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REVIEW-THEMED ISSUE

Special considerations for clinical trials in fibrodysplasia ossificans progressiva (FOP)

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Clinical trials for orphan diseases are critical for developing effective therapies. One such condition, fibrodysplasia ossificans progressiva (FOP; MIM#135100), is characterized by progressive heterotopic ossification (HO) that leads to severe disability. Individuals with FOP are extremely sensitive to even minor traumatic events. There has been substantial recent interest in clinical trials for novel and urgently-needed treatments for FOP. The International Clinical Council on FOP (ICC) was established in 2016 to provide consolidated and coordinated advice on the best practices for clinical care and clinical research for individuals who suffer from FOP. The Clinical Trials Committee of the ICC developed a focused list of key considerations that encompass the specific and unique needs of the FOP community – considerations that are endorsed by the entire ICC. These considerations complement established protocols for developing and executing robust clinical trials by providing a foundation for helping to ensure the safety of subjects with FOP in clinical research trials.

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Introduction

Clinical trials in orphan diseases are becoming increasingly common. Orphan drug disease designations are one of the fastest areas of growth. One such orphan disease, fibrodysplasia ossificans progressiva (FOP; MIM#135100), is characterized by widespread progressive heterotopic ossification (HO) of skeletal muscle and soft connective tissues [1]. The course of FOP is cumulative, leading to progressive loss of function and independence [2]. Furthermore, HO in FOP can be spontaneous or be triggered by trauma and inflammatory events throughout life [1–4]. Although HO is by far the most prominent clinical feature in FOP, other organ systems such as the central nervous system can also be affected [1, 5]. The unique phenotypes of FOP, as well as the high risk of complications, pose significant challenges for clinical care and clinical trial design that must be considered to optimize subject safety. Here, we propose FOP-specific clinical trial considerations that are agreed upon by international FOP clinical experts.

Clinical manifestations of FOP

FOP is a severely disabling heritable disorder of connective tissue characterized by the classic features of congenital malformations of the great toes and progressive HO that forms qualitatively normal bone in characteristic extra-skeletal sites [2]. The worldwide prevalence is estimated at 1/1 300 000 to 1/2 000 000 [6]. There are no ethnic, racial, gender or geographic predilections to FOP. Children who have FOP appear normal at birth except for congenital malformations of the great toes. Radiological findings can assist with diagnosis of the disease [7]. During the first decade of life, sporadic episodes of painful soft tissue swellings ('flare-ups') occur spontaneously or can be precipitated by soft tissue injury, intramuscular injections, viral infection, muscular stretching, muscular fatigue or falls. These flare-ups transform skeletal muscles, tendons, ligaments, fascia and aponeuroses into heterotopic bone, progressively rendering movement impossible. Classic FOP is caused by a recurrent activating mutation (c.617G>A; p.R206H) in the gene encoding **Activin A receptor type I/Activin-like kinase 2** (*ACVR1/ALK2*), a bone morphogenetic protein (BMP) type I receptor [8]. There are a few patients with exceedingly rare genetic variant forms of FOP [9] that may show the classical phenotypic presentation, or more severe phenotypes.

The diagnosis of FOP can easily be made by clinical evaluation. Confirmatory genetic testing is available. Delayed diagnosis still occurs, despite the hallmark changes in great toes. Differential diagnoses are varied but often include progressive osseous heteroplasia (POH), osteosarcoma, lymphoedema, soft tissue sarcoma, desmoid tumours, aggressive juvenile fibromatosis, calcinosis of skin and muscles, infection and non-hereditary (acquired) heterotopic ossification. Although most cases of FOP are sporadic (non-inherited mutations), a small number of inherited FOP cases show germline transmission in an autosomal dominant pattern.

At present, there are no definitive treatments for FOP, but a brief, 4-day course of high-dose corticosteroids combined with nonsteroidal anti-inflammatory drugs (NSAIDs), started within the first 24 h of a flare-up, may help to reduce the intense inflammation and tissue oedema seen in the early stages of the disease [2]. Preventative management is based on prophylactic measures against falls, respiratory decline and viral infections. The median estimated lifespan is 56 years [10]. Most patients are wheelchair bound by the end of the second decade of life and commonly die of complications of thoracic insufficiency syndrome [1, 10].

The dramatic presentation of FOP and growing understanding of the disease's pathogenic mechanisms have triggered strong and growing interest in clinical trials for novel treatments in FOP. These studies have highlighted the need for understanding the unique clinical features of FOP and how they affect clinical trial design and execution.

