Received: 5 September 2022 | Revised: 17 October 2022 | Accepted: 20 October 2022

DOI: 10.1111/cts.13459

ARTICLE

Clinical, methodology, and patient/carer expert advice in pediatric drug development by conect4children

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Abstract

Many medicines are used "off-label" in children outside the terms of the license. Feasible pediatric clinical trials are a challenge to design. Conect4children (c4c) is an Innovative Medicines Initiative project to set up a pan-European pediatric clinical trial network aiming to facilitate the development of new medicines for children. To optimize pediatric trial development by promoting innovative trial design, c4c set up a European multidisciplinary advice service, including the voice of young patients and families, tailored to industry and academia. A network of experts was established to provide multidisciplinary advice to trial sponsors. Experts were selected to join clinical and innovative methodology expert groups. A patient and public involvement (PPI) database, to include the expert opinion of patients and parents/carers was formed. A stepwise process was developed: (1) sponsors contact c4c, (2) scoping interview takes place, (3) ad hoc advice group formed, (5) advice meeting held, and (6) advice report provided. Feedback on the process was collected. Twenty-four clinical and innovative methodology expert groups (>400 experts) and a PPI database of 135 registrants were established. As of September 30, 2022, 36 advice requests were received, with 25 requests completed. Clinical and methodology experts and PPI representatives participated in several advice requests. Sponsors appreciated the advice quality and the multidisciplinary experts from different countries, including experts not known before. Experts and PPI participants were generally satisfied with the process. The c4c project has shown successful proof of concept for a service that presents a new framework to plan innovative and feasible pediatric trials.

*The list of contributors is listed in the Acknowledgment section of this paper.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Pediatric clinical trial designs may not be feasible to conduct leading to challenges in completion of Pediatric Investigation Plans/Pediatric Study Plans and delay in the availability of new medicines for children. Access to appropriate expert advice by sponsors can be challenging and patchy.

WHAT QUESTION DID THIS STUDY ADDRESS?

How to best support pediatric drug development by optimizing study design/pediatric development plans through expert advice from clinical and methodology experts as well as patient/carer representatives, for both industry and academia.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The c4c project showed successful proof of concept for an international, one-stop multidisciplinary advice service on pediatric drug development.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The development of better medicines for children, babies, and young people through the provision of expert advice to industry and academic sponsors on trial design on for example, natural history, outcomes, feasibility, and appropriate innovative methodology.

INTRODUCTION

Improvements in child health depend partly on access to new and improved medicines. Many medicines (over 50%) are used "off-label" in children[1] outside the terms of the license, because efficacy and safety have not been demonstrated in clinical trials leading to labeling. The need to include a pediatric drug development plan was mandated for companies developing medicines for adults, in 2002 in the United States and in 2006 in the European Union. The implementation of the Pediatric Regulation in the European Union, as reported in the 10-year Report from the European Commission (2017), has led to an increase in the number of pediatric clinical trials for approval and more authorized medicines for children.[1] However, the proportion of all medicines authorized for adults that have been studied adequately for safety and efficacy in children remains low at 38%.[2] Conducting and completing clinical trials in children is challenging and there is a continued need to support the development of more safe, effective, and innovative pediatric medicines in Europe.

Specifically, there remain significant challenges in developing medicines for children, especially in rare diseases, including gaps in understanding the basic science of disease as well as limitations in the knowledge of the mechanism of action of products.[3] There are also difficulties in recruiting into and completing pediatric clinical trials, particularly in small populations, leading to long gaps between initial adult authorization and subsequent authorization of a pediatric indication. Whenever possible, it is important to leverage information from additional sources, such as extrapolation from adult data or other pediatric subgroups. To overcome the hurdles of a traditional large phase III study more pediatric development plans could make use of innovative trial design (e.g., adaptive designs, Bayesian statistical analysis to borrow data, modeling and simulation of pharmacokinetic data, and use of real-world data).[3] To facilitate scientifically sound, as well as innovative and feasible drug development plans, multidisciplinary expert advice to include a range of experts, such as clinical and/or methodology experts and patient and carers, could play an important role. Industry teams and academic researchers developing new medicines for children can benefit from this multidisciplinary expert advice. Patients and parents' contributions to the development of pediatric studies are also critical to ensure that end points and assessments are meaningful and feasible.

