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EDITORIAL

The Twilight Zone: Benefit, Risk & Hope in Clinical Trials for Fibrodysplasia Ossificans Progressiva (FOP)

From The International Clinical Council on FOP (ICC)

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Recent developments in clinical trials for fibrodysplasia ossificans progressiva (FOP; MIM # 135100) have left us feeling as if we are in the twilight zone – "that neutral territory somewhere between the real world and fairyland" as the author Nathaniel Hawthorne described [1,2]. On the one hand, we have emerging results from some clinical trials that inspire hope (NCT03312634; NCT03188666) [3, 4]; while on the other hand, the same trials have been paused due to the emergence of serious adverse events or concern for futility [5, 6]. The International Clinical Council on FOP (ICC) has monitored and will continue to monitor these occurrences with vigilance.

This is a critical time to reflect where we have been, where we are now, how we got to where we are now, and where we are going as a community, if indeed we can know. It is not a risk-free journey, and we have been reminded that there are obstacles along the path. But, neither is it a journey devoid of hope; quite the opposite, in fact.

The discovery of the FOP gene heralded the emergence of a new grammar for drug discovery in FOP and the explosion of interest and laser focus of the biopharmaceutical industry on the well-defined and evolutionarily-conserved bone morphogenetic protein (BMP) signaling pathway [7-11]. Like dominoes in descent, the FOP gene discovery enabled the development of genetically correct animal models of FOP – which has been instrumental in testing novel therapeutics for druggable targets [12, 13]. Animal models validated the dysregulated BMP signaling pathway in FOP, the pathophysiology of heterotopic ossification (HO) in FOP, and progenitor cells responsible for HO in FOP

[14-25]. Dramatic basic science discoveries coupled with a comprehensive understanding of the natural history of FOP and methodologies to detect early bone formation further fueled the advent of clinical trials [26-30]. The grammar of investigational drug discovery rapidly became a babble of promising new approaches that were rapidly cast on the stage of human clinical trials – a dazzling place to be for an ultra-rare condition that had existed in the backwaters of medicine for over three centuries and for which no approved treatment and no discernible hope previously existed. But beware of good news. As Shakespeare said, "Roses have thorns and silver fountains mud [31]."

While dramatic advances showed that the FOP gene discovery could enable identification of druggable targets, it also revealed that drug development would likely be constrained by an ancient and highly-conserved signaling pathway that was redundant and iterative thus making therapeutic specificity difficult [10, 11]. While the desired goal of targeting the dysregulated BMP signaling pathway in FOP is clearly the abrogation of HO, the BMP pathway is critically important in the maintenance and repair of nearly every major organ system, thus expanding the risks of collateral side effects of potentially therapeutic drugs [11]. In addition, there are important logistical considerations and constraints of model systems, not the least of which is that FOP mice are laboratory-raised, pathogen-free genetic clones and are not people with FOP, and thus do not inherently manifest either the immunological vitality or genetic variability that underlies both the range of potential benefits and the range of potential risks that

human beings will inevitably display [32]. Thus, while translational studies are essential to enlighten the way forward, they in no way guarantee an unobstructed path.

Potential benefits and inherent risks need to be weighed - not just at the outset but continuously throughout a clinical trial. Aspirational outcomes of successful treatments may vary from one clinical trial to another based on the mechanism of action of the investigational drug and the pre-determined, primary outcome of a clinical trial. Possible long-term benefits of patient involvement in a clinical trial may theoretically include but are not limited to decreased flare-ups, decreased HO, preservation of joint mobility, retardation of joint degeneration, liberation of joints ankylosed with HO, pain relief, frequent medical monitoring, increased self- and FOP-awareness, improved quality of life, a pioneer spirit, contribution to a greater good or contribution to future generations.

Individual participation in a clinical trial must be balanced by a thoughtful consideration of potential benefits and risks. Clinical trials are not proven treatments, but rather an opportunity to determine if a potential therapy is effective and safe. Potential risks may vary from one clinical trial to another. These are assessed based on pre-clinical toxicology studies, phase-1 clinical trial results, or knowledge of the mechanisms of action of an investigational drug. However, these assessed risks may not be comprehensive and new risks may be identified when potential therapies are tested in a clinical trial. Common categories of risk include the inconvenience of participating in a clinical trial – especially during a pandemic, the uncertainty of knowing whether one is initially randomized to a placebo group or a treatment group, the occurrence of annoying or harmful side effects both anticipated and unanticipated, potential allergies to a drug, adverse drug reactions, non-response, resistance to possible therapeutic effects, intolerability of a drug, and worsening of FOP despite pre-clinical data that suggest the therapy in question may be helpful.

