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Optimizing expert and patient input in pediatric trial design: Lessons learned and recommendations from a collaboration between conect4children and European Patient-Centric Clinical Trial Platforms

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Abstract

Advice from multiple stakeholders is required to design the optimal pediatric clinical trial. We present recommendations for acquiring advice from trial experts and patients/caregivers, derived from advice meetings that were performed through a collaboration of the Collaborative Network for European Clinical Trials for Children (c4c) and the European Patient-Centric Clinical Trial Platforms (EU-PEARL). Three advice meetings were performed: (1) an advice meeting for clinical and methodology experts, (2) an advice meeting for patients/caregivers, and (3) a combined meeting with both experts and patients/caregivers. Trial experts were recruited from c4c database. Patients/caregivers were recruited through a patient organization. Participants were asked to provide input on a trial protocol, including endpoints, outcomes, and the assessment schedule. Ten experts, 10 patients, and 13 caregivers participated. The advice meetings resulted in modification of eligibility criteria and outcome measures. We have provided recommendations for the most effective meeting type per protocol topic. Topics with limited options for patient input were most efficiently discussed in expert advice meetings. Other topics benefit from patient/caregiver input, either through a combined meeting with experts or a patients/caregivers-only advice meeting. Some topics, such as endpoints and outcome measures, are suitable for all meeting types. Combined sessions profit from synergy between experts and patients/caregivers, balancing input on protocol scientific feasibility and acceptability. Both experts and patients/caregivers provided critical input on the

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presented protocol. The combined meeting was the most effective methodology for most protocol topics. The presented methodology can be used effectively to acquire expert and patient feedback.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Patient and public involvement (PPI) in clinical trial design is crucial due to expected improvement of quality and efficiency of trials. However, there is no set methodology on how to acquire PPI input, and how to combine it with the input received from clinical and methodological experts.

WHAT QUESTION DID THIS STUDY ADDRESS?

How to best acquire input on clinical trial design from both clinical trial experts and patients and caregivers, resulting from a collaboration of two Innovative Medicines Initiative (IMI)/Innovative Health Initiative (IHI) projects: the Collaborative Network for European Clinical Trials for Children (connect4children [c4c]) project and the European Patient-Centric Clinical Trial Platforms (EU-PEARL) project.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

We provide recommendations for the most effective advice meeting type for various protocol topics. Most topics benefit from patient/caregiver input, either through a combined meeting with experts or a patients/caregivers-only advice meeting. Combined sessions profit from synergy between experts and patients/caregivers, balancing input on protocol scientific feasibility and acceptability.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The presented methodology can be used effectively to acquire expert and patient feedback on clinical trial designs. It has the potential to optimize pediatric clinical trial design, leading to more high-quality clinical trials.

INTRODUCTION

The launch of the Pediatric Regulation by the European Union in 2007 marked the beginning of increased recognition of the need for medicines specifically developed for children.¹ There remains a large knowledge gap regarding the efficacy and safety of medicines in children, especially in subpopulations like neonates and children with rare diseases. Studies have shown that the proportion of off-label prescriptions in hospitalized children can be as high as 99.5%.²⁻⁴ Off-label prescriptions may lead to decreased drug efficacy and increased incidence and severity of adverse drug reactions,^{3,5} underlining the need for medicines specifically developed for pediatric patients. With less than 10% of pediatric rare diseases having a US Food and Drug Administration (FDA)-approved drug, the need in this patient group is particularly evident.⁶

The 10-year review of the Pediatric Regulation identified barriers that inhibited the successful conduct of

trials.¹ The design and conduct of pediatric clinical trials remains a significant challenge, with difficulties reported in patient recruitment, trial authorization by national authorities, and operational challenges in multicentric trials.^{1,7} They will be especially prevalent in trials for rare diseases, where patient numbers are low and geographically dispersed, further complicating the recruitment of adequate sample sizes.⁸

