Patient Centricity: Design and Conduct of Clinical Trials in Orphan Diseases: Third of Three Sets of Expanded Proceedings from the 2020 ISCTM Autumn Conference on Pediatric Drug Development

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Innov Clin Neurosci. 2023;20(1–3):25–31.

ABSTRACT

This article expands on a session, titled "Patient Centricity: Design and Conduct of Clinical Trials in Orphan Diseases," that was presented as part of a two-day meeting on Pediatric Drug Development at the International Society for Central Nervous System (CNS) Clinical Trials and Methodology (ISCTM) Autumn Conference in Boston, Massachusetts, in October 2020. Speakers from various areas of pediatric drug development addressed a variety of implications of including children in drug development programs, including implications for rare/orphan diseases. The speakers have written summaries of their talks. The session's lead Chair was Dr. Joan Busner, who wrote introductory and closing comments. Dr. Simon Day, regulatory consultant, outlined some of the past mistakes that have plagued trials that did not consult with patient groups in the early design phase. Dr. Atul Mahableshwarkar provided an industry perspective of a recent trial that benefited from the inclusion of patient input. Drs. Lucas Kempf and Maria Sheean provided regulatory input from the perspectives of the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA), respectively. Dr. Judith Dunn outlined a novel approach for assessing and rank ordering patient and clinician clinical meaningfulness and the disconnect that may occur. Dr. Busner provided closing comments, tied together the presented issues, and provided a synopsis of the lively discussion that followed the session. In addition to the speakers above, the discussion included two representatives from patient advocacy groups, as well as an additional speaker who described the challenges of conducting a pediatric trial in the US and European Union (EU), given the often competing regulatory requirements. This article should serve as an expert-informed reference to those interested and involved in CNS drug development programs that are aimed at children and rare diseases and seek to ensure a patient-centric approach.

KEYWORDS: Patient centricity, CNS orphan drug development, CNS pediatric drug development, CNS rare disease drug development

INTRODUCTION—JOAN BUSNER, PhD

The Autumn 2020 International Society for Central Nervous System (CNS) Clinical Trials and Methodology (ISCTM) special, two-day meeting on Pediatric Drug Development finished with a three-hour session, titled "Patient Centricity: Design and Conduct of Clinical Trials in Orphan Diseases." The session brought together regulators from the United States (US) and European Union (EU), medical/science leaders from industry and government, and, importantly, patient advocates currently involved in trial consultation and design. The session was an outgrowth of the ISCTM Working Group on Rare Disease/Orphan Drug Development, chaired by Drs. Joan Busner and Gahan Pandina.

Dr. Simon Day, a regulatory consultant from the United Kingdom (UK) and active member of the working group, who has long recommended the collection and analysis of real-life trial examples from sponsors, introduced the session with provocative statements about the many mistakes that might have been avoided had patient groups been included in the initial design of trials.

The next two speakers, Dr. Eva Kohegyi of Otsuka Pharmaceuticals and Dr. Atul Mahableshwarkar, then at Emalex, provided candid discussions of actual CNS pediatric trials they have overseen. Dr. Kohegyi discussed the challenges of satisfying more than one regulatory agency (in this case, the US Food and Drug Administration [FDA] and EU European Medicines Agency [EMA]) in adhering to pediatric drug development rules in an adolescent schizophrenia trial, and Dr. Mahableshwarkar explored some of the challenges and additional patient burden imposed by regulatory requests to add measures to a protocol, as well as the challenges posed by the COVID-19 pandemic.

We then received regulatory responses and perspectives from Dr. Lucas Kempf, formerly

FUNDING: No funding was provided for this article.

DISCLOSURES: Dr. Busner is a full-time employee of Signant Health and may own stock/stock equity. **Dr. Pandina** is a full-time employee of Janssen Research & Development, LLC, and a Johnson & Johnson stockholder. **Dr. Mahableshwarkar** was a full-time employee of Emalex Biosciences and is currently the President/Owner of ARM Pharma Consulting. All other authors have no conflicts of interest relevant to the content of this article.

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with the FDA's Office of Rare Diseases and currently with Parexel, and Dr. Maria Sheean of the Orphan Medicines Office of EMA.