The International Clinical Council on FOP (ICC)

The ICC was established in 2016 to provide consolidated and coordinated advice on the best practices for clinical care and clinical research for those who suffer from FOP. The founding members are 19 internationally recognized physicians who are clinical experts in FOP and who have a deep understanding of the challenges and the needs of patients with FOP. The missions of the ICC are:

- to educate on best practices for the care of individuals with FOP;
- to advise on the design and conduct of interventional trials in patients with FOP;
- to update the FOP clinical guidelines;
- to advocate for a robust infrastructure for data sharing and collaboration on vital and emerging matters of clinical concern to the FOP community;
- to identify less-explored areas of caring for patients with FOP and issues that may drive insight into research;
- to share valuable clinical experiences from the care of patients with classic and variant FOP; and
- to better understand the variable phenotype of FOP and the systemic nature of FOP pathology.

One of the key challenges identified by the ICC was the need for FOP-specific guidelines to support the development of safe and transformative treatments for patients with FOP worldwide. The ICC seeks to provide research scientists at university laboratories, pharmaceutical companies, biotechnology firms and government agencies with expert advice on clinical research trials tailored to the FOP community. Here, we discuss the major challenges and considerations for successful clinical trials that are specific to the FOP community. These considerations are meant to complement the standard approaches for clinical trial design and execution by highlighting considerations specific to the FOP community.

Methods

We identified an unmet need for a consolidated collection of clinical trial considerations directly relevant to the FOP

community, with a particular focus on safety and clinical trial procedures. The Clinical Trials Committee, composed of eight experts in clinical trials and FOP clinical care, met using a longitudinal round-table discussion format via web conferences and in-person meetings. The committee reviewed the clinical course and management of FOP in the literature and in personal experience; the current treatment guidelines [1]; current US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommendations for the design of clinical trials; and discussed personal experiences with clinical studies related to patients with FOP. The committee focused on the four main steps of a clinical trial (preclinical, trial design, trial execution and post-trial evaluation) to identify areas where FOP-specific considerations were particularly important, as they could substantially affect the success of a trial and the safety of subjects. These topic areas were reviewed by the full ICC, which included 21 clinical experts in FOP and one patient representative. The Clinical Trials Committee then consolidated and further developed the recommendations. The final considerations were then reviewed by the committee and by the full ICC.

Results

The ICC Clinical Trials Committee identified challenges that were important for both investigator-initiated and industry-sponsored studies. In addition, the committee recognized that these considerations are not exclusive, and that the considerations are not meant to be used to dictate specific clinical trial design or methods, as those considerations are often agent or location specific and best left to trial investigators. Furthermore, the committee recognized that ongoing clinical studies and improvements in clinical care will continue to reveal more FOP-specific considerations as our knowledge about FOP disease pathogenesis improves. Thus, the Clinical Trials Committee and the entire ICC sought to establish a common foundation for discussions about critical considerations that are specific to the FOP community.

Pre-clinical study development

Engage established experts in FOP clinical care, such as the members of the ICC, as a resource during early study design. Investigators and companies are encouraged to use the ICC as an advisory resource for discussing trial design and potential strengths/weaknesses of a particular study. The ICC will not serve as a governing body or require ICC approval for a study, as primary responsibility lies with the primary investigators (PIs) and sponsor. The ICC will have mechanisms for maintaining confidentiality.

Engage the FOP community, including patients with FOP, early on in study design. Patients with FOP have unique limitations and requirements for participating in a study. Understanding these requirements early in the study design process can help to maximize the success of a study and safety for FOP participants.

Clinical studies should be based on preclinical rationales in model systems. Trial rationales should be supported by appropriate preclinical data in an appropriate preclinical model. This could include demonstration of efficacy in established genetic mouse models of FOP, with demonstration of *in vitro* signalling or biological effects, as appropriate. Whenever possible, assessment of non-HO effects should be included, including but not limited to potential reproductive, neurological, cardiac, pulmonary, gastrointestinal, growth and developmental, oral/dental and haematological complications.

Ideally, preliminary studies should include sufficient assessment in humans for safety in an appropriate parallel population with age- and sex-matched subjects. Ideally, human preliminary data should be used to maximize safety. These should include information in both sexes and in an appropriate age range relevant to the study and potential follow-up studies.

Trial design

Use of the best possible clinical trial designs to assess potential therapies. Formal clinical trials, performed in a way consistent with future regulatory approval and with strong scientific rigour, are the best way to determine the efficacy and safety of any potential therapy. The small population of patients with FOP necessitates careful planning, to ensure that the results are as robust as possible.