Pediatric clinical trial networks may also play important roles and currently such pediatric clinical networks are established or under development in the United States, the European Union, Canada, and Japan in an effort to ultimately provide global interoperability.[4–6]

In the European Union, the conect4children (c4c) project is a public-private partnership funded by the Innovative Medicines Initiative (IMI) to set up a sustainable, integrated pan-European collaborative pediatric clinical trial network that will speed up and facilitate the running of high-quality clinical trials in children, while ensuring that the voices of young patients and their families are heard.[4,7] The plan is to build the infrastructure and capacity to conduct multinational pediatric clinical trials

across all disease areas, in all pediatric age groups and all phases of the clinical drug development process.[8]

One focus of c4c is to promote innovative trial design to optimize pediatric development plans and protocols. This will be done through the provision of expert advice to sponsors, initially the c4c industry and academic beneficiaries, and, as of mid-2023, in the successor c4c legal entity, to any sponsor.[9] The goal of this workstream is to meet the needs of the sponsor and children and provide high-quality expert advice on any topic within pediatric drug development to improve pediatric medicine development plans and delivery. We developed a service within c4c for providing advice. The key elements of the service are:

1. Identifying experts and forming expert groups, including children, young people, and their families.
2. Managing advice requests, including the provision of timely reports to sponsors.
3. Using consistent consultancy agreements.
4. Quality improvement plans for the expert groups.

The aim of this paper is to describe the set up and piloting of an expert advice service in c4c. Proof of concept was assessed by piloting advice requests from c4c partners and assessing the extent to which this advice service, and its elements, could be delivered.

METHODS

The service was developed iteratively through discussion between academic and industry c4c partners and involved identifying user needs and provider capabilities. Needs and capabilities were reconciled to provide a pragmatic and useful service.

Within c4c, expert advice is termed strategic feasibility advice to differentiate it from the European Medicines Agency (EMA) regulatory procedure, Scientific Advice.[10] This feasibility is distinct from site identification and feasibility. The scope of advice to be given by c4c experts was defined to provide advice on a wide range of pediatric development topics. These could include, for example, a pediatric development plan, a pediatric study protocol, specific topics such as end points or study population, advice on a regulatory submission such as response as part of a pediatric investigation plan (PIP) to the EMA/Pediatric Study Plan (PSP) submission to the US Food and Drug Administration (FDA), PIP modification, postmarketing commitments, and grant applications (Figure 1).

Industry and academic leads of c4c developed a process for sponsors to seek and obtain advice from c4c experts, based on the industry and research networks' prior experience in setting up advisory boards with experts in the field. The aim was to improve the process and outcomes, particularly by providing tailored, multidisciplinary expert advice and faster contracting.

Selection of experts and formation of expert groups

A large network of c4c experts, within a database was established; these experts could be drawn upon to provide strategic feasibility advice to the advice requestors. Following an open public call for expression of interest in

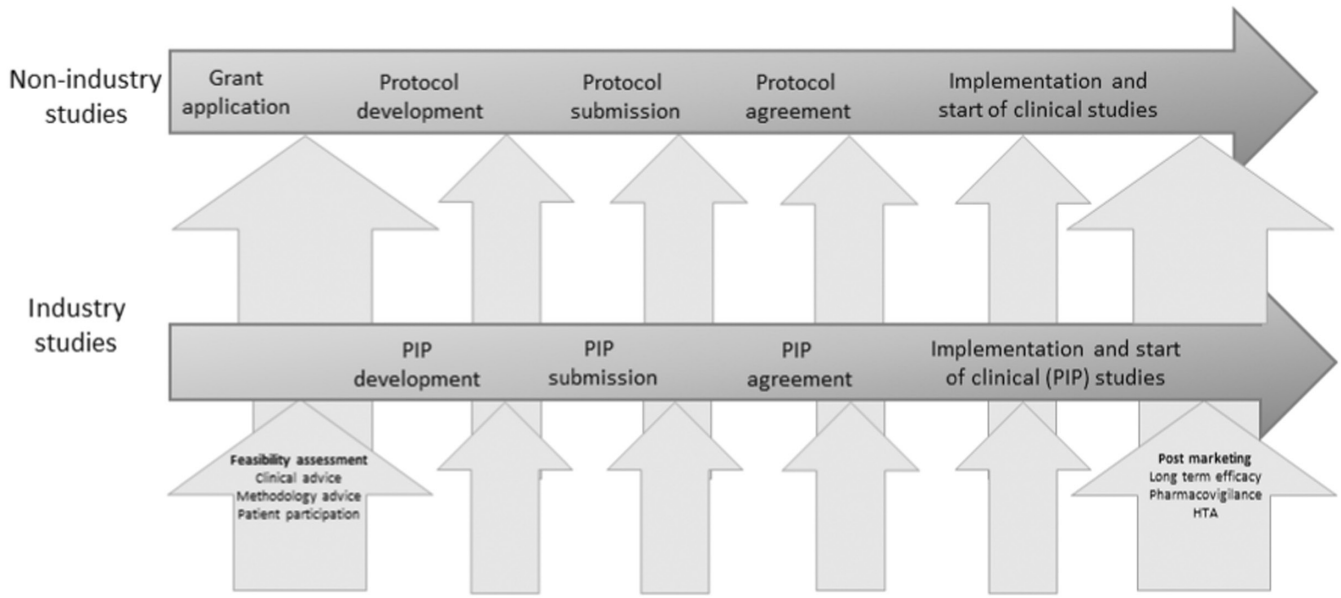

FIGURE 1 Roadmap for advice. HTA, Health Technology Assessment; PIP, pediatric investigation plan

