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Introduction. Advances in treatment of rare disorders have been slow and few. In contrast, dramatic improvements have been made in the treatment of equally rare childhood cancers over the past 30 years. Much of the difference can be traced directly to organized, national clinical trials that provide all patients diagnosed with cancer the opportunity to participate in clinical research. The treatment of rare disorders has instead been driven by experience and expert opinion rather than formal clinical trials because of the significant barriers in place to conducting traditional random, placebo controlled, national studies. This observation is certainly true for fatty acid oxidation disorders (FODs). In spite of the fact that FODs represent the most common group of disorders identified through expanded newborn screening, only one medication (carnitine) for treating them is currently approved by the Food and Drug Administration (FDA); and even it's use is controversial in many FODs. What is a clinical trial, why are they so important in guiding therapy, and should you participate in them? This article will explore these questions and discuss how to best advance our knowledge in treatment of FODs.

A Brief Example. Everyone has been "talking" on the internet about a new supplement. It's available over the counter and from a variety of suppliers. Some families have tried it and rave that it gives their child more energy. Others have questioned its effect. There doesn't seem to be much published information in the medical literature on the compound. Which statement best describes your feelings on trying the new supplement?

I have to try it because it might make a difference.

I'll do some more reading and make up my mind about trying it after that.

I'll ask my doctor his/her opinion on trying the new supplement.

I can't see how something like this will work so I won't try it.

I would be very interested in participating in a clinical trial.

While the first four answers are the ones we most frequently hear relative to trying new therapies, the last one is in reality the one that provides the best path forward to new therapies. Let's examine why this is true.

Evidence Based Medicine. The idea of clinical trials is grounded in evidence based medicine, which holds that therapy should be based on firm scientific investigation rather than expert opinion. It presupposes that alternative treatments for a disease can be compared through direct testing in a large enough number of patients to discern if one or the other is better. This process is more complicated in FODs and other rare disease, but it is still critical to adhere to the guidelines as much as possible in order to advance clinical knowledge in these disorders. Insurance companies are also increasingly demanding documentation of clinical efficacy before authorizing payments for therapies.

Barriers to Clinical Trials. Because of the clinical complexity of FODs, much of our current

therapy has evolved from clinical experience supported liberally by theoretical biochemical considerations (*i.e.*, expert opinion). Unfortunately, in an era when "evidenced-based medicine" has become a political rallying cry driving health care reform, essentially no controlled trials have been conducted for FODs.

There are three major barriers to conducting clinical trials in FODs. First, the treatment ethic in rare disorders often borders on "miss no chance" rather than "do no harm". New suggestions for treatment that are logical are embraced by families and physicians alike without insisting on proof of efficacy. Both should recognize that resorting to unproven treatments is counterproductive, and interferes with true progress in advancing therapy. Second, FODs are sometimes viewed as not being amenable to clinical therapeutic trials because of their rarity. This is not true. Advances in the treatment of even rare tumors have been facilitated by organized, national clinical trials that would have been impossible to conduct at any single institution. The ultra rare disorders that include FODs present special challenges and perhaps require a unique infrastructure, but the concentration of most patients in the hands of a relatively small number of practitioners provides a fertile substrate for collaborative studies. Thus, for ultra-rare disorders, developing and promoting innovative approaches to small size clinical trials becomes a priority.

This brings us to the final barrier. Well-controlled, multi-center, national collaborative studies are expensive. Biotech and the pharmaceutical industry have stepped up to meet the need for some diseases and have been responsible for developing many of the clinically validated medications for inborn errors of metabolism currently on the market. But well-intentioned investigators (academic and industrial) may find themselves stalled before they can start by FDA regulations designed for drugs that treat thousands or millions of patients. Moreover, the financial incentives provided to companies under the auspices of the Orphan Drug Act have opened them to criticism over the high prices of their products, and the single producer model has sometimes led to bottlenecks in supply.

Solving the Problems. Recognizing these challenges, a number of concrete measures can be taken to improve our clinical science with the ultimate goal of improving our clinical care. The most obvious is to increase federal resources dedicated to dealing with rare disorders. With trillion dollar deficits and health care reform looming on the horizon, now may not be the most opportune time to lobby for funds. However, the savings to the health care system by prevention or reduction of chronic care needs, along with elimination of expenses associated with needless therapies, should facilitate this discussion. But money isn't the real (or at least only) answer. The development of a national collaborative infrastructure that provides a framework for clinical trials is crucial. There are some promising initiatives already underway. The Office of Rare Disease Research (ORDR) and the FDA Office of Orphan Products Development have played key roles in much of the development of drugs for treatment of inborn errors of metabolism to date. The NIH-funded ORDR Rare Disease Clinical Research Network, HRSA sponsored newborn screening regional collaboratives, and the related HRSA rare disease Translational Research Network are good examples of attempts to move beyond the isolation of individual institutions. While these programs represent a beginning, the ultimate goal should be the offer entry into a clinical trial for all patients diagnosed with an FOD, rather than being started on whatever treatment regimen is currently in vogue. While

individual investigators will by need and interest develop and coordinate specific protocols, all metabolic centers should be able to enroll patients and participate in all studies.

Clinical Trials in FODs. The number of clinical trials for FODs will likely be growing in coming years. Not all trials will be suitable for everyone. Clinical trials are by definition experiments in medical care. Risks are carefully managed to be as low as possible, but they can't be eliminated completely. Clinical trials often involve comparison of a test medication to a placebo (an inactive compound made to look like the test medication). Some families and patients find this a difficult concept to accept, wanting rather that they or their child get the "real treatment". It is critical in this setting to remember that the clinical investigators really don't know if the new treatment is better (or even worse) than the old one. So there is no intent to withhold an effective new therapy for an older one. The trial is necessary to prove one or the other is better. Patients and families should always feel comfortable with all aspects of a clinical trial before agreeing to participate. Investigators in a trial should be willing to take as much time as necessary to explain exactly what will happen in the trial. You should know what procedures or treatments are involved and if any expenses might be incurred. Most (but not all) trials will cover all expenses related to the trials. In the end, a clinical trial is a partnership between the study team and the patient and family.

When exploring clinical trials, patients and families should be familiar with www.clinicaltrials.gov. This site compiled by the National Institutes for Health accumulates information on existing clinical trials and allows on line searching for those related to specific diseases. The FOD Family Support Group web site and listserve should also be aggressive in updating information for families and providing access to investigators enrolling studies.

Currently, my program is conducting clinical trials on the use of triheptanoin (c7) to treat long chain fatty acid oxidation defects, and enrollment is lagging behind projections. Patients older than 7 are eligible and families can contact Stephanie Deward (Pittsburgh, PA; Stephanie.DeWard@chp.edu) or Julie Martin (Portland, OR; martijul@ohsu.edu) for information on participating. A trial for a new medication to treat MCAD deficiency will be starting soon.

Conclusion. A move to evidence-based medicine in the treatment of FODs is not only desirable but will be necessary to move forward in a changing medical economy. Therapies based on compassion without knowledge will inevitably promulgate confusion. The ready accessibility of clinical trials to all patients and metabolic physicians will dampen the immediate urge to do everything possible and instead, redirect the considerable energy of both groups into doing everything known to be effective, while identifying additional new therapies that work. And always remember that without clinical trials, no new medications to treat FODs will be developed and the effectiveness of new therapies will never be proven.