Basket Trials for Rare Diseases:
Where Innovation Meets Unmet Need

Rare diseases, which affect >30 million individuals in the United States (US), have historically taken a back seat to more common diseases such as cancer, diabetes, and heart disease in the clinical trials landscape, primarily due to trial design challenges in limited patient populations. Through public meetings and behind-the-scenes engagement with patients, the US Food and Drug Administration (FDA) has heard that regulatory flexibility is paramount to advancing drug development for rare diseases. Many of these diseases share molecular etiologies, and patients with those diseases could equally benefit from treatment with a single agent. Some of the most debilitating rare diseases affect the most vulnerable and cherished population – children. However, clinical trial design regulations and very small patient populations complicate the initiation of studies for these rare diseases. The use of basket trials – an approach that has led to the approval of groundbreaking oncology products – could be one solution to faster, more successful development of products for the rarest of rare diseases by targeting shared molecular etiologies instead of specific diseases.

Innovative Clinical Trial Designs for Rare Diseases

After the passage of the 21st Century Cures Act in 2016, innovative regulatory approaches paved the way for master protocol designs for oncology clinical trials. In the FDA's 2022 *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics: Guidance for Industry*, a basket trial is defined as "a master protocol designed to test a single investigational drug or drug combination in different populations defined by different cancers, disease stages for a specific cancer, histologies, number of prior therapies, genetic or other biomarkers, or demographic characteristics."[1] The agency emphasises that because master protocols are so complex, it is important that they are "well designed and well conducted" to ensure patient safety and to collect quality data that could support product approval.[2]

The rare disease community has had its eye on the basket design for years. Great efforts have been made to mirror this process for rare conditions such as mitochondrial diseases and diseases with mutations in the same genes that can result in different phenotypes, mutations in different genes that can affect the same pathway, and the same mutation types in different genes.[3] During a presentation at the Drug Information Association 2024 Global Annual Meeting, Philip Brooks, PhD, National Institutes of Health, stated that despite the presence of thousands of rare diseases throughout the world (>7,000 in the US), far fewer etiologies exist. Given that there are four main gene mutation types – abnormal RNA splicing, dominant mutations, missense mutations, and nonsense mutations – it could be possible to develop clinical trials that target molecular etiologies instead of specific diseases.

Despite the promise that basket trials show, several challenges delay their initiation, such as small patient populations, the clinical heterogeneity of rare diseases, identification of methods to measure response, the complicated process of enabling extrapolation from one condition to another, and varying safety concerns given the variability among patient populations. One of the major roadblocks is funding, a common difficulty in rare disease drug development given the lack of profit for drug developers of products that treat small disease populations. Enrolling participants with rare diseases from all over the world is a clinical trial barrier that many disease communities face, but rare diseases are often undiagnosed or occur in locations with minimal healthcare access.

However, the FDA has increased efforts to engage patients in the drug development cycle by launching initiatives such as patient-focused drug development and collecting patient preference information. Accumulating patient experience data, which is described in section 569C(c)(2) of the Federal Food, Drug, and Cosmetic Act as data collected by any persons that are "intended to provide information about patients' experiences with a disease or condition," is crucial for understanding the lengths to which patients are willing to go to obtain a cure for their rare disease.[4] Given the progressive nature of many rare diseases, time is valuable. Randomised placebo-controlled trials can be devastating for a rare disease patient whose disease has progressed while participating in a study and receiving placebo. In this close-knit scientific community, use of a placebo is considered unethical due to the lack of other treatment options for rare diseases. Thus, creative and efficient approaches to clinical trial design are necessary.

The Rare Disease Endpoint Advancement Pilot Program, which fulfills a commitment under the seventh iteration of the Prescription Drug User Fee Act (PDUFA VII), allows the FDA to engage with sponsors frequently to advance novel endpoints and determine efficacy for rare diseases that do not have accepted endpoints. A common recommendation to sponsors from the FDA at public meetings is to communicate with the FDA early and often, even during the pre–investigational new drug application stage, to avoid delays in conducting clinical trials and receiving approval for new drug applications and biologics license applications.

In the FDA's Office of Orphan Products Development, the Clinical Trials Grants Program funds clinical trials for rare diseases and encourages the use of innovative clinical trial methods, such as basket trials.[5] The agency's Center for Drug Evaluation and Research launched the Center for Clinical Trial Innovation in May 2024, which provides a central hub supporting innovative approaches to clinical trials that are designed to improve the efficiency of drug development. In May 2022, the agency hosted a public meeting to discuss advances in rare diseases and explore "regulatory fitness" in rare disease clinical trials. During the meeting, presenters highlighted rare diseases that could potentially benefit from and be appropriate candidates for

basket trials, including mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) and Leber hereditary optic neuropathy plus (LHON-Plus). The FDA's accelerated approval pathway has also contributed to significant scientific advancements in rare diseases. Despite these efforts, few products have been approved by the agency based on results from basket trials, but several are under investigation for various rare diseases.