the spring of 2019 and 2022, experts were selected to form expert groups in a pediatric clinical subspecialty or in study methodology. An expert group lead was selected for each group. Predefined criteria were used to select expert group leads and experts with the use of a scoring system to ensure fair selection. Expert group leads were selected based on recognition as "senior" by peers in a specific field in Europe and worldwide and active at the time of selection, awareness of regulatory requirements for clinical trials, deep knowledge of the disease/methodology and experience in clinical trials, and willingness and capacity to provide expert advice at short notice. Expert group members were selected according to similar criteria, including relevant experience of more than 5 years, knowledge of clinical trials, knowledge of pediatric drug development and regulatory requirements, and capacity to provide advice on a minimum of two occasions per year. Not all criteria were required for selection. Additionally, diversity within each expert group was a criterion taking into account gender, level of seniority, and geographic location (to account for cultural and standard of care differences).

To ensure the provision of high-quality and up-to-date advice, a quality improvement process, to determine and prioritize potential areas for improvement, was set up. Each expert group was asked to develop a Quality Improvement Plan (QIP), which is revised annually and includes defined quality improvement actions for the upcoming year as well as an evaluation of the quality improvement topics performed in the previous year.

A Patient and Public Involvement (PPI) database comprising patient organizations, parents/carers, young adult patients, and young persons' advisory groups (YPAGs) was formed to ensure the involvement of patients and carers in shaping study design by enabling patients and/or parents to contribute to the advice provided to the sponsor. YPAGs are typically made up of one to 12 members, aged 8–21 years who have experience of participating in a clinical trial and/or have a chronic disease or general interest in health, research, and science. An open invitation to self-register was placed on the c4c website.[11] This database remains open for ongoing registration.

Strategic feasibility advice process

Step 1: Advice request and expert selection

The c4c industry or academic partners use a single-entry point into c4c to access services, the single point of contact (SPoC) email address. To initiate an advice request, a requestor from one of the c4c industry or academic partners submits the request to the SPoC who forwards it to the secretariat, currently based at RadboudUMC, The Netherlands. An initial scoping interview is held virtually between members of the secretariat and the requesting team to understand the nature of the advice request and the type of expert(s) needed. Relevant information on the pediatric development program and/or the advice request would be discussed at this stage. Based on the outcome of the scoping interview, the secretariat reviews the potential experts in the database and following consultation with the relevant expert group lead, sends a list of proposed experts to the requesting team for agreement to participate in the advice meeting. The selected experts form an ad hoc strategic feasibility advice group, which is therefore tailored for each advice request enabling a bespoke group of experts to advise on a specific topic. The c4c advice process is summarized in Figure 2.

Step 2: Contracting

Contracts are needed between the company and individual expert prior to sharing confidential information on the study and compound; the usual practice is for individual consultancy agreements to be set up. The initial c4c process followed standard company processes with consultancy agreements between the industry partner and each expert set up. In addition, an agreement between the industry partner and RadboudUMC was set up. As consultancy agreements are often a time-limiting step in holding advisory boards for companies, c4c industry partners expressed a need for a central contracting process using a master services agreement (MSA) to facilitate and accelerate the contracting timelines. An MSA template was drafted and agreed for use by the majority of the c4c industry partners. Similarly, a master consultancy agreement (MCA) template to reflect the language used in the MSA between industry partner and the secretariat was drafted and agreed for use by the secretariat and the experts. Advice requests using this central contracting process were piloted in 2021/2022. Following execution of the individual consultancy agreements or MSA, the requesting company shares relevant background documentation, including specific questions, with the agreed experts. Payments to experts were and continue to be, according to Fair Market Value assessments (price at which expert and sponsors are willing to do business without acting under any compulsion) of each individual sponsor.

Step 3: Advice meeting and report

The secretariat schedules a (virtual) advice meeting for requesting team members and experts to attend. After the meeting, the secretariat drafts a meeting report which can