The second half of the session was devoted to examples of unique and successful patient-centric approaches.

Dr. Judith Dunn of Fulcrum reported the methodology and results of a comprehensive study designed specifically to establish and rank order patient/caregiver treatment goals for Fragile X syndrome (FXS). The study provides a means of eliciting clinical meaningfulness to patients, as well as other stakeholders, and can be applied to other conditions.

Next, Traceann Rose of the Children's Tumor Foundation presented on the extraordinary inroads that her organization and other patient advocacy groups have made, both in helping pharmaceutical companies design trials and helping regulators evaluate trial outcomes.

An engaging discussion followed the sessions.

INVOLVING PATIENTS IN DESIGN OF CLINICAL STUDIES—SIMON DAY, PhD

It seems incredible to many of us that we would design a study (in a rare disease or otherwise) without actually talking to the people who are affected by that disease. Do companies that produce shampoo, dog food, or cars not get feedback from their potential customers? In developing new medicines, medical devices, and so on, patients are not only the ultimate customer, but companies need patients to take part in their trials. Patients are not an optional extra, but the reality is that, yes, many companies do still try to develop new therapies without seeking out patient and caregiver feedback on the design of studies, choice of important endpoints, dosing, or even treatment packaging. The situation is improving, but it is improving from a very low baseline.

Legislation to recognize orphan indications is nearly 40 years old in the US (the Orphan Drug Act was signed on January 4, 1983; it became Public Law 97-414). Other regions of the world took longer to follow this path—and some countries still have no legal recognition of the situation—but the difficulties of how to study rare diseases and generate sufficient evidence on the efficacy, safety, and benefit-risk balance of therapies when there are very few patients available to study have only been addressed more recently.

Around the end of the 1990s and early 2000s, there was almost no written guidance on what seemed to be, at the time, the intractable problem of doing "proper" clinical trials when the numbers of patients were extremely limited. The European regulators (Committee for Medicinal Products for Human Use [CHMP]) began writing guidance late in 2001, around the same time that the Institute of Medicine published a monograph, titled *Small Clinical Trials: Issues and Challenges*.[1] That monograph was initiated by the National Aeronautics and Space Administration (NASA), who were interested in the very obvious problem of how to do medical experiments on their astronauts, who were clearly in limited supply! While the monograph contains many useful ideas, it is not at all clear that the involvement of astronauts in the design of studies was a particularly high priority. Recommendation 1 from the report says, "A multidisciplinary team of experts should be assembled to plan the research effort…" and "…individuals experienced in trial design, statistics, and medicine are needed…."[1] No mention then of patients (or astronauts). It was not until March 2005 that the CHMP guidance was released for public comment, and 15 months later, a final version was published.[2] Again, it has to be said that patient and caregiver engagement was not featured (the introduction says that the expertise of the drafting group, "includes clinicians, epidemiologists and statisticians…"[2]), but at least ideas on how to obtain and evaluate evidence on new therapies were beginning to see the light of day. The FDA also issued guidance similar to that of the CHMP, initially in August 2015, and then later in a revision in January 2019.[3] Both documents were (and are still) labeled as "draft," although their content is undoubtedly helpful. While the 2015 draft was silent on patient engagement, the 2019 revision was not. Section IX(A) is titled "Participation of Patients, Caregivers, and Advocates" and, although it is only a single paragraph, it has infinitely more consideration than previous documents had contained. In recent years, the FDA has issued a variety of additional guidance documents in the broad area of rare diseases, and patient involvement features highly in these.

A major program in the EU, the Seventh Framework Program, funded three notable methodological research projects during the period of 2014 to 2017. These were the Innovation in Small Populations Research (InSPiRe), Advances in Small Trials dEsign for Regulatory Innovation and eXcellence (ASTERIX), and Integrated DEsign and AnaLysis of small population group trials (IDEAL) programs.[4–6] Many research papers on methods for design, analysis, and interpretation of trials in rare diseases were published, and it is good to note that patients and caregivers were involved in these projects, albeit to a greater or lesser extent depending on the subject matter.