All studies should have ethics committee approvals. All clinical trials should obtain the approval of the applicable local ethics committee and be scientifically validated before any investigational therapy is given to a subject.

Pediatrics as the battleground. Trials that can include children are encouraged, provided that the appropriate safety data, indications and preliminary data are present and in compliance with local regulations such as those proposed by the European Commission [11]. Trials of medications that may already be used in paediatric populations for other conditions, and drugs that may be generic or of lower cost, are of particular interest.

Protection for a vulnerable population. Patients with FOP are considered disabled and are thus a vulnerable population. Appropriate protections for consenting and data sharing should be implemented. Genetics studies should have adequate protections, given the extremely small population of patients with FOP and the high risk of de-identification, particularly when combined with imaging. All genetic studies, such as those including DNA sequencing, RNA sequencing and microbiome studies, need to be appropriately de-identified and properly consented. Likewise, imaging data, particularly whole-body imaging, are unique to each subject and could allow de-identification based on HO patterns.

Emphasis on safety. Trials need to be designed with subject safety as the topmost priority. We encourage all companies and research groups to share primary data from safety trials directly with the investigators, and not rely solely on

summary data often presented in investigator brochures. This is particularly important for investigator-initiated studies, as safety information may not be readily available or scrutinized by regulatory agencies, such as the FDA or EMA. We recognize that some of these data may be sensitive, so a two-way nondisclosure agreement is preferable within the project team. We also encourage investigators to use the ICC as a resource to support and maintain safety.

FOP-specific health considerations should be included in trial design and safety assessments. Key considerations unique to FOP are listed below. These considerations, as well as study-specific risks, should be clearly discussed with all subjects with FOP.

a. **Repeated blood draw/intravenous access complications:** patients with FOP can tolerate peripheral blood collection when performed carefully by an experienced phlebotomist. It is critical that the procedure be performed in as gentle and minimally invasive manner as possible. Tourniquet time and number of blood draw attempts should be minimized, according to the current FOP treatment guidelines. Consultation with clinicians who are familiar with the care of patients with FOP is critical.
b. **Respiratory complications:** Patients with FOP are at risk of restrictive lung disease because of chest wall HO, congenital malformation of the costovertebral joints [1] and possibly changes in lung physiology [12]. Patients with FOP are also extremely difficult to intubate owing to their cervical spine malformations, jaw involvement and HO [1, 13]. Clinical trials should consider these risks, and whether monitoring is needed. In addition, healthcare providers should be trained with a standard operating procedure for managing patients with FOP in the event of anaphylaxis or respiratory failure. These procedures should include FOP-specific processes for intubation of the trachea, following the current FOP treatment guidelines [1] and best practices of airway management of patients with FOP [13].
c. **Infection complications:** Although patients with FOP are not known to be at higher overall risk for infections, respiratory infections can be especially devastating, given the respiratory compromise present in affected patients with FOP and the lack of immunizations [1]. Appropriate management strategies, including the use of universal precautions and contact precautions, as well as prophylactic medications such as oseltamivir (Tamiflu), should be incorporated into study protocols as appropriate. In addition, extra care should be taken to prevent hospital-acquired infections. These are best documented with a standard operating protocol for the team.
d. **Gastrointestinal complications:** Many patients with FOP have decreased mobility of their jaw. In addition, a number of patients with FOP report frequent nausea or vomiting. This should be considered as vomiting in a patient with FOP may be associated with a higher risk of pulmonary aspiration. Limited jaw mobility may also affect choice of how an oral medication is administered (i.e. pill size, or need for powders or liquids). Monitoring of maximal jaw opening, or assessments of salivary flow, may be incorporated depending on the trial design and pharmacological compound.
e. **Neurological considerations:** Patients with FOP have reported a higher incidence of neurological concerns including pain, both during and out of a FOP flare [1, 14]. In addition, some patients with FOP have neurological changes, as seen on magnetic resonance imaging (MRI), such as central nervous system demyelination [5]; however, the significance of these changes is unclear. Pain measures should be included in any clinical trials, with appropriate clinical management available for subjects.
f. **Potential complications of blood pressure measurements:** Blood pressure measurements have been anecdotally reported to be associated with the triggering of FOP flares but clear correlation with flares has not been studied systematically. Blood pressures should be taken as infrequently as possible, in a manner that follows the current FOP clinical guidelines [1]. Blood pressure should be taken manually, with minimal cuff inflation, and with as short of a duration of cuff inflation as necessary. Repeated blood pressure measurements should be avoided whenever possible.
g. **Radiology considerations:** Although patients with FOP have no known increase in complications from radiation exposure, transportation to a radiology site and positioning for the appropriate imaging can be extremely challenging because of the HO and body positioning. Subjects, care givers and healthcare staff should be trained about the limitations of mobility. Adequate soft padding and safe transfer equipment should be provided to the radiology team to position a subject properly for imaging. Finally, some subjects will not be able to be imaged owing to their ankylosed joints. Clinical trials should consider this at the time of enrolment and during the study, as a subject's status may change over the duration of a study.
h. **Mechanism for rapid response to a FOP flare-up:** FOP flares can occur spontaneously, with no clear triggering event. The standard operating protocol of all trials should include mechanisms for rapid assessment, response and treatment of potential FOP flare-ups to decrease the risk of HO formation.
i. **Travel risks**: As FOP affects joint mobility, patients with FOP are at increased risk of injury during travel, particularly in busy transportation hubs such as airports. Sufficient times for transfers, as well as pre-arrangements for wheelchairs and transport assistance, and the need for caregivers to travel with subjects, should be discussed with any potential subject and incorporated into the standard operating protocols for clinical studies. Potential risks for physical strain should also be considered at all steps along a travel route. In addition, the screening of potential subjects for safety during travel (i.e. the risk of respiratory failure during a long flight) should be performed routinely as part of any trial.