Every drug has side-effects, but with investigational drug development for FOP, the spectrum of side-effects may not be fully known until the drug is tested in FOP patients, despite extensive pre-clinical toxicology studies. Even approved and re-purposed drugs may have different side-effects in the FOP population than are seen when the same drug is used in other conditions. Potential risks can often be assuaged, but even with safety nets and firewalls in place, certain risks can elude prompt detection. And then, there are the "unknown unknowns" [33] – the unanticipated and unpredictable risks that arise out of nowhere and take everyone by surprise. Often these risks are relatively minor, but sometimes – to the consternation of all – they might be harmful or even fatal.

Our early foray into FOP clinical trials reminds us what we knew from the very beginning - that clinical trials are not proven treatments; they are human experiments, guided by the best available knowledge at the time the trial was designed. They have theoretical benefit and palpable risk that are spelled-out in informed consent. Informed consent is not just a quaint formality; it is a solemn requirement and an ongoing process at every step of the clinical trials journey. Further, patient safety is hard-wired into all clinical

trials in the form of an independent Data Safety Monitoring Board (DSMB) comprised of 3-6 experts in various disciplines related to the study drug and trial design that monitors occurrences such as unexpected serious adverse events and can pause or stop a trial in its tracks if it detects an unforeseen problem that may be related to an investigational drug. A DSMB can also stop a clinical trial early if the beneficial effects are so overwhelming to suggest that continuation of the trial would not be necessary or if it was determined that the investigational drug is futile. Thus, the DSMB, the sponsor or regulatory authorizes for that matter have the jurisdiction to pause or stop a clinical trial for any reason at any time. And, of course, the trial participant has the absolute right to bail-out at any time, for any reason, or for no expressed reason at all. As one sponsor observed, "There is not an endeavor on the planet that is more highly regulated than clinical trials [34]." Clinical trials are, after all, not proven treatments; not yet at any rate. Some may be. Some may never be. It is worth remembering.

As patients are bombarded by possibilities and choices – by good news and bad – where does that leave them? For the moment – in the twilight zone – somewhere between an old world of symptomatic management and a brave new world of therapeutic possibilities [35-37]. That ultimate gateway is possible only through clinical trials – and patients who embark on that journey are courageous pioneers. Patients and parents must always be aware that there are risks - some known and closely monitored – and some unknown and clearly unexpected – the "unknown unknowns" [33]. So, how should patients proceed? Obviously with caution, but not paralyzed by fear; obviously with hope, but also with respect for the unknown. Novel therapies can emerge only from an FOP community working together. Without clinical trials, there will be no approved treatments and all our efforts will be in vain.

So what is the take-home message? There are two. First, clinical trials are not proven treatments. They have the potential to become treatments if they prove efficacious and safe. They must be both. Each individual (or surrogate) must weigh the potential benefits and risks of enrolling in a clinical trial and decide for themselves if it is right for them - with ongoing informed consent as the guiding light; it is a deeply personal decision. Second, clinical trials are the only path to an approved treatment, and we all have an abiding hope and belief that well-designed and executed clinical trials will be the path that will lead there [30]. We are greatly encouraged that so many pharmaceutical companies are developing novel therapeutics for such a rare and complex disease as FOP - and that they are doing this carefully, responsibly and at great risk to themselves. Side-effects, adverse effects and even unanticipated effects will likely occur. Nobody wants them, but in every case they will be assiduously monitored and immediately investigated by the sponsors and researchers to determine if and how they are related to the investigational drug. And, if and when risks are identified that may be related to the investigational drug, appropriate risk management measures and mitigations will be incorporated into further iterations of the clinical trial to ensure ongoing patient safety. Scientists, doctors, patients, clinical research personnel, pharmaceutical companies and regulatory authorities will continue to work together to make this effort as safe, transparent and successful as possible. This vigilance to

safety and transparency on everyone's part will lead us together through the twilight zone.

In summary, clinical trials are painstaking processes that weigh potential benefits to the patient and society against potential harm to the individual enrolled. Clinical trials are a bold step into the future, along a path like no other - a path that is hopeful, but with obstacles, to be sure. But as someone famously said, "Obstacles along the path are not obstacles – they ARE the path [38]." That is our hope.

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MAZ is on the data safety monitoring board for Ipsen/Clementia Pharmaceuticals.

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