As time moves on, it is encouraging to see patients and caregivers making a more mainstream contribution to the discussion of evidence generation and the design and interpretation of research studies. Of note, the International Rare Diseases Research Consortium (IRDiRC) initiative—with aims including getting at least 1,000 new therapies for rare diseases approved by 2027, the majority of which should focus on diseases without approved options—instigated a task force on small population clinical trials that comprised clinical and methodological experts, regulators and, with no hesitation at all, patient representatives.[7,8] There are other groups and initiatives that equally engage with patients, such as ISCTM and the International Collaboration on Rare Diseases and Orphan Drugs (ICORD).[9]

However, the value of the contribution of patients is not fully embraced everywhere. For example, in the UK, the application form for ethical review of a study asks in what way patients are being involved in the intended research project; we still see examples such as "patients will be the subjects in the clinical trial," and no more than that. In discussion about design of clinical trials, we see examples from commercial sponsors such as, "Investigators have told us that patients would be unwilling to enter a placebo-controlled trial," and "The sponsor believes it is not ethical to randomize patients in a trial lasting longer than x months," both of which beg the question, did no one think to ask the patients what they think? We still see far too little of comments to the effect of, "We have asked patients and they have informed us…."

However, it is encouraging to note that, in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) is making positive steps forward. As of March 2021, when applications for new active substances and new indications are received, the applicant company is asked for evidence on the patient involvement activities the applicant undertook when developing their product, and this information is documented in medical assessment reports.[10] It is not yet a legal requirement for applicants to engage in such patient involvement activities, but this requirement to document what was (or was not) done is clearly sending a strong positive message.

All of us should welcome the involvement of patients and caregivers in future trials. It can only be beneficial to patients. And "patients" is why we do all this.

LESSONS FROM A TOURETTE'S STUDY—ATUL MAHABLESHWARKAR, MD

Study design. What is patient centricity in the context of a clinical trial? Yeoman et al[11] conducted a series of interviews, questionnaires, workshops, and validation exercises that led to patient centricity being defined as, "Putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family." If this definition is kept in mind while designing a clinical trial, not only would one have to consider a study that is least burdensome to the patient and their family, but also what they expect a beneficial outcome from the clinical trial to be. These burdens and desired outcomes are likely to be different in trials with adults as participants versus those involving children/adolescents. A brief description of designing and conducting a trial in children/adolescents with Tourette's syndrome (designated by the FDA as an orphan condition) and the impact of COVID-19 and shelter-in-place restrictions follows.

A randomized, parallel group, double-blind, placebo-controlled trial in patients with Tourette's syndrome between the ages of 6 to 17 years was designed to determine the efficacy of ecopipam, a dopamine D1 antagonist.[12] The study was designed after conducting meetings with members of the Tourette Association of America, expert clinicians who treat patients with Tourette's syndrome, and regulatory agencies (FDA, MHRA, and EMA Pediatric Committee). In addition to the primary efficacy measure (Yale Global Tic Severity Scale), the following secondary measures, the Clinical Global Impression of Severity and Improvement, a patient-completed quality of life measure, and a parent-completed improvement scale, were used to assess efficacy. Additionally, scales to evaluate changes in attention deficit hyperactivity disorder (ADHD), depression, anxiety symptoms, suicidal ideation and behavior, akathisia, and abnormal movements were also administered to patients, and additional study visits were added after discussions with regulators.

Completion of all these assessments leads to long study visits, which adds to the study burden of participants and caregivers and does not contribute to the desire of a "least burdensome study"[11] that has been defined by Yeoman et al. The scales and number of visits that were added after regulatory interactions showed that, even with a desire to design a minimally burdensome study, safety and other questions may require adding burdens to a study.

Study initiation and conduct. To recruit 150 patients for the study, about 60 sites in seven countries (US, Canada, France, Germany, Hungary, Italy, and Poland) were planned to be initiated; however, sites in Hungary and Italy chose not to participate. The first site was activated in May 2019, and by the time COVID-19-related shelter-in-place restrictions were declared in March 2020, 38 other sites were activated, and 32 subjects were randomized, which points to the importance of having a clearly defined study start up strategy; closely working with contract research organizations (CROs), solution providers, and others; and understanding potential differences in pediatric study requirements in different regions of the world to ensure that plans and reality converge.