Considerations for paediatric patients with FOP. Clinical trials involving children should utilize a team with experience in caring for paediatric patients with FOP. Study procedures, such as phlebotomy and imaging, can be very difficult and anxiety-provoking. In addition, some procedures that are normally conducted with sedation or general anaesthesia, such as imaging studies in very young children, are associated with much higher risks in children with FOP because of respiratory compromise, restricted neck

movement, restricted jaw movement and anaesthesia risks in patients with FOP (see respiratory complications in the 'FOP-specific health considerations' section above). Clinical studies should also be designed to consider the needs of children, including prevention of fatigue, minimization of procedures, using the lowest radiation doses possible, minimizing the stresses of travel/time zone changes and keeping days missed from school to a minimum. Additional considerations for the families, including the need for families to identify childcare support for younger siblings or for the family to travel together, should be incorporated into the study design. Finally, recognition of the specific social/emotional needs of children and adolescents (such as empowerment in decision making) can be extremely valuable for successful trial execution in this subject population [15].

International cooperation. Multinational trials are strongly encouraged. This is important for recruitment but also for spreading key resources and knowledge about FOP. Although medical management is largely standardized according to the FOP treatment guidelines [1], management of FOP complications can vary significantly, based on the availability of local resources (i.e. mobility devices, management strategies and so forth).

Limited subject availability. As with other rare and orphan diseases, trials need to be designed with an understanding and appreciation of the very limited number of patients with FOP in the world, as well as the even more limited number of centres with the multidisciplinary clinical expertise for successfully executing trials. Where and when appropriate, subjects with non-*ACVR1* R206H variants of FOP should be included.

Innovative trial design. Placebo-controlled trials are important for scientific integrity but can be challenging for FOP families because of the rarity and severity of the disease, and is likely to present ethical challenges once even partially effective medications become available. We encourage innovative trial designs, including randomized trials with a crossover of the placebo group to active treatment, use of annotated historical control data, and non-inferiority designs using active comparators in studies where efficacy has already been proven. We encourage trial designs that allow subjects to continue on the medications after the trial ends (i.e. open-label phase or other equivalent system) if the medications show evidence of efficacy. This is especially important in less-resourced countries where post-trial access to therapy may be a challenge because of cost. As a result of new paediatric legislation in Europe and North America, it is now customary for industry-sponsored clinical trials with new medications to involve centres in less-resourced countries [11].

Common study endpoints. Data, including those derived from subjects who receive placebo or are in observational studies, should have common assessments and outcome measures. Plans should be established for the raw data to be shared whenever possible [i.e. via the International FOP Association (IFOPA) registry]. This will help to maximize the impact from the small number of subjects by allowing for direct comparisons of outcomes. It will also increase the number of subjects that could be used as a virtual control arm, particularly as treatment-naive subjects become less common. These common assessments should include the following:

a. **A core set of baseline data** should be obtained, covering baseline patient characteristics (i.e. demographics, extent of HO, functional status, associated FOP features, genetic variants, and pain assessments) and baseline flare-up activity (i.e. frequency, duration, locations and flare symptoms).
b. **Common assessments** of the investigational agent should be collected, including but not limited to the effect on frequency of flares, extent of established and new HO, functional assessments and tolerability/toxicity of the agent concerned.
c. **Functional assessment** should include the cumulative analogue joint involvement scale (CAJIS) [16], assessed by a physician.
d. **Patient-reported outcomes** should include activities of daily living and quality of life assessments [such as the FOP Independent Activity of Daily Living (FOP I-ADL) Questionnaire or FOP-Physical Function Questionnaire (FOP-PFQ) and EuroQol 5 dimensions questionnaire with a three-level scale (EQ-5D-3 L)].
e. **Volumetric measurements of ossification** via total body (preferred) or site-specific new HO by low-dose computed tomography (CT) should be included. This will also allow quantitation of bone formation. Other related assessments, such as ^{18}F sodium fluoride positron emission tomography (PET)/CT can also be considered [17, 18]; however, availability may be limited in some institutions.
f. **Where alternate scores or measures are used, these need to be demonstrated to be at least equivalent in performance** to the recommended measures, and ideally have known and close correlation with the recommended measures.

Clinical trial execution

Sufficient resources should be allocated for execution of the study. People affected by FOP have unique needs and often do not travel frequently owing to their high care needs. In addition, sufficient resources for robust documentation, consistency and high data quality are important for all studies, following international and local medical and ethical standards. We recommend close consultation with FOP expert centres, the ICC and the FOP community, to make sure that assessments are practical, safe and will yield usable data.

Travel considerations. The transportation of a patient with FOP involves many factors. Pretrial assessment may require close coordination with the local physicians and FOP experts, particularly if there is a risk of respiratory compromise, as patients with FOP are at increased risk of complications from hypoxia, injury and fatigue [1, 19]. Appropriate medical management teams should be available on site to assist with potential complications. Appropriate caregivers should be allowed to travel with the subjects on site (usually one or two

caregivers) for routine assistance, as well as injury prevention during travel. Specific travel considerations are discussed below.

a. **Travel seating:** Patients with FOP have a limited range of motion, limbs fixed in awkward positions and areas of heterotopic bone that may be protruding. Seating in aircraft, trains or other vehicles should accommodate these by providing sufficient padding, comfort and support, including those customized for or currently used by the FOP subject. In addition, rest breaks should be provided, to minimize the risks of developing pressure sores and deep vein thrombosis. Whenever possible, transport in the patients' own wheelchair should be accommodated, as this often has the best support to minimize fatigue and injury.
b. **Hotels and lodging must be Americans with Disabilities Act (ADA) accessible:** Although some hotels are considered ADA accessible, they may not be fully compatible with motorized wheelchairs or patients with FOP (i.e. located at the top of a hill or unable to accommodate subjects with significant physical deformities such as outstretched extremities). Prescreening of facilities and asking the subjects for details about their needs can be very helpful for visit planning.
c. **Trial visits:** Fatigue is a major issue for patients with FOP. Consideration for preventing subject fatigue (i.e. by minimizing travel or by scheduling half-day assessments with sufficient rest) are important for reducing injuries or flares related to the trial visit.
d. **Blood draws in patients with FOP can be difficult** owing to poor venous access, contractures and unusual positioning. A consistent, experienced phlebotomy team experienced with patients with FOP is critical for success. This includes any outpatient or home care blood draws. Use of a vein finder/ultrasound can be extremely helpful. Documentation of prior attempted and successful phlebotomy sites, and any complications related to blood draws, is beneficial for maximizing safety. In addition, established protocols for minimizing phlebotomy and trauma are critical (including a recommended tourniquet time of less than 1 min to minimize risks of hypoxia).
e. **Considerations for children with FOP:** Fasting blood draws are extremely difficult and anxiety provoking. Child Life Services should be engaged whenever possible, and needle desensitization training [20] under the care of an experienced professional should be considered if available. Imaging with ionizing radiation should be kept to a minimum owing to risks in all paediatric populations [21]. Procedures that place children with FOP at additional risk (such as the use of general anaesthesia for imaging, or increased risk of fatigue from long clinic visits or multiple sequential assessments) should be carefully planned or minimized whenever possible.
f. **MRI, CT and PET/CT scanning options may be limited owing to contractures and HO.** Careful and creative positioning may be needed (i.e. scanning cranial and caudal portions separately). MRIs may not be possible, depending on the nature of the contractures or immobility. We recommend considering obtaining subject photographs prior to arrival and screening, so that the positioning or suitability of an imaging modality can be assessed beforehand. Imaging facilities should have plans in place for safe transfer of subjects onto the imaging table (lifts or dedicated lift teams).