Some of the challenges encountered in clinical trials can be addressed during protocol design (e.g., increasing willingness to participate by assuring patients' needs are reflected in the trial protocol). In order to design a trial with optimal methodology, advice is often gained from a variety of stakeholders: healthcare professionals, statisticians, methodology experts, experts on medicine formulations and ethics, and patients. For studies to be conducted in pediatric populations, advice from the children's caregivers is also essential. Patient and public involvement (PPI) is not only crucial due to expected improvement of

quality and efficiency of trials,⁹ but regulatory and funding bodies also encourage PPI involvement in clinical studies.^{10,11} Although guidance documents exist that describe when PPI input is desired,¹² there is no set methodology on how to acquire PPI input, and how to combine it with the input received from clinical and methodological experts.

The aim of this study is to report the lessons learned from a series of advice meetings in which both trial experts and patients/caregivers participated, that resulted from a collaboration of two Innovative Medicines Initiative (IMI)/Innovative Health Initiative (IHI) projects: the Collaborative Network for European Clinical Trials for Children (conect4children [c4c]) project¹³ and the European Patient-Centric Clinical Trial Platforms (EU-PEARL) project.¹⁴

Involved IMI/IHI projects

c4c is a collaborative European network that aims to facilitate the development of drug therapies for the pediatric population by developing a sustainable, pan-European pediatric clinical trial network for the efficient set-up and conduct of high-quality clinical trials in children.^{15–17} c4c formed a group of over 400 experts in pediatric clinical subspecialties and innovative methodology, as well as patients and caregivers in various disease areas.¹⁷ Academic or industry sponsors can request advice from c4c experts regarding their (planned) pediatric studies.

EU-PEARL is a European collaborative project, aiming to establish integrated research platforms (to develop new medicines for patients in areas of unmet medical need).¹⁴ EU-PEARL work-package 7 (further referred to as “EU-PEARL”) is dedicated to the condition neurofibromatosis, including neurofibromatosis type 1 (NF1). This condition is unique to EU-PEARL due to its rarity, and the fact that children form a substantial part of the target population.

METHODS

Research question

After prioritizing the challenges in NF1,¹⁸ EU-PEARL designed a platform trial that aims to investigate the effectiveness of systemic investigational agents in NF1. Three protocols in this trial will include pediatric patients. Due to the novelty and complexity of this trial design, advice from clinical and methodology experts as well as patients

and caregivers was needed to maximize trial accessibility for pediatric patients. EU-PEARL aimed to gain advice during protocol development, to timely detect potential problems with the trial design, enrollment of pediatric patients, and endpoints.

After considering the expected benefits and limitations of exclusively organizing separate meetings for experts and patients, we decided to use three different methodologies: (1) an advice meeting for clinical and innovative methodology experts, (2) a combined meeting with both experts and a patient and caregiver, and (3) patients/caregivers advice meetings.

Recruitment of attendees

c4c has set up a European multidisciplinary advice service that aids in the planning of innovative and feasible pediatric trials.¹⁹ c4c created a database with over 400 clinical and innovative methodology experts, divided over 24 expert groups based on their expertise. Based on a scoping interview between EU-PEARL and c4c, the best suited experts for the requested advice were selected in collaboration with the leads of the relevant expert groups.²⁰ A list of c4c proposed experts was shared with EU-PEARL, and c4c established agreements with the experts.

Patients and their families were recruited by c4c from the European Neurofibromatosis umbrella patient organization and from patients with NF1 of pediatric physicians included in c4c expert database and/or linked to c4c National Hubs.²¹ We aimed to recruit patients/caregivers from a minimum of three European countries. The numbers of participants depended on the number of patients/caregivers who were willing to participate and able to join the advice meetings in the desired timelines.

Accessibility

For the combined advice meeting, English language skills were mandatory for participating patients. English language skills were not mandatory for the patients/caregivers advice meetings, as this would have limited the number of potential participants significantly. We organized separate advice meetings in the native language of patients from countries for which a PPI expert from c4c could facilitate the moderation and translation to EU-PEARL representatives. As there were no participants with hearing impairments, live captioning or language interpreters were not used. To accommodate participants with visual impairments, these participants were regularly asked if

they had sufficient time to take in the material presented on the screen.