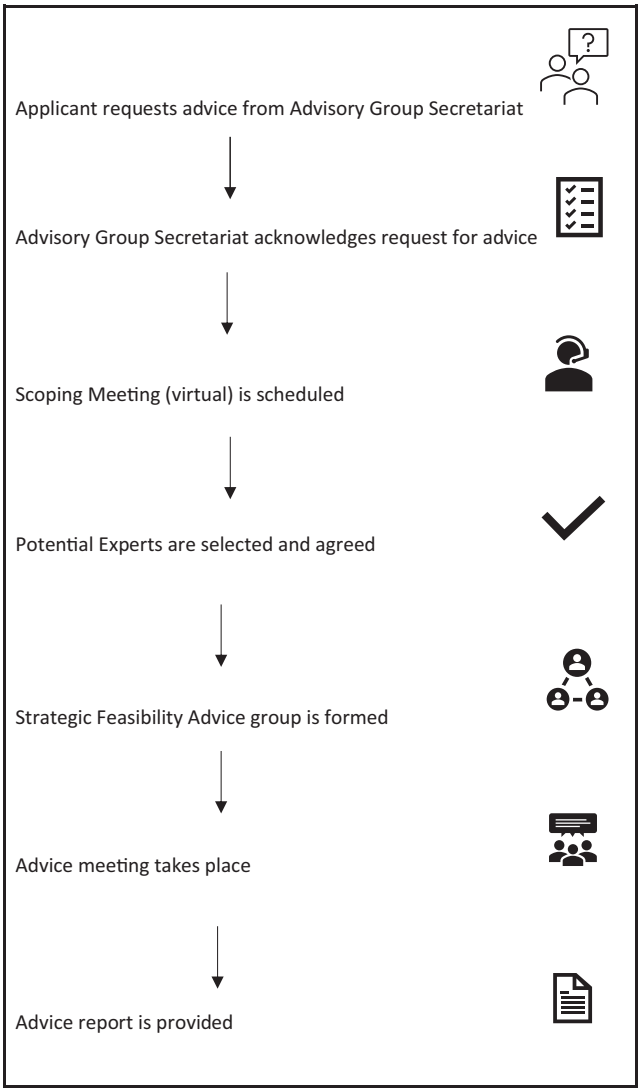

FIGURE 2 Outline of c4c strategic feasibility advice process

be in a shorter format appropriate for submission to regulatory authorities, if required by the industry partner.

Step 4: Feedback and quality improvement

After finalization of an advice request, feedback addressing the quality of the advice and the c4c service was collected from the requestor of the advice and the experts who provided the advice. A questionnaire using a five-point Likert scale was used, where responders specify their level of agreement to a statement with: (1) strongly disagree; (2) disagree; (3) neither agree nor disagree; (4) agree; and (5) strongly agree (Figure 3).

A process map for comparison of the process that companies use to seek advice prior to the set-up of the c4c advice process is shown in Figure 4. Once the process of obtaining advice had been developed and agreed, c4c industry and academic partners were invited to pilot the service by submitting advice requests to the secretariat. The secretariat logged all activity and generated summary statistics about the number of requests and progress through the stages of the service. After completion of the advice report, requesting teams and experts are invited to provide feedback on the process and the quality of the advice to the secretariat. A further follow-up request is sent to the requesting team to seek feedback on the impact of the advice (e.g., to what degree was the advice followed and was the advice accepted by regulatory authorities).

RESULTS

Expert groups and experts

Twenty-four clinical and innovative methodology expert groups, as listed in Table 1, were established. Each expert group is chaired by one or two expert group leads. This resulted in a total of 27 expert group leads from 10 different countries. The expert group leads have links with over 20 existing networks/learned societies within their expertise to assure collaboration between c4c and the existing networks/learned societies.

Experts from 49 countries (31 European and 17 non-European) applied through open calls in 2019 and 2022 to join 16 clinical expert groups, eight methodology expert groups leading to the selection of 402 individual experts. Overall, 45 different countries are represented by the selected experts. The male:female ratio across the expert groups is ~50:50. The methodology groups include disciplines, such as study design and clinical trial methodology, formulation, ethics, health technology assessment, pharmacovigilance, and developmental pharmacology. The clinical groups include different clinical disease areas, such as cardiology, nephrology, respiratory, and infectious diseases.

As well as a database of clinical and methodology experts, a database of patient/carer (PPI) experts was established. This database contains 135 registrants as of September 30, 2022. Within the database, four subgroups are defined; (1) professional of a patient organization, (2) YPAG facilitator, (3) adult patient, and (4) carer of a young patient. Patients under 18 years of age are not permitted to register themselves.

Advice requests

A total of 36 advice requests were received between April 29, 2019, and September 30, 2022. These requests came from seven c4c industry partners, four academic