Subjects and accompanying care providers should have adequate health and travel insurance. This is critical, as subjects with FOP are at high risk of complications from any injury with transportation, and of a worsening of any flares due to travel injuries or fatigue. Appropriate medical insurance that is effective at all points along the travel route should be provided, with the ability to cover pre-existing conditions (i.e. those related to FOP). This should be explicitly described to the potential subject. International patients are particularly vulnerable, given differences in coverage in their host country, as well as longer or more challenging travel requirements.

Post-clinical trial

Timely publication/data release. Trials should have a plan for rapid public release of data, both positive and negative. This is critical for the safety of patients and for the scientific integrity of the field. All clinical trials should include rapid adverse event recording and the sharing of findings whenever possible.

Cooperation for the benefit of the patients. We strongly encourage companies and all researchers to work with each other to the highest extent possible, including the sharing of baseline data, assessment tools and patient care experiences, as the number of subjects available for trials is extremely limited, and also because any major adverse event (i.e. death or disability) will have a major negative impact on all trials in the FOP arena.

Shared common data elements. Clinical trials should be designed to support ancillary observational trials, whenever possible (i.e. of baseline data). Trials should be performed with the assumption that the data collected and findings made will be maximally shared. Shared common data elements and endpoints are encouraged, such as quantitation of total HO, functional assessments (e.g. CAJIS score) and serum biomarkers. In addition, common data elements following public guidelines, such as through the National Institutes of Health (NIH) Common Data Element Initiative (https://www.nlm.nih.gov/cde/glossary.html) or shared elements with the IFOPA patient registry, are strongly encouraged.

Data deposition at end of trial. We encourage discussion with the IFOPA to leverage the global patient registry as a potential point for data sharing, particularly of placebo or baseline results that will be important for understanding the natural history of the disease. We also encourage public release of the raw data (such as sequencing data) following guidelines of large public agencies such as the NIH (https://grants.nih.gov/policy/sharing.htm) and using public repositories. This should be done at the time of publication, so that the field can benefit and potentially decrease risk to the patients with FOP.

Postmarketing/post-trial surveillance should be conducted for all agents. Many countries already require postmarketing studies for orphan drugs. However, all therapies tested in both investigator-initiated and industry-sponsored studies should have a procedure for long-term postmarketing or post-trial follow-up, to ensure the long-term safety and efficacy of the treatments. It is important to show how functional mobility changes over the long term since differences may not be readily detected in the shorter studies used for drug approvals. These longitudinal assessments should be implemented into the long-term postmarketing assessments.

Long-term access to effective experimental medications should be developed if possible and appropriate. Mechanisms for access to an effective experimental medication via a compassionate use programme or follow-up studies should be developed whenever possible. Consideration for less-resourced countries should be incorporated into the postclinical trial plan.

Leftover biospecimens should be shared whenever possible. Clinical trials provide a rare opportunity to study large numbers of patients with FOP together. Whenever possible, leftover biospecimens with appropriate annotations (but de-identified) should be made available for other researchers. This should be included in the consenting process.

Discussion

The recent interest in clinical trials for novel treatments for FOP is an exciting development for this rare but extremely severe disease. During the past few years, this interest has led to recognition that there needs to be a better understanding of the unique challenges that patients with FOP face in clinical trials. Understanding the social, emotional and disease context of each patient group can help to improve trial design and safety. This global approach is similar to the World Health Organization's International Classification of Functioning, Disability and Health framework [22]. Here, we identified the major considerations for clinical trials in FOP, including disease-specific factors such as risks of injury from trauma and unique requirements for transportation, as well as how the rare nature of FOP affects clinical trial design and execution. As in all clinical studies, subject safety takes utmost priority and should include a full consent process that allows for voluntary participation without coercion.

The results of our discussion among 21 clinical experts in FOP and one family representative allowed us to develop a strong consensus statement with key considerations for effective clinical trials in FOP. One major challenge that the ICC identified was the small number of clinicians with experience of caring for significant numbers of patients with FOP. This resource bottleneck meant that many investigators may have conflicts of interest related to their work in clinical trials, but would otherwise be highly qualified to serve in advisory roles. This is similar to other areas of rare-disease research. The ICC felt that open, early and public declaration of these potential conflicts, and the avoidance of anonymous consultations (i.e. via third-party data gathering companies, where potential conflicts cannot be identified), was the best strategy for promoting knowledge and safety in FOP-related clinical studies. An ethics committee within the ICC was constituted to support this open strategy.