Setting and design of the advice meetings

All meetings were hosted virtually through GoToMeeting. Only invited attendees could access the meeting, using a privately sent link and access code. The meetings were recorded to enable the writing of a final advice report. Records were erased after the completion of the report. All logistics were arranged via c4c Advisory Group Secretariat.

Clinical and innovative methodology expert advice meeting

The goal of the clinical and innovative methodology expert advice meeting was to receive input on the general trial design and a variety of topics, including, but not limited to: medication specifications for children (dosing and formulations), endpoints and outcomes, the informed consent process, required sample sizes, and ethical challenges. A presentation was prepared in advance, containing a brief introduction on EU-PEARL, the NF1 platform trial and the protocol for the trial. This presentation was sent to the experts 1 week prior to the meeting as pre-reading material. The meeting had a semistructured design and had a duration of 3 h. Following the introduction of the trial design, the different sets of eligibility criteria, response definitions, and assessment schedules were presented. The discussion was guided by specific questions to the experts. Experts were encouraged to share their insights and questions at all times. The order of answering the prespecified questions could subsequently be modified dynamically to adhere to the natural flow of the discussions.

Combined clinical and innovative methodology expert and patients/caregivers advice meeting

The design of this meeting was nearly identical to the expert advice meeting. Because a patient and their caregiver would be joining, the language of the presentation was somewhat simplified to make it understandable to lay persons. In addition to the topics discussed during the expert advice meeting, we sought to receive input from the patient/caregiver about the acceptability of the trial design, assessment schedule (including acceptability of the medical procedures), and the endpoints. We were particularly

interested if there were any topics with disagreement between the experts and the patients.

Patients/caregivers advice meetings

The aim of the patients/caregivers advice meetings was to explore the acceptability of the trial design and the informed consent process. EU-PEARL requested specific input on the acceptability of assessment schedules (including medical procedures) and participant preferences on endpoints. A presentation was developed by EU-PEARL in collaboration with c4c. c4c PPI experts provided guidance on how to present the trial design in an understandable way to teenage patients and their families. The presentation was subsequently translated from English to the target language by c4c PPI experts (Spanish and French). A c4c PPI expert was assigned to lead and moderate each of the three meetings, depending on their native language. EU-PEARL representatives held the presentation in English and French. For the advice meeting for the Spanish families, the presentation was translated by the leading PPI expert. The meetings were semistructured in design, but more structured than the expert advice meeting: questions to the participants included open questions regarding the trial, but predominantly consisted of more specific questions. Naturally, participants were invited to speak up at any time if they had questions or remarks. The planned duration was 2 h.

Ethics statement

Patients and their caregivers were invited to the meetings as advisors, not as study subjects. Ethical approval of an institutional review board was not necessary.

RESULTS

Clinical and innovative methodology expert advice meeting

The meeting was held on February 18, 2022. Ten pediatric trial experts participated in the advice meetings. The experts represented seven different expert groups, assuring all relevant pediatrics aspects could be covered (Table 1).¹⁷ The expert advice meeting was effective in receiving feedback from a group of pediatric trial experts with different backgrounds, allowing the leverage of their expertise on various topics (Table 1). The discussions focused primarily on the

TABLE 1 Characteristics, strengths, and limitations of the different types of advice meetings.

