Encephalopathies	1
	1	Leigh Syndrome	1
TOTAL	48	TOTAL	35

¹Data from Supplemental Table 1.²Defined as RCTs specific to a defined nuclear or mitochondrial DNA mutation or closely related mutations.³Defined as a mitochondrial disease syndrome that includes potentially several distinct nuclear and/or mitochondrial DNA mutations.

Table 2.Therapeutic Interventions in Randomized Controlled Trials of Mitochondrial Diseases¹

Xenobiotics		Naturally Occurring	
Intervention	No. Trials	Intervention	No. Trials
Acipimox	1	Alpha-tocopherolquinone (vitamin E quinone)	2
Amantadine HCL	1	Arginine/Citrulline	1
Bezafibrate	4	Cocktail (2 naturally occurring products)	3
Bupropriion/Citalopram	1	CoQ10	3
Dichloroacetate (DCA)	5	Creatine	2
Defereiprone	1	Curcumin	1
Elamipretide	4	Dietary Interventions (eg. High fat)	5
EPI-743	3	EGB 761 (Ginko biloba)	1
Idebenone	8	L-Carnitine	1
KH176	2	Levorotatory form of 5-hydroxytryptophan (Oxitriptan)	1
KL 1333 (quinone oxidoreductase)	2	Nicotinamide (vitamin B3)	1
LU AA24493 (Carbamylated erythropoietin)	2	Resveratrol	2
MIN-102 (Peroxisome proliferator-activated receptor gamma agonist)	1	SPP-004 (5-aminolevulinic acid/sodium ferrous citrate)	2
MTP-131 (Bendavia)	1	VP 20269 (indolepropionic acid)	1
Omaveloxolone	2	Total	26
Pioglitazone	1		
RG2833 (histone deacetylase inhibitor)	1	Other	
RhuEPO (recombinant human erythropoietin)	1	Intervention	No. Trials
		Device	1
RT001 (11, 11-di-deutero-linoleic acid ethyl ester)	1	Exercise	2
Sodium pyruvate	2	Genetic (GS010 [AAV2 gene tx], Interferon gamma 1b, epoetin alfa)	7
TAK-831 (d-amino acid oxidase inhibitor)	1	Total	10
Triheptanoin/Trioctanoin	1		
Varenicline	1		
Total	47		

¹Data from Supplemental Table 1.

Table 3.

Primary Outcome Measures for Phase II and Phase III Randomized Controlled Trials for Mitochondrial Diseases¹

Outcome measure	Phase II	Phase III
Safety; adverse events	5	
Neurological imaging or function	1	
Ophthalmological function	1	7
Exercise physiology or endurance	11	4
Biochemical measure	3	
Patient/observer rating scale (incl. QOL) ²	3	6
Uncertain/undocumented	2	

¹Data from Supplemental Table 1.

²Observer defined as family member, guardian or healthcare professional; QOL, quality of life.

Table 4.

Typical Funding Limits of Federal Grants Supporting Rare Disease Randomized Controlled Trials

Agency	Funding Mechanism	Annual Budget Ceiling	Maximum Funding Duration
NICHD/NINDS	R01	\$500K DC	5 yr
SBIR/STTR	Phase I ¹	\$150,000 TC ³	6 yr
SBIR/STTR	Phase II ²	\$1 million TC	2 yr
SBIR/STTR	Phase IIB	\$1 million TC	3 yr
OPD (pre 2019)	R01	\$400K TC	4 yr
OPD (2019)	R01	\$500K DC	4 yr

¹ Note this terminology refers to the phase of the funding source, not to a particular phase of a clinical trial.

² A “Direct Phase II” grant may be applied for that bypasses the Phase I stage.

³ Funding ceilings for SBIR and STTR awards may vary among participating federal agencies. For additional information, consult <https://www.sbir.gov/about/about-sbir>.

DC, direct costs; TC, total (direct + indirect) costs.