Another major challenge that the ICC identified was the difference between investigator-initiated and industry-sponsored clinical trials – an area that has been explored in many disciplines [23]. Although trials that are designed to support a drug approval or application process must also follow established regulatory guidelines, other trials that are smaller or exploratory may be more limited in scope and resources. Our committee recognized that there are strengths and limitations in all formats of trials [24], but that investigator-initiated trials should also strive to meet similar standards for data quality and subject safety to larger trials or those sponsored by industry. Likewise, all clinical trials involving patients with FOP should take into account the increased resources and effort needed for safe and successful enrollment of subjects with FOP. Finally, we firmly believe that strong cooperation between academics, industry, clinicians and patient support groups is absolutely critical for developing effective therapies for this devastating disease.

These guidelines are not exclusive or comprehensive. They are not meant to be used to dictate specific clinical trial design or methodology – those types of concerns are often agent- or location-specific and best left to trial investigators. Rather, the ICC seeks to establish a common foundation for discussions about critical considerations that are specific to the FOP community, with the main focus being patient safety. Together, we believe that these FOP-specific considerations, along with established processes for robust and safe clinical trials, will help to enhance FOP subject safety and maximize clinical trial result yield for the entire FOP community.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [25], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [26].

Competing Interests

E.C.H., M.D.R., M.Z., M.A.M., R.J.P., C.N., R.K., G.B., M.A.B., C.D.C., P.D., N.H., F.S.K. and E.M.W.E. receive clinical trials research support from Clementia Pharmaceuticals. R.J.D. and R.M. are consultants for Clementia Pharmaceuticals. M.Z. is on the data safety monitoring board for Clementia Pharmaceuticals. E.C.H., M.A.M., R.J.P., M.D.R., M.A.B., E.M.W.E., R.K., and F.S.K. receive clinical trials research funding from Regeneron Pharmaceuticals. R.M. is a paid consultant for Regeneron Pharmaceuticals. E.C.H., C.N., R.K., G.B., M.A.B., C.D.C., M.D.R., R.J.P., M.Z., P.D., C.S., N.H., K.Z., R.M., F.S.K. and E.M.W.E. also serve as unpaid volunteers on the International FOP Association Medical Registry Advisory Board. E.C.H., E.M.W.E., R.J.P. and F.S.K. serve as unpaid

volunteers on the FOP Biomarker Consortium. E.C.H. also serves as an unpaid volunteer on the Fibrous Dysplasia Foundation Medical Advisory Board. M.D.R. is a consultant and/or speaker for Sanofi-Genzyme, Shire, Alexion, Biomarin, Chiesi, Clementia Pharmaceuticals, and Regeneron Pharmaceuticals. M.D.R. receives clinical trial research support from Sanofi, Genzyme, Alexion, Enzyvant. A.C. is a trustee of the Radiant Hope Foundation and trustee of the Ian Cali FOP Research Fund - PENN Medicine - Center for Research in FOP & Related Disorders, and is an unpaid volunteer with Clementia Pharmaceuticals Burden of Illness Advisory Group. P.D. is an unpaid medical advisor for FOP Brazil. M.A.M. and M.Z. are nonpaid consultants for BioCryst. E.M.W.E. is an advisor for AstraZenica and Blueprint Pharmaceuticals. Z.G. is a nonpaid consultant for the Natural History Study on FOP Board. R.K. also receives research support from UltraGenyx; is a paid consultant for Clementia Pharmaceuticals, Regeneron Pharmaceuticals, UltraGenyx, Internis, and Alexion; and is a nonpaid member of the Medical Advisory Board for the UK Brittle Bone Society.

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References

1 Kaplan FS, Shore EM, Pignolo RJ, Hsiao EC, FOP TICCo. The medical management of fibrodysplasia ossificans progressiva: current treatment considerations. Clin Proc Intl Clin Consort FOP 2011; 4: 1–100.

2 Pignolo RJ, Bedford-Gay C, Liljesthröm M, Durbin-Johnson BP, Shore EM, Rocke DM, *et al*. The natural history of flare-ups in fibrodysplasia ossificans progressiva (FOP): a comprehensive global assessment. J Bone Miner Res 2016; 31: 650–6.

3 Kaplan F, Shore E, Gupta R, Billings P, Glaser D, Pignolo R, *et al*. Immunological features of fibrodysplasia ossificans progressiva and the dysregulated BMP4 pathway. Clinic Rev Bone Miner Metab 2005; 3: 189–93.

4 Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. Pediatrics 2005; 116: e654–61.