Meeting type	Clinical and innovative methodology expert advice meeting	Combined expert and patients/caregivers' advice meeting	Patients/caregivers advice meetings and the one-on-one interview
Attendees	10 c4c experts of the following expert groups: Study design and clinical trial methodology Pharmacovigilance Formulation (2) Adolescent medicine Neuroscience and epilepsy (2) Ethics (2) Omics	6 c4c experts of the following expert groups: Study design and clinical trial methodology Pharmacovigilance Formulation (2) Neuroscience and epilepsy Ethics 1 patient + caregiver PPI expert	French meeting: 3 teenage patients with NF1 5 caregivers Spanish meeting: 3 teenage patients with NF1 3 caregivers UK meeting: 3 teenage patients with NF1 3 caregivers One-to-one interview: 1 teenage patient with NF1 2 caregivers PPI expert
Duration	3 h	3 h	2 h each
Language	English	English	Native language of patients
Perspective on trial design	Methodological approach: scientific feasibility of trial	Mixed approach: scientific feasibility + acceptability from the patient perspective	Patient-view: acceptability of trial design
Strengths	Trial design examined and criticized by different expert groups, allowing for effective evaluation Acquires expert feedback on specific topics Geographic distribution of experts allows for pinpointing differences between countries	Input from the patient's perspective Synergy between experts and patients generates unique input and insight Allows experts and patients to reach consensus Generates equal feedback on trial design: balance between scientific feasibility of the protocol and patient input on acceptability	Social benefits: allows patients and caregivers to exchange experiences Multiple meetings for different countries allowed for the identification of cultural differences Focusses on conducting the trial from a patient's perspective Acquires input from patients on topics that might not have been (fully) considered
Limitations	No input from patients Topics that can be discussed will depend on trial design and phase of protocol development	Less suitable to discuss topics that patients can provide less input on More time is spent on patient-related topics, leaving less time for others Patients can be overwhelmed by expert presence and be afraid to speak up	Language barrier, need for translation Multiple meetings needed to discuss same topics Only assesses protocol on topics that patients can provide input on One-to-one interview lacked interaction between participants

Abbreviations: c4c, Collaborative Network for European Clinical Trials for Children; NF1, neurofibromatosis type 1; PPI, Patient and public involvement.

acceptability of the trial design as seen from a regulatory perspective. The importance of including patients with various ages and age stratification were emphasized, to account for the different pathological aspects of manifestations as patients get older. Based on clinical expertise, a successful example of a similar trial involving adolescent and adult patients studying a new treatment was identified.^{22,23} The eligibility criteria were considered, as well as the expected consequences for recruitment rates, resulting in some criteria being omitted from the protocol. The discussion regarding the proposed outcome measures focused on the

relevance, validity, and suitable age ranges of these measures. Critical input was provided on the contents of the assessment schedule, the expected compliance and the effects on dropout rates. In addition, input was provided on the randomization procedure and possible differences between European countries (availability of investigational agents, regulatory requirements, and ethical challenges). Feedback was also provided on statistical considerations (e.g., given the expected small sample sizes alternative statistical designs were suggested), such as a historical and trend response analysis.

Combined clinical and innovative methodology expert and patients/caregivers advice meeting

The advice meeting was organized on February 22, 2022. Six experts, a teenage patient with NF1 and their caregiver attended (Table 1). The topics were similar to those discussed during the expert advice meeting. In addition, outcome measures, endpoints, and the assessment schedule were discussed from the patient perspective. The discussions focused primarily on the acceptability of the protocol as seen by the patient, such as the frequency of hospital visits and medical procedures in the context of a trial. To help define the endpoints and responder definition, expert and patient preferences in terms of radiological versus patient-reported outcomes (PROMs) were explored.

The participation of experts and the patient/caregiver provided unique insights into the trial design. This was especially apparent when discussing endpoints and the responder definition, where the patient input significantly influenced the final combined advice. The synergy between the experts and the patient led to an effective discussion, resulting in more balanced input between scientific feasibility and acceptability (Table 1). Interestingly, experts and the patient always reached consensus on discussed topics. After discussion they agreed that a composite endpoint (consisting of both magnetic resonance imaging [MRI] and a PROM for pain) would strongly be preferred, whereas the experts initially inclined toward using radiographic images only.

Patients/caregivers-only advice meetings

Three separate advice meetings were organized for patients and families from the United Kingdom, France, and Spain. The meetings were hosted on March 17, March 24, and April 4 in 2022. As one patient was not able to join the main French meeting, but very willing to participate, a separate one-on-one interview was organized. This interview had the same aim and semistructured design as the patients/caregivers advice meetings. No EU-PEARL representatives were present for this interview. The interview was performed by the dedicated French c4c PPI expert on March 31, 2022. In total, nine teenage patients with NF1 and (one of) their caregivers participated in these meetings (Table 1).