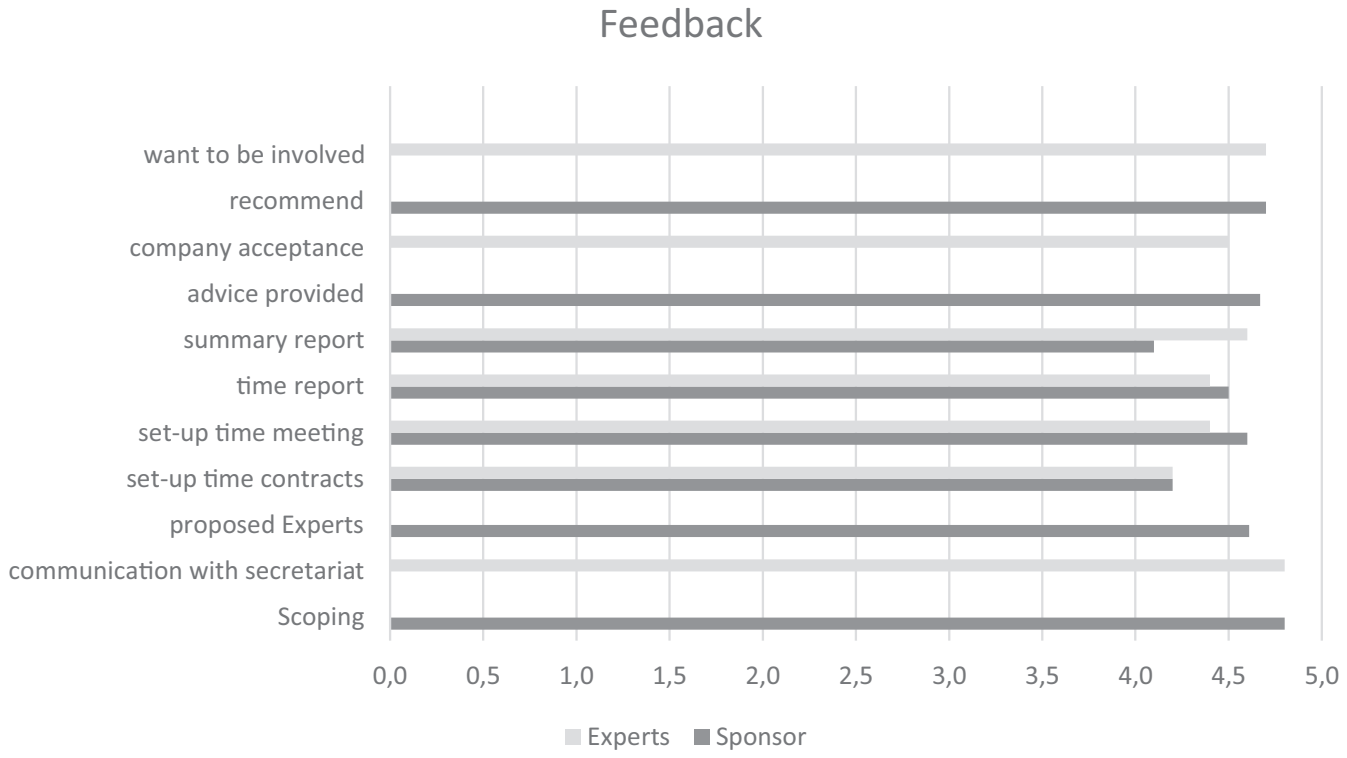

FIGURE 3 Feedback from advice requesters and experts

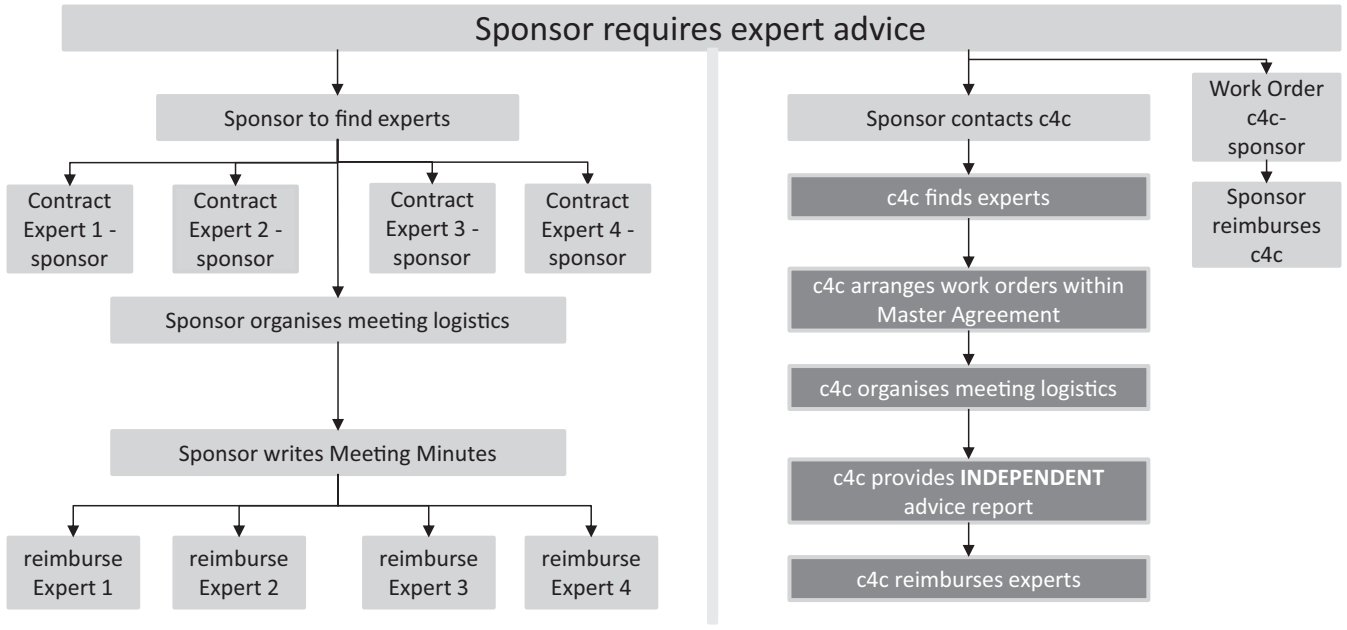

FIGURE 4 Process map. c4c, conect4children

institutions, and one other IMI project. After the scoping interview, eight did not proceed due to reasons including unfeasible timelines, availability of new data (e.g., adult data), companies' internal procedures, and contracting too time-consuming. Of the 28 requests that progressed after the scoping interview, 25 have been completed and three are ongoing (September 30, 2022).

Of these 28 advice requests, 23 included one or more experts from the clinical expert groups, 14 included one or more experts from the innovative methodology expert groups, and nine included participation of patients and/or parents. Distribution of these advice requests across the different expert groups are listed in Table 2. Seven of the requests included a report for regulatory authorities.

TABLE 1 Expert groups within c4c

Clinical expert groups	Innovative methodology expert groups
Adolescent medicine	Developmental pharmacology
Cardiology	Ethics
Endocrinology and diabetes	Formulations
Gastroenterology and hepatology	Health technology assessment
Metabolic diseases	Pharmacogenomics and other OMICS technologies
Neonatology	Pharmacometrics
Nephrology	Pharmacovigilance
Neuroscience and epilepsy	Study design and clinical trial methodology
Neuromuscular diseases	**Patient and public involvement database**
Oncology (and hematology)	Parents/carers
Psychiatry	Patient organizations (representative)
Respiratory	Young Persons Advisory Groups
Rheumatology and autoimmune diseases	Patients
Respiratory syncytial virus	
Infectious diseases and vaccinology	
Intensive care	

Abbreviation: c4c, conect4children.

Up to September 30, 2022, feedback on the completed advice requests was received from 24 advice requesters (66%), 61 clinical and methodology experts (68%), and seven PPI participants (54%) (Figure 3).

Advice requesters indicated their appreciation of the quality of the advice and the input of multidisciplinary experts from different countries, including experts they had not worked with previously. Contracting was listed as the most challenging and time-limiting factor. The average scoring for the advice report by requesters rose from 3.6 in 2019–2020 to 4.4 in 2021 to 4.5 on September 30, 2022, on reports written.