Once COVID-19-related shelter-in-place restrictions were in effect, we faced the following questions: 1) Should currently enrolled participants continue in the trial? 2) Should new participants be enrolled in the trial? and 3) Should new study sites be activated for the trial? The first principle we followed was that participant safety is paramount and best decided by the principal investigators who are directly responsible for it; the second principle was that trial integrity and data quality have to be maintained, and that is the responsibility of the study team.

We contacted all active and potential study sites and determined those that were able to continue to work through the restrictions and manage participant safety. Sites that were active maintained trial activities, and we also initiated new sites that could recruit trial participants. Sites that had closed down research activities or were not initiating new activities were contacted periodically to assess changes in their situation, then activated as appropriate.

We took a number of steps to continue the study, while maintaining participant safety and study quality. A number of us participated in webinars wherein these issues were discussed, and we shared our experiences with colleagues in the industry. Following written, regulatory guidance, we amended the study protocol to permit remote assessments and engaged solution providers to implement Health Insurance Portability and Accountability Act of 1996 (HIPAA)-compliant platforms to permit remote evaluations of study participants. The trial statistical analysis plan was also amended to account for data that were not collected, and additional analyses were planned to understand the impact of such missing data. Arrangements were made to ship the study drug to participants' homes and, when necessary, arrangements were made with healthcare providers who could visit participants at their homes to collect labs, electrocardiograms (ECGs), and other tests. Since travel restrictions were in place, limiting physical visits to sites, monitoring of trial data collected at sites and verification of source data were also done remotely by providers.

One year after shelter-in-place restrictions were implemented, we had initiated an additional 34 sites, and 130 participants had enrolled in the study; the study was fully enrolled by June 2021. By working together with trial sites and learning from and sharing our knowledge and experiences with others like us, we maintained awareness of regulatory guidance and implemented necessary steps so that we were able to continue the trial safely and complete recruitment.

US REGULATORY PERSPECTIVE ON PATIENT-FOCUSED DRUG DEVELOPMENT IN RARE DISEASES—LUCAS KEMPF, MD

As a result of the 21st Century Cures Act and the FDA Reauthorization Act of 2017 Title I, the FDA has made recent efforts in patient-focused drug development. This focus is particularly important for rare diseases, since they have little-to-no current treatments. These efforts follow four stated goals, which include facilitating and advancing the use of systematic approaches to collecting and utilizing robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making; encouraging the identification and use of approaches and best practices to facilitate patient enrollment and minimizing the burden of patient participation in clinical trials; enhancing understanding and the appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes; and identifying the information related to treatment benefits, risks, and burdens that is most important to patients and how to best communicate that information to support their decision-making.[13,14]

These efforts have been implemented through a series of guidances, consistently advising patient groups and sponsors to engage early in the drug development process through critical path innovation meetings (CPIMs), patient-focused drug development (PFDD) meetings (both internally and externally led), patient listening sessions, and working with the National Organization for Rare Disorders (NORD) to identify experts to answer questions about diseases for which the FDA has little-to-no previous understanding; NORD also provides scientific advice on ways to improve inclusion and access to clinical trials operationally and scientifically to make a more representative sampling for diseases with unmet medical needs and has incorporated methods to assure that trial endpoints are fit for purpose and trials are efficiently designed for small populations. As more drugs are developed for this previously neglected area with little natural history information, a focus on making drugs that are meaningful for patients' unique problems is important.

PATIENT CENTRICITY: DESIGN AND CONDUCT OF CLINICAL TRIALS IN ORPHAN DISEASES—EMA REGULATOR'S VIEW—MARIA SHEEAN, MD

Patient engagement at the EMA. The EMA has interacted with patients since its early beginnings in 1996. These interactions evolved over time and resulted in a gradual inclusion of patients and patient representatives in EMA committees. For example, patients are represented in the EMA Management Board, the Committee for Orphan Medicinal Products (COMP), the Pediatric Committee (PDCO), the Committee for Advanced Therapies (CAT), and the Pharmacovigilance and Risk Assessment Committee (PRAC). In addition, the EMA has incorporated methods to collect patient input through direct consultation. In 2005, a framework was established to facilitate regular interaction with a network of European patient and consumer organizations. The framework aims at supporting the EMA to access real-life experiences of diseases and their management and obtain information on the current use of medicines. This contributes to understanding the value, as perceived by patients, of the scientific evidence provided during the evaluation process for the purposes of benefit-risk decision-making. In addition, the framework allows for more efficient and targeted communication with patients and consumers to support their role in the safe and rational use of medicines. Lastly, regular patient involvement enhances patient and consumer organizations' understanding of the role of the European medicines regulatory network.