The dynamic of including multiple patients and their families, as well as a PPI expert familiar with this methodology, proved advantageous. There was a relaxed atmosphere which allowed for everyone to speak freely, and patients and families were able to exchange their experiences. Patients and their families provided input on the

general trial design, the outcome measures, assessment schedule, and the responder definition. They also provided advice on the informed consent process by describing which type of informational material would be most fitting for patients of different age groups (e.g., teenage patients preferred videos and other digital material over information on paper). Finally, they shared their reasoning why they would or would not participate in the presented trial, and what could be modified in the protocol to make them more likely to participate.

These meetings verified that EU-PEARL's trial design was appealing to patients and their families. The different meetings for each country revealed cultural differences, such as the average travel time to the hospital, which influenced the acceptability of assessment schedules (Table 1). Patients and their families made useful remarks about practical topics that were not extensively considered by EU-PEARL team, such as the use of local healthcare facilities to perform routine check-ups, to reduce the number of required visits to the hospital that runs the trial.

Recommended advice meeting types

The topics discussed most effectively differed among the four methodologies. Based on our experiences, we have provided recommendations for the most effective meeting type per protocol topic (Table 2). Topics that have limited options for patient-input are best reserved for clinical and methodological expert advice meetings (e.g., statistics and formulations). Other protocol topics benefit from patient/caregiver input, either through a combined advice meeting, or separate patients/caregivers advice meetings. Some topics, like endpoints, outcome measures, and assessment schedules are suitable for all meeting types. However, the synergy between experts and patients/caregivers in the combined advice meeting resulted in an effective discussion on these topics, making it the preferred meeting type. Not all protocol topics were discussed in the advice meeting due to the status of the discussed protocol. For these topics, we provided recommendations on which meeting type would hypothetically be most effective, based on the experience of the trial and PPI experts.

Examples of changes in protocol design

The combination of the three types of activities resulted in changes made to the NF1 platform trial protocol. Multiple eligibility criteria were added, removed, or modified. The inclusion criterion regarding a minimum life-expectancy was removed, as this is subjective and hard to determine. Removing this criterion also allows for more sick patients

TABLE 2 Description of participants who provided critical input per protocol topic, and our recommendations of most effective meeting type per topic.

Protocol topics	Critical expert input	Critical patient/caregiver input	Most effective meeting type	Examples of different aspects discussed by experts and patients/caregivers
Trial design	X	X	1, 2, and 3	Experts: Acceptability of design Patients/caregivers: Acceptability of design (observational and treatment phases), randomization procedure, informed consent procedure
Trial population	X		1	
Eligibility criteria	X		1 and 2	
Endpoints	X	X	2	Experts: Validity and acceptability by regulatory agencies Patients/caregivers: Patient preferences regarding radiological vs. patient-reported endpoints
Outcome measures	X	X	2	Experts: Validity, age-range for outcome measures; value of binary vs. continuous outcome measures Patients/caregivers: Acceptability of outcomes (medical procedures for study purposes); patient preferences regarding radiologic vs. patient-reported outcome measures
Assessment schedules	X	X	2	Experts: Ethical justification of assessment schedule; expected compliance; effects on dropout rates; risk-benefit assessment Patients/caregivers: Acceptability of assessment schedule; comparison with current personal standard-of-care; effect of schedule on work and school
Responder definition	X	X	2	Experts: Acceptability by regulatory agencies; defining response Patients/caregivers: Patient preferences regarding inclusion of PROMs into responder definition; value of radiologic vs. patient-reported outcome measures
Pharmacogenomics, OMICS technologies	~		(1)	
Pharmacometrics	~		(1)	
Pharmacovigilance	~		(1)	
Formulations	~		(1)	
Ethical considerations	X		1	
Statistical considerations	X		1	
(Potential) differences between EU countries	X	X	1 and 3	Experts: Differences in ethical, legal and regulatory aspects Patients/caregivers: Differences that could impact trial enrollment and compliance, such as travel times to hospital

Note: ~—Not discussed due to trial/protocol status. (1)—Not discussed, but hypothetically input would have been most effective from clinical/methodology expert advice meeting; 1—Clinical/methodology expert advice meeting; 2—Combined expert and patients/caregivers advice meeting; 3—patients/caregivers advice meetings.