Experts were, in general, satisfied to very satisfied with most aspects of the process and indicated time to set up contracts to be the lowest scoring aspect. Due to interest and an opportunity to learn, they requested feedback on how the advice was implemented by the requesting team. Subsequently, a process was implemented to ensure that feedback from the requestor is shared with the participating experts.

All the PPI participants were satisfied with the overall activity and indicated the topics discussed were meaningful and appropriate. Eighty percent of the PPI participants expect that the advice provided will be implemented.

Contracting

To facilitate the contracting process, a centralized contracting system is being implemented and piloted. Between February 2021 and September 2022 ~78% (237/304) of MCAs were fully executed. Agreement to use the centralized contracting structure and on the MSA template was reached with eight of the 10 c4c industry partners as well as one academic institution. Timelines were reduced by ~25% (5 weeks) for advice meetings requested by industry partners using the c4c centralized contracting process compared with advice meetings set up by c4c using individual contracts.

Quality improvement plans

Expert group-specific QIPs were authored for all innovative methodology expert groups,[8] 15 of the 16 clinical expert groups, as well as one QIP on the overall c4c advice process, which was created by the c4c advice service leadership in 2021. In 2022, all QIPs were revised and updated to reflect the progress made and the upcoming focus areas for improvement. The outstanding expert group-specific clinical QIP was created during the annual revision period in 2022.

DISCUSSION

At the midpoint of the c4c project funding, an expert network and advice service has been built successfully. Proof of concept was shown by piloting with c4c industry and academic beneficiaries. The c4c experts have provided advice to industry and academic partners on pediatric regulatory plans, study protocols, regulatory responses, and grant proposals. The service was highly rated for quality and organization of the advice service by both requestors and experts. This unique pediatric advice service presents an important tool to improve development and conduct of feasible pediatric drug development plans or protocols. Due to the expansion of the c4c project, a second call for new experts opened in Q1 2022. The advice service sits within a larger service portfolio of the c4c clinical trial network.