The EMA has developed a robust system for involving patients, consumers, and their representative organizations in its activities, including the development of policies, regulatory guidance, and product-related evaluation. As a result, patient input is sought and considered by the EMA during the medicine life cycle. Opinion documents published by the EMA are written in plain English, with the aim of transparency and accessibility to lay readers, who may be patients or their relatives.

The type of involvement of each individual patient representative is varied at the EMA, spanning from representing the whole community (e.g., EMA Management Board), to representing organizations (e.g., during workshops and consultations) or lending individual expertise (e.g., during scientific advice or review of documents). This allows for flexibility of involvement, depending on the individual preference of the patient representative. In connection to an early medicine development plan, a retrospective, three-year survey (unpublished) shows that the number of patients involved in the EMA scientific advice is increasing. A vast majority of patients agree with the advice given to the applicant, and approximately half of discussions result from patients' comments, when patients are involved. Over half of these discussions result in a modification of the final advice. This indicates that patient voices are heard and systematically sought in the process of scientific advice at the EMA.

Methodology and lessons learned. The process of patient involvement requires flexible engagement methodologies. Depending on the context, patients need to be able to choose how they would like to contribute to the discussion, be it through face-to-face meetings, written statements, or patient preference surveys. The aim of this flexibility is to adapt to individual needs and improve chances for interactions. However, since regulators and stakeholders often use specialized language, appropriate support and training is needed. The EMA organizes training days and offers an array of published resources (e.g., information sheets, videos, and webpages) to support the education of patients. Continuous development of training methods is also encouraged. In the context of rare diseases, it's worth mentioning that regulatory awareness and clinical development basics are the subject of training organized for patients and offered by Eurordis, the European association of rare disease organizations, analogous to the US organization, NORD.

Finally, patient engagement is not always easy, and several challenges that merit future focus and continuous effort have been identified. In the EU, which comprises 27 member states and where many languages are used, patient availability and language barriers can pose a challenge. Therefore, tailored support to facilitate and enhance participation is needed. Due to many regulatory contexts in which patients may be engaged, it is also of extreme importance to

provide clear definitions and expectations. As with all stakeholders, the EMA has to manage potential conflicts of interest as well, since many patients are actively collaborating with pharmaceutical companies or other stakeholders. Finally, as much as patient input is considered important for regulatory decision-making, representativeness of this input needs to be gauged by taking into consideration multi-stakeholder communication.

Different small populations, different regulatory frameworks. Since this session is focused on patient centricity in orphan diseases, it is worth clarifying that the EMA developed various regulatory pathways applicable for various small population indications, which are not all orphan from the regulatory point of view. Some tools, such as scientific advice or the opportunity to apply to the Priority Medicines (PRIME) scheme, are valid for all kinds of developments targeting a small population. However, incentives associated with orphan designation would only be available to medicines targeting eligible rare diseases.[15,16] In the European framework, subsets of common diseases (e.g., biomarker-driven or agnostic indications) and personalized medicine approaches (e.g., innovative trials and product approaches) have not been considered eligible for orphan designation[17] and are sometimes better suited to regulatory consultation with the Innovative Task Force (ITF) platform at the EMA. Some orphan indications contain a pediatric element. In contrast to the FDA, all developments in pediatric indications, independent of their orphan status, are obliged to participate in the EMA's Pediatric Investigation Plan (PIP).