5 Kan L, Kitterman JA, Procissi D, Chakkalakal S, Peng CY, McGuire TL, *et al*. CNS demyelination in fibrodysplasia ossificans progressiva. J Neurol 2012; 259: 2644–55.

6 Baujat G, Choquet R, Bouee S, Jeanbat V, Courouve L, Ruel A, *et al*. Prevalence of fibrodysplasia ossificans progressiva (FOP) in France: an estimate based on a record linkage of two national databases. Orphanet J Rare Dis 2017; 12: 123.

7 Bauer AH, Bonham J, Gutierrez L, Hsiao EC, Motamedi D. Fibrodysplasia ossificans progressiva: a current review of imaging findings. Skeletal Radiol 2018; 47: 1043–50.

8 Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho TJ, Choi IH, *et al*. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet 2006; 38: 525–7.

9 Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, Carroll L, *et al*. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat 2009; 30: 379–90.

10 Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. J Bone Joint Surg 2010; 92: 686–91.

11 Ruperto N, Vesely R, Saint-Raymond A, Martini A. Paediatric Rheumatology International Trials Organisation (PRINTO). Impact of the European paediatric legislation in paediatric rheumatology: past, present and future. Ann Rheum Dis 2013; 72: 1893–6.

12 Wentworth KL, Bigay K, Chan TV, Ho JP, Morales BM, Connor J, *et al*. Clinical-pathological correlations in three patients with fibrodysplasia ossificans progressiva. Bone 2018; 109: 104–10.

13 Kilmartin E, Grunwald Z, Kaplan FS, Nussbaum BL. General anesthesia for dental procedures in patients with fibrodysplasia ossificans progressiva: a review of 42 cases in 30 patients. Anesth Analg 2014; 118: 298–301.

14 Kitterman JA, Strober JB, Kan L, Rocke DM, Cali A, Peeper J, *et al*. Neurological symptoms in individuals with fibrodysplasia ossificans progressiva. J Neurol 2012; 259: 2636–43.

15 Wulf F, Krasuska M, Bullinger M. Determinants of decision-making and patient participation in paediatric clinical trials: a literature review. Open J Pediatr 2012; 1: 1–17.

16 Kaplan FS, Al Mukaddam M, Pignolo RJ. A cumulative analogue joint involvement scale (CAJIS) for fibrodysplasia ossificans progressiva (FOP). Bone 2017; 101: 123–8.

17 Eekhoff EMW, Botman E, Coen Netelenbos J, de Graaf P, Bravenboer N, Micha D, *et al*. [18F] NaF PET/CT scan as an early marker of heterotopic ossification in fibrodysplasia ossificans progressiva. Bone 2018; 109: 143–6.

18 Eekhoff EMW, Netelenbos JC, de Graaf P, Hoebink M, Bravenboer N, Micha D, *et al*. Flare-up after maxillofacial surgery in a patient with fibrodysplasia ossificans progressiva: an [18F]-NaF PET/CT study and a systematic review. JBMR Plus 2018; 2: 55–8.

19 Wang H, Lindborg C, Lounev V, Kim JH, McCarrick-Walmsley R, Xu M, *et al*. Cellular hypoxia promotes heterotopic ossification by amplifying BMP signaling. J Bone Miner Res 2016; 31: 1652–65.

20 McMurtry CM, Noel M, Taddio A, Antony MM, Asmundson GJ, Riddell RP, *et al*. Interventions for individuals with high levels of needle fear: systematic review of randomized controlled trials and quasi-randomized controlled trials. Clin J Pain 2015; 31 (Suppl. 10): S109–23.

21 Mulvihill DJ, Jhawar S, Kostis JB, Goyal S. Diagnostic medical imaging in pediatric patients and subsequent cancer risk. Acad Radiol 2017; 24: 1456–62.

22 World Health Organization. International Classification of Functioning, Disability and Health. Geneva: World Health Organization, 2001.

23 Laterre PF, Francois B. Strengths and limitations of industry *vs*. academic randomized controlled trials. Clin Microbiol Infect 2015; 21: 906–9.

24 Reed CR, Camargo CA Jr. Recent trends and controversies in industry-sponsored clinical trials. Acad Emerg Med 1999; 6: 833–9.

25 Harding SD, Sharman JL, Faccenda E, Southan C, Pawson AJ, Ireland S, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acids Res 2018; 46: D1091–106.

26 Alexander SPH, Fabbro D, Kelly E, Marrion NV, Peters JA, Faccenda E, *et al*. The Concise Guide to PHARMACOLOGY 2017/18: Enzymes. Br J Pharmacol 2017; 174: S272–359.