Glycerol Tributyrate

MELAS and LHON-Plus are two rare progressive neurodegenerative diseases with clinical neurological symptoms that are overlapping and divergent. They both have no cure. According to the National Organization for Rare Disorders, MELAS is inherited from the mother, and most cases (approximately 80%) are caused by variants in the mitochondrially encoded tRNA leucine 1 (*MT-TL1*) gene.[6] Individuals with MELAS syndrome can have stroke-like episodes, seizures, memory loss, dementia, muscle weakness, and difficulty with physical activity. They typically have normal development early in childhood but develop learning difficulties, frequent headaches and vomiting, hearing loss, peripheral neuropathy, and short stature between ages 2 and 15 years. Treatment for MELAS consists of managing symptoms.

In the case of LHON-Plus, which is also inherited from the mother, the primary symptom is sudden, painless loss of central vision. The United Mitochondrial Disease Foundation explains that the "plus" is attributed to patients with non-vision symptoms that could be associated with their LHON variant (*e.g.*, muscle weakness, peripheral neuropathy, tremors, migraine, cardiac issues, bladder issues).[7] Initial vision loss can appear at any age, and no treatments are available to slow or reverse the vision loss in LHON-Plus patients.

The George Washington University has planned a parallel-arm, non-randomised, dose-escalation, open-label basket exploratory phase 1 clinical study (NCT06792500) to evaluate glycerol tributyrate, a novel small molecule-based therapy in patients with MELAS and LHON-plus. Participants will undergo simultaneous enrollment in 2 disease-based arms to evaluate the safety and potential for efficacy of daily oral doses of glycerol tributyrate. This first basket trial for MELAS and LHON-Plus will provide a "blueprint" for other rare mitochondrial diseases, Anne Chiaramello, PhD, the principal investigator of the study, stated.[8]

Setmelanotide

In December 2024, Rhythm Pharmaceuticals, Inc, announced that the FDA approved an expanded indication for Imcivree (setmelanotide) to include younger children in the originally approved indication.[9] Setmelanotide is indicated to reduce excess body weight and maintain weight reduction long term in patients aged ≥2 years with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or genetically confirmed deficiency in pro-opiomelanocortin (*POMC*), including proprotein convertase subtilisin/kexin type 1 (*PCSK1*), or leptin receptor (*LEPR*) deficiency. *POMC*, *PCSK1*, and *LEPR* (collectively called PPL) and BBS deficiencies are rare melanocortin-4 receptor (*MC4R*) pathway diseases with characteristics that include hyperphagia, impaired satiety, persistent and abnormal food-seeking behaviors, and early-onset obesity.

This approval was based on results from an open-label phase 3 basket trial (Venture; NCT04966741) to evaluate the efficacy, safety, and tolerability of setmelanotide via subcutaneous injection over 1 year of treatment in 12 pediatric participants aged 2 to <6 years with obesity due to either biallelic variants of PPL or BBS.[9] Participants were assigned to 1 of 2 baskets: the PPL group or BBS group. Of the 12 participants who completed the study, 10 (83%) had a ≥0.2-point reduction in body mass index (BMI) Z-score per World Health Organization methodology at week 52 (95% confidence interval [CI]: 58.7, 99.8). The mean percent change in BMI from baseline at week 52 was -18% (standard deviation [SD] = 13) in the overall safety population. The mean percent change in BMI at week 52 was -26% (SD = 11) in participants with *POMC* or *LEPR* deficiency and -10% (SD = 9) in those with BBS. All adverse events were mild or moderate; the most common were skin hyperpigmentation, vomiting, nasopharyngitis, upper respiratory tract infection, and injection site reactions.

Hope for Rare Disease Basket Trials

Funding, patient engagement, and scientific breakthroughs are necessary to finally give a voice to patients who have remained in the background of drug development due to the rarity of their diseases and a lack of successful clinical trials and treatments. Regulatory flexibility and frequent engagement between the FDA and drug developers could be the key to finally unlocking treatments for those who currently cannot be cured.

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Jaime Gavazzi

Jaime Gavazzi is a Principal Content Analyst for the Cortellis suite of life science intelligence solutions at Clarivate. Her previous roles include writing and editing for books, online magazines, educational coursework, government proposals, and government regulatory publications. Her primary assignments at Clarivate include reporting on FDA drug/device advisory committee meetings and drug approvals. She is also living with a rare disease and waiting for a cure.

Email: jaime.polychrones@clarivate.com