Examples of different aspects discussed for the topics that received critical input from both experts and patients/caregivers.

Abbreviation: PROMs, patient-reported outcome measures.

with high treatment need to be included. In addition, there was uncertainty whether to set the performance score (measured through the Karnofsky and Lansky Performance Scale Indices) to a minimum of 50% or 70%. Following discussion with c4c innovative clinical and methodological experts, the minimum was set to 50%. For one of the discussed tumor manifestations, the criterion

“tumor shows substantial growth” was removed, due to it being subjective and hard to standardize across participating centers.

Suggested outcome measures were incorporated into the protocol and the assessment schedules. Originally, only the Numeric Rating Scale (NRS-11) was included as the outcome measure for pain. However, this measure is

only validated for patients aged 8 years and older. To also measure pain in younger patients, the outcome measure “Face, Legs, Activity, Cry, Consolability scale (FLACC scale)” was added. The timing of performing these measurements was also discussed. It was proposed to not only collect data on pain at a specific day, but also measure the pain experienced over a certain time period.

Prior to this study, the responder definition for one of the manifestations was an unresolved issue. EU-PEARL clinicians were unsure whether to use a single outcome measure to define response in a tumor manifestation (MRI scan results), or to use a composite outcome measure (both MRI and a PROM for pain). The use of PROMs as primary endpoints has been increasingly important in clinical trials; however, regulatory agencies will not always accept them. The combined advice meeting allowed EU-PEARL to decide on the composite outcome measure, after both experts and patients expressed their strong preference for including a PROM in the primary endpoint.

DISCUSSION

We report the lessons learned from a series of advice meetings that resulted from a collaboration of the IMI/IHI projects, c4c,¹³ and EU-PEARL,¹⁴ in which pediatric trial experts and patients provided feedback on a trial protocol for NF1. The combination of the performed activities resulted in major changes to the NF1 platform trial protocol. Eligibility criteria were added, deleted, or modified. One of the endpoints was changed to a composite endpoint, following the strong preference of both patients and experts. Based on our experiences with the different meeting types and their strengths and limitations, we have provided recommendations for the most effective meeting type for various protocol topics.

The majority of topics benefit from input provided by patients. A combined advice meeting is generally the preferred meeting type for discussing outcome measures, the assessment schedule, endpoints, and the responder definition, in order to assess the scientific feasibility and acceptability of the protocol. Yet, this type of advice meeting has drawbacks. It is less suitable for topics that patients can provide less input on (as defined by the PPI expert), as this removes the beneficial synergy between experts and patients. This could lead to more time being spent on patient-related topics. It could also be challenging for patients to discuss topics like eligibility criteria: certain criteria that lead to an optimal methodology, could make them feel excluded from the trial and may be subject to bias. Additionally, patients and their families could feel overwhelmed by the experts' presence, discouraging them from speaking up. By regularly addressing the patient

and their caregiver directly and setting ground rules for the meeting, we were able to engage them in the ongoing discussions. The dedicated PPI expert joining the meeting was very helpful. Being familiar to the family, she acted as a connecting link between the experts and the patient. The inclusion of a person that could serve as a family liaison (e.g., in our study, the PPI expert that invited the patients/caregivers to the advice meetings) should be considered for future combined advice meetings, to optimally engage patients and caregivers in the discussions.

We recommend that topics with limited possibilities for patient input, like statistical considerations and medication specifications, are reserved for the expert advice meetings. Some topics, like endpoints and outcomes, are also suitable for these meetings if more technical questions need answering, such as validity of outcomes and setting cutoff points for response definitions.