An added value in providing this service through c4c, is having a SPoC with an up-to-date multispecialty network

TABLE 2 Distribution of advice requests

Clinical expert groups	Advice requests (*n*)	Innovative methodology expert groups	Advice requests (*n*)
Adolescent medicine	4	Developmental pharmacology	3
Cardiology	5	Ethics	7
Infectious diseases and vaccinology	3	Formulations	2
Intensive care	2	Health technology assessment	1
Neonatology	3	Pharmacogenomics and other OMICS technologies	2
Nephrology	3	Study design and clinical trial methodology	8
Neuroscience and epilepsy	4	**Patient and public involvement database**	
Oncology (and hematology)	4	Parents/caregivers	5
Psychiatry	2	Patient organizations (representative)	2
Respiratory	5	Patients	3
RSV	1	**Other**	
		Dermatology	1

Abbreviation: RSV, respiratory syncytial virus.

of pediatric experts to provide independent advice on methodology and clinical aspects including the patient perspective. The independent advice provided by c4c experts may be used for regulatory discussions and grant submissions. The centralized contracting structure of c4c results in the company needing only one standing contract with the secretariat rather than individual contracts between each company and expert. The c4c process also helps industry sponsors to identify experts rapidly and facilitates contracting.

A literature search was conducted through PubMed and no publications from other organizations that provide an expert advice service were identified. However, c4c is aware of advice processes within other existing networks, These include the TREAT-NMD Advisory Committee for Therapeutics (TACT), a multidisciplinary, international group of basic scientists, healthcare professionals, patient advocacy representatives, regulatory experts, and industry experts, the European Joint Programme for Rare Disease (EJP-RD), which has an online support office providing support for clinical investigators in the preparation of clinical studies for the development of new treatments, the European Cystic Fibrosis Society Clinical Trial Network, which has a protocol review committee that reviews protocols submitted by pharmaceutical companies, the Pediatric Rheumatology International Trials Organization (PRINTO), which has an advisory council that provides leadership and guidance for PRINTO research activities consisting of eight clinicians, and the Innovative Therapies for Children with Cancer (ITCC) European network, which provides expert advice on biological and preclinical rationale, clinical development plans, and regulatory advice to biopharmaceutical companies in order to define whether an asset is worth being developed in children and, if yes, how.[12–16] In addition, the EMA Scientific Advice procedure is available to medicine developers for guidance on study design.[10]

It is important to note that the advice process of the specialty networks listed above differs from c4c's. These networks are part of the c4c expert groups to ensure collaboration and avoid duplication of effort. The key advantage of the c4c advice process is that it covers all subspecialties, a broad range of methodologies, and the voice of the patients/parents in a single process. c4c provides tailored multidisciplinary advice, including adhering to timelines of requesting team and coordinating the whole process from finding the right experts to contracting and organizing the advice meeting to writing the advice report. The c4c advice process provides the opportunity to design patient-centric clinical trials in partnership with

young patients and caregivers together with clinical and methodology experts; this is unique to c4c. Quality processes for experts and the advice process have also been implemented.

Several learnings from our experience in piloting the advice service have been observed to date. Not surprisingly, contracting was challenging. When consultancy agreements were set up in the usual way between company and expert, the time taken to execute these contracts sometimes delayed the timing of the meeting. The concept of a central contracting structure was agreed quickly by c4c. However, implementation using master agreement templates took many months to achieve final agreement across the partners' legal departments. The initial scoping interview for the secretariat to better understand the nature of the advice request and for the sponsor to understand the advice process proved to be essential in selecting the most appropriate experts. The wide range of different types of experts was valued by the academic and industry partners and, for several advice requests, experts were proposed and selected who were not previously known to the company. The experts involved in the advice requests to date appreciated the opportunity to provide feedback on the process and found it valuable to receive feedback from the advice requesters on whether their advice is implemented. The secretariat has also gained insights on the expectations and preferences of companies on the advice meeting reports (e.g., on whether informal or formal language is used or whether a detailed report or a high-level summary is preferred).

The remaining period of the IMI project will focus on refining the advice process as feedback is received and an assessment will be made on the need to create new expert groups, such as dermatology. The c4c project will aim to improve on the time taken from initial advice received to the advice meeting and provision of the meeting reporting.

Study limitations

Due to limitations of working within IMI framework we have not promoted the service outside of the c4c consortium. The advice service during the c4c project is limited to the consortium partners. The successful piloting demonstrates a sustainable model for the future advice service in the successor c4c network. Future advice requests could be from other European Federation of Pharmaceutical Industries and Associations (EFPIA) companies, smaller companies, for example, small and mid-size enterprises (SMEs), Biotechs, start-ups who have less experience in pediatric development than the current c4c industry partners, as well as academia. Currently, the scope is pediatric drug development and we have not provided advice on development of medical devices relevant to children.

Another future goal of c4c is to provide global advice, with access to experts from the European Union and the United States at the same meeting. This would be of great interest to sponsors who usually plan global pediatric development plans and studies and could be achieved through collaboration with the US pediatric clinical trial network, I-ACT, and KidsCAN.[5,17]

This report does not include comparisons with existing approaches taken by sponsors with respect to process, duration, or quality of advice requests. In addition, at this time, we are not able to comment on how this service addresses its ultimate goal of improving the quality of pediatric drug development.