It is well recognized by EU regulators that developing a medicine in a rare population poses unique challenges. Applicants are therefore encouraged to initiate dialogue with the EMA during the product life cycle, selecting the appropriate route. Scientific advice is key to aligning the clinical development plan with regulatory expectations, and the financial burden of scientific advice is reduced/waived for holders of orphan designations or pediatric-only advice. There is a concerted and continuous effort from regulators of several jurisdictions to work together in sharing views and improving harmonization of regulatory decisions and advice. For example, the EMA offers access to parallel FDA-EMA scientific advice and joint health technology assessment (HTA) bodies-EMA scientific advice. Small-to-medium enterprise (SME) representatives can also seek regulatory support with the SME office at the EMA. Developers of patient registries may, in turn, seek advice from the Registries Task Force. Discussions with the PDCO may also offer clarity and regulatory alignment for the entire development plan, especially if paired with scientific advice. As mentioned before, all of these procedures may involve patient representatives from the EMA. However, applicants are also encouraged to initiate dialogue with patients early and consider their input in clinical development plans.

Lastly, to support stakeholders designing small population trials, several publications authored by the EMA staff can offer guidance.[8,18–21]

CAREGIVER PREFERENCES FOR THE TREATMENT OF MALE INDIVIDUALS WITH FRAGILE X SYNDROME—JUDITH DUNN, PhD

Understanding the treatment goals of patients and caregivers is the first step to incorporating these preferences into clinical trials. Recognizing the outcomes that patients value can and should influence clinical trial endpoint selection, as well as guide the development of sensitive and reliable assessment tools. The ability to robustly quantitate patient and caregiver preferences may also inform the statistical considerations associated with demonstrating clinical relevance.

FXS is characterized by a diversity of physical, cognitive, communicative, behavioral, and motor manifestations. The selection of clinical outcome measures relevant to patients and caregivers is particularly challenging in FXS due to this symptom heterogeneity.

FXS is a non-Mendelian trinucleotide repeat disorder that occurs in approximately 1 out of every 4,000 male individuals and 1 out of every 8,000 female individuals.[22] FXS is associated with distinctive physical features, including elongated face, protruding ears, and hyperextensible finger joints, which become more apparent in older children.

Additionally, FXS is the most common cause of inherited intellectual disability. Cognitive impairments include challenges in executive functioning, coordination, memory, and attention.[23] The psychiatric phenotype includes anxiety, stereotypic behaviors, aggression, agitation, and challenges with social functioning.[24]

Advances in molecular genetics have elucidated that FXS results from cytosine-guanine-guanine repeat expansions in the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene[25] on the X chromosome. This expansion causes disruption in the expression of fragile X mental retardation protein (FMRP), responsible for regulating the synthesis of many synaptic proteins. The absence of FMRP leads to abnormalities in brain development and function. Progress in understanding the developmental biology underlying FXS has led to increased clinical trial execution exploring potential new targeted medications. There has, however, been limited success. FXS remains a highly unmet medical need, as few, if any, clinical studies have demonstrated recognized value to patients.

Methodological issues, including inadequate efficacy benchmarking and lack of established endpoints, have contributed to these clinical failures. For example, between 2002 and 2017, almost two dozen trials evaluated seven different primary endpoints using 10 different tools.[26] To address these challenges, a working group convened by the National Institutes of Health (NIH) made a number of recommendations aimed at improving clinical trials in FXS, including collaborations to identify core measures, creation of a new behavior rating scale, and inclusion of input from patients or their proxies and caregivers.[27] The group recognized the limited information on reliability, validity, and sensitivity and limited quality of current instruments for treatment and suggested the continued development of objective measures that reflect meaningful improvements in quality of life.[28]

Consistent with the recommendation from the working group, a discrete choice experiment, supported by Genentech, was designed and conducted to collect caregiver perspective on unmet medical needs in FXS.[29] Choice experiments present respondents with a structured set of trade-off questions in which improvements in different disease

outcomes vary systematically between treatment options. Statistical analysis of the resulting pattern of choices revealed the implicit preference weights respondents attached to treatment outcomes.[29] Caregivers of individuals with FXS provide a unique and important perspective on desired outcomes and could contribute to establishing consensus on relevant endpoints.