The patients/caregivers advice meeting focused on the acceptability of the trial design. This meeting type addressed a level of detail most relevant for trial participants, omitting the discussion of specific protocol elements, like eligibility criteria. This activity induced fewer changes in protocol content than the other two meetings. Yet the lessons learned from these advice meetings were helpful to EU-PEARL on other levels, especially due to the practical advice received on the conduct of the trial.

In the case of international trials, a point of attention would be to involve experts and patients from all target countries. Country and cultural differences will influence the way patients and experts view a protocol. An assessment schedule with less frequent hospital visits was regarded as more critical to the Spanish families, because travel distances to academic NF1 centers tend to be large in Spain. This underlines the need to recruit an international set of experts and patients for the advice meetings. For our study, this meant that multiple patients/caregivers meetings were organized to discuss the same topics in different languages. Although this required more resources and extended the project's timelines, this was outweighed by the benefits of acquiring feedback representative for multiple countries and patient populations.

Another point of consideration is diversity in the type of patients that can participate in the meetings. In our study, we included patients and families that did not have previous experience with providing feedback on clinical trials. Other patients can be trained or more experienced with this task, for example, patients that have followed the Patient Expert Training Programme by EUPATI.²⁴ Although not described in the literature, trained patients will probably assess a trial protocol differently than non-trained patients. In c4c, PPI experts decide what level of expertise is required from participating patients and caregivers, dependent on the research question.

The combination of the three types of meetings resulted in effective and practical recommendations from experts and patients, allowing the development of the protocol to advance substantially. Additional to previous studies that have shown when PPI input is meaningful,¹² we now showcase a methodology that could be used to combine this input with input from trial experts. The utilization of the existing c4c expert database allowed for easy recruitment of clinical and innovative methodology experts. We believe that this methodology could be beneficial to other researchers or sponsors who seek advice on their protocol. Although the described advice meetings were designed to gather input on a platform trial design, they can be readily adapted to other methodologies and trial types. This does not have to be limited to pediatric trials, but could be expanded to adult trials as well. All meeting types seem suitable to answer research questions in various developmental stages of a trial protocol, although the patient and family advice meetings may work best in a more advanced stage, given that there will be specific topics and questions for patients to provide input on. Based on the timing of the advice meeting with respect to the status of the protocol, the types of experts invited to the meeting can also be adjusted accordingly.

This study had some limitations. Due to the design and phase of development of the NF1 platform trial, some topics could not be discussed in detail. Specifics regarding topics, such as drug toxicity and formulations, could not be discussed, given the drug-agnostic design of the trial. Hypothetically, these topics would have been best discussed in the expert meeting, although patient input on acceptance of toxicity levels could also prove valuable. Second, there were no experts from regulatory agencies present during the meetings. Although these kind of expert and PPI activities are generally performed before a protocol is submitted to a regulatory body, acquiring early regulatory input would be more efficient and time saving. Third, only one patient/caregiver pair could attend the combined advice meeting. Last, there was a language barrier between EU-PEARL and the participants in the French and Spanish meetings. Whereas c4c PPI experts provided excellent translations, this could have led to a subtle but relevant loss of information.

Involving patients in the design of clinical trials requires preparation, resources, and flexibility of all stakeholders involved.²⁵ Nonetheless, it is likely to improve trial compliance and enrollment rates, especially if patients living with the disease participate in the organized activities.⁹ The presented methodology could be used to gain the described benefits, but more research is needed to assess the cost effectiveness, the impact at various stages of trial design, the effect of involving pediatric versus adult patients, and trained versus untrained patients.

CONCLUSION

Both experts and patients provided critical input on the presented protocol. The combined meeting was the most effective methodology for most protocol topics. The presented methodology can be used effectively to acquire expert and patient feedback. It has the potential to facilitate the development of high-quality clinical trials, based on the recommendations of two of the most important stakeholders: trial experts and patients.

AUTHOR CONTRIBUTIONS

B.D. and F.M. wrote the manuscript. B.D., F.M., P.D., S.G., B.N., and R.O. designed the research. All authors performed the research. F.M. and B.D. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

All authors declared no competing interests for this work.

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