In conclusion, the c4c consortium has shown successful proof of concept for a European, multidisciplinary, full-service advice service for pediatric drug development, available to both industry and academic partners. This service presents a new framework to facilitate innovative and feasible pediatric trials.

AUTHOR CONTRIBUTIONS

K.C., F.M., I.L., B.N.E., S.B., G.V., J.C., R.P., T.v.G., and S.N.d.W. wrote the manuscript. K.C., F.M., I.L., B.N.E., S.B., G.V., J.C., N.N.P., R.P., G.P., M.B., T.v.G., M.T., and S.N.d.W. designed the research. F.M., I.L., B.N.E., N.N.P., and S.N.d.W. performed the research. F.M. analyzed the data.

ACKNOWLEDGMENTS

The list of contributors: Dirk Lanzerath German Reference Centre for Ethics in the Life Sciences, University of Bonn, Bonn, Germany; Catherine Tuleu, University College London School of Pharmacy, London, UK; Matthias Schwab, Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; Departments of Clinical Pharmacology, and of Pharmacy and Biochemistry, University of Tuebingen, Tuebingen, Germany; Anne Smits, KU Leuven, Department of Development and Regeneration University Hospitals Leuven, Neonatal Intensive Care Unit; Jean-Marc Treluyer, Universite de Paris, Pediatric and Perinatal Drug Evaluation and Pharmacology, Paris, France; Unite de Recherche Clinique Universite de Paris Necker-Cochin, AP-HP, Paris, France; CIC-1419 Inserm, Cochin-Necker, Paris, France; Francesco Moretti, Arsenal.IT-Centro Veneto Ricerca e Innovazione per la Sanita digitale, Padova, Italy; Ian Wong, Department of Pharmacology and Pharmacy; Centre of Pediatric Pharmacy Research; Kit Roes, Department of HEV, Radboud Institute Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; Carmen Moreno, Department of Child and Adolescent Psychiatry,

Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marafi6n, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM, Madrid Spain; Karel Allegaert, KU Leuven, Department of Development and Regeneration; KU Leuven, Department of Pharmaceutical and Pharmacological Sciences; Erasmus MC University Medical Center, Department of Hospital Pharmacy; Wim Helbing, Department of Pediatric Cardiology, Erasmus MC-Sophia Children's Hospital, The Netherlands; Estelle Naumburg, Institution of Clinical Sciences, Pediatrics, Umea University, Umea, Sweden; Matthijs de Hoog, Intensive Care Unit, Departments of Pediatrics and Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; Tuuli Metsvaht, Tartu University Hospital, Tartu, Estonia; Thomas Danne, Diabetes Centre for Children and Adolescents, Kinder- und Jugendkrankenhaus AUF DER BULT, Hannover, Germany; Maurizio Scarpa, MetabERN, Regional Coordinating Center for Rare Diseases, Udine University Hospital, Udine, Italy; Nicola Ruperto, Instituto Giannina Gaslini, IRCCS, UOSID Centro Trial, Genoa, Italy; Theoklis Zaoutis, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; Jonathan Grigg, Centre for Child Health, Blizard Institute, Queen Mary University of London, London, UK; Nick Croft, Blizard Institute, Queen Mary's University of London, Barts and The London School of Medicine, London, UK; Franz Schaeffer, Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany; Alessandro Zuddas[†], University of Cagliari, Italy; "A. Cao" Pediatric Hospital, "G. Brotzu" Hospital Trust, Cagliari, Italy; Volker Straub, John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; Louis Bont, Department of Pediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands; Helen Cross, Developmental Neurosciences Programme, UCL-NIHR BRC Great Ormond Street Institute of Child Health, London, UK.

The authors acknowledge the assistance of Henriëtte Burgers for editorial support.

FUNDING INFORMATION

The conect4children (c4c) project has received funding from the Innovative Medicines Initiative. 2 Joint Undertaking under grant agreement No. 777389. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

CONFLICT OF INTEREST

K.C. is an employee of Johnson & Johnson, UK. S.B. is an employee of Bayer, Germany. R.P. is an employee of Novartis, USA. G.P. is an employee of Novartis, Switzerland. All other authors declared no competing interests for this work.

DISCLAIMER

The publication reflects the authors' views and neither Innovative Medicine Initiative (IMI) nor the European Union, European Federation of the Pharmaceutical Industries and Associations (EFPIA), or any Associated Partners are responsible for any use that may be made of the information contained therein.

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How to cite this article: Cheng K, Mahler F, Lutsar I, et al. Clinical, methodology, and patient/carer expert advice in pediatric drug development by conect4children. *Clin Transl Sci*. 2023;16:478-488. doi:10.1111/cts.13459