The National Fragile X Foundation announced the survey on its website and Facebook page. Over 600 caregivers of male patients with FXS compared hypothetical treatment outcomes that varied in efficacy across six abilities: learning and applying new skills, explaining needs, controlling behavior, taking part in new social activities, caring for oneself, and paying attention. The abilities included in the survey were formulated by FXS experts, as well as family members of children and adults diagnosed with FXS. The relative importance of outcomes was quantified by both severity (transformed to a 10-point scale) and patient age group (child, adolescent, and adult).[29]

This was the first study to quantify the relative importance that caregivers place on improving different disabilities associated with FXS and established that significant differences exist in how different outcomes are valued. Improving the ability of individuals with FXS to control their own behavior (score: 10.0) and care for themselves (score: 9.9) were identified by caregivers as the most important treatment outcomes. Of the abilities compared, taking part in new social activities was rated as relatively least important (score: 4.2). Importantly, data also demonstrated that partial improvement of some outcomes was valued more than full resolution of other symptoms.[29]

Inclusion of patients and caregivers in the research process has the potential to improve our ability to detect and design for meaningful therapeutic effects in clinical trials. Tools such as discrete choice experiments may be helpful in the design of future studies, as they enable researchers to measure outcomes that are identified as demonstrating value recognized by patients and other stakeholders.

DISCUSSION—JOAN BUSNER, PhD

A highly productive and interactive discussion then followed, chaired by Drs. Lucas Kempf and Simon Day. In addition to the speakers listed above, a parent advocate, Renie Moss, MA, from the Tumor Foundation, joined and provided the perspective of a parent of a child with a rare disease. Ms. Moss discussed patient engagement training and the critical contributions her family has been able to make toward helping sponsors when developing treatment trials with clinical meaning for patients. Traceann Rose further described the role of preparing patients via the patient engagement training provided by the Children's Tumor Foundation.

Dr. Day asked the industry and regulatory representatives whether patient advocacy was routinely incorporated into drug development strategies. From the FDA perspective, Dr. Kempf mentioned the PFDD meetings held by the FDA, many of which he chaired. He reminded the group that for autism, patient advocates made it clear that a frequent industry treatment target, the reduction of repetitive behaviors, was not viewed as valid by many in the autism community, and that many patients believed these behaviors were adaptive and helped them cope.

Dr. Kohegyi mentioned that her company works frequently with patient advocacy groups, then added the personal rewards she's reaped by volunteering further with advocacy groups. Others said they had similar experiences.

Dr. Pandina noted that company emphases and studied disorders change over time, highlighting the need to maintain a network of internal and external therapeutic experts, as well as patient advocacy groups.

Dr. Mahableshwarkar mentioned the value of networking with large national advocacy groups. Ms. Rose added that other important national websites include the FDA website, which maintains minutes from PFDD meetings, as does NORD, the EU Patients Active in Research and Dialogues for an Improved Generation of Medicines (PARADIGM), and the National Tumor Foundation. These can all help inform trial designs and outcomes.

Dr. Busner wondered about the role of simulated trials, a concept in which patient advocates are asked to roleplay and comment on the feasibility of a proposed trial's schedule of procedures prior to its finalization. Ms. Moss noted the value of this method, but also highlighted the need to ensure that families don't feel pressured to respond in the manner they believe the pharmaceutical company is seeking.

Drs. Day and Pandina brought up some of the ethical considerations when families want the opportunity to access a treatment allowed by regulators, such as in the US via accelerated approval programs or in the EU via conditional marketing approval, and how this may then compete with the need to run a placebo-controlled trial to generate the best possible evidence. Dr. Pandina noted that this was an area in which an organization, such as ISCTM, might play a strong role in developing cross-company and cross-indication guidance.

Dr. Sheean noted the progress that the EMA is making in incorporating patient views into trial design, including the Innovative Medicines Initiative (IMI) and the PARADIGM program, and suggested the potential value of using experienced patient advocates to help educate less experienced patient advocates, so as to improve their ability to meaningfully participate in the full process.

AUTHORS' NOTE

Drs. Busner and Pandina served as Co-Chairs of the Patient Centricity Session. Drs. Day, Mahableshwarkar, Kemp, Sheean, and Dunn served as invited speakers.

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