

# Disease-specific clinical trials networks: the example of cystic fibrosis

Kris De Boeck<sup>1</sup> · Veerle Bulteel<sup>2</sup> · Isabelle Fajac<sup>3,4</sup>

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**Abstract** This article describes the steps of the development and the structure of a disease-specific clinical trials network for cystic fibrosis in Europe. Activities such as reviewing study protocols, feasibility assessments, training and standardizing of procedures, and outcome measurements help to bring high-quality clinical trials to the patients. Cooperation with the pharmaceutical industry, other research networks, patient organizations, and regulatory agencies is very important throughout all activities.

**Conclusion:** The European Cystic Fibrosis Society—Clinical Trials Network facilitates the development of new treatments for a rare disease and could be a prototype for other diseases.

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✉ Kris De Boeck  
christiane.deboeck@uzleuven.be

Veerle Bulteel  
veerle.bulteel@uzleuven.be

Isabelle Fajac  
isabelle.fajac@parisdescartes.fr

<sup>1</sup> Department of Pediatric Pulmonology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium

<sup>2</sup> Department of Development and Regeneration, KU Leuven – University of Leuven, Herestraat 49, 3000 Leuven, Belgium

<sup>3</sup> Université Paris Descartes, Sorbonne Paris Cité, Paris, France

<sup>4</sup> Service de Physiologie et Explorations Fonctionnelles, Hôpital Cochin, AP-HP, 27, rue du fg St Jacques, 75014 Paris, France

## What is Known:

- Clinical research has led to the first approved treatments targeting the basic Cystic Fibrosis defect.
- For a rare disease like Cystic Fibrosis, multicenter international collaboration is needed to obtain solid evidence when testing possible new treatments.

## What is New:

- The Clinical Trials Network established by the European Cystic Fibrosis Society has grown to a fully operational network with well-defined structures, procedures and partnerships.
- Standardization of outcome parameters, protocol review, feasibility assessment and other activities help to develop high quality, efficient, relevant and feasible clinical trials, with the aim to bring new treatments to the patients.

**Keywords** Rare diseases · Cystic fibrosis · Clinical trials · Research network

## Abbreviations

CF	Cystic fibrosis
CFF	Cystic fibrosis foundation
CFTR	Cystic fibrosis transmembrane conductance regulator
CRO	Contract research organization
CTN	Clinical trials network
DSMB	Data safety monitoring board
ECFS	European cystic fibrosis society
ECFSPR	European cystic fibrosis society patient registry
EMA	European medicines agency
EnprEMA	European network of pediatric research at the European medicines agency
FEV <sub>1</sub>	Forced expiratory volume in 1 second
GCP	Good clinical practice

SOP	Standard operating procedure
TDN	Therapeutics development network
USA	United States of America

## Introduction

Clinical trials networks are large operational groups formed to facilitate development of new treatments. The cancer research groups pioneered this initiative [4]. The enormous progress in survival in nearly every field of oncology is probably the best testimony to the gain in outcome that can be achieved. Indeed, when an individual center tackles a research question, the investigator has access to only a relatively small sample size and this often does not lead to conclusive evidence [3]. When clinicians in several centers work together in a structured way with the aim of prospectively assessing outcome of interventions according to strict research protocols with adequate statistical power, solid evidence of efficacy or lack of efficacy can be obtained.

When working in the field of rare diseases, a clinical trials network becomes even more important to facilitate the process of developing new treatments. It thus seemed logical to develop clinical trial networks for the most common rare disease in Europe, cystic fibrosis (CF). On the other hand, CF is the most frequent of the rare disorders and, therefore, a potential prototype for other even more rare disease areas. We therefore describe the path we took to develop a European clinical trial network dedicated to CF. This initiative can possibly inspire other learned societies or patient organizations. Therefore, we further describe how we started, how we grew, and how we work at present. We also highlight what have been our successes and the challenges.

### Understand the disease and develop a master plan

Cystic fibrosis affects about 35,000 people in Europe, and more than 75,000 worldwide. It is a life shortening autosomal recessive multisystem disorder [14]. At present, in most countries, the number of adults with CF equals or exceeds the number of children with CF. But despite a complex treatment, chronic airway obstruction and infection usually lead to respiratory insufficiency and premature death. Other major morbidity is associated with the gastrointestinal tract. Pancreatic insufficiency is present in 85 % of subjects, but many other complications occur like intestinal obstruction, liver disease, gall stones, etc. Males are nearly always infertile due to vas deferens obstruction. Salt loss syndromes occur: excessive salt loss via sweat on hot days can lead to acute dehydration, and chronic salt depletion can lead to electrolyte abnormalities and pseudo Bartter syndrome.

Structured follow-up in dedicated centers and guidelines for optimal treatment were shown to improve outcome [12].

Although steady progress in survival was achieved, the median age at death in developed countries is still in the late twenties, mainly due to lung disease. This median age of death is even earlier when access to specific follow-up and treatment is difficult [13]. These morbidity and mortality data are gathered from CF registries, including the European Cystic Fibrosis Society Patient Registry (ECFSPR) [<https://www.ecfs.eu/projects/ecfs-patient-registry/intro>]. This registry was developed around 2000 and now contains data from 35 EU and non EU countries and more than 29,000 patients [18]. For rare diseases, registries are critical to learn the natural history of the disorder, to understand the major morbidities, and to observe the impact of specific follow up or new treatments.

The discovery of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene in 1989 [15] greatly boosted the understanding of the basic CF defect. The structure and function of the CFTR protein as an anion channel was explored, as was the insight how mutations in the *CFTR* gene lead to defects in the synthesis (e.g., premature stop codon mutations, aberrant splice mutations, abnormal CFTR protein trafficking or folding) or function (abnormal gating or conductance) of the CFTR protein [17]. The function of the normal CFTR protein as an anion channel was confirmed as well as its importance in regulation of other ion channels at the cell surface. Ion channel dysregulation leads to a decreased height of the periciliary liquid and abnormal mucociliary clearance which links the basic CFTR defect to chronic infection and inflammation in the lung, the major cause of death of patients with CF. As a consequence of this improved knowledge, the goal within the CF community became bolder and a master plan on how to majorly improve outcome for patients with CF by targeting the basic CF defect was born. Several routes are being explored; for recent reviews, see [1] and [2]. We succinctly mention the major strategies. Although initially hoped for, gene therapy did not prove to be an easy success. Many hurdles need to be overcome, including the size of the *CFTR* gene. Directly targeting the abnormal mRNA may prove more successful. The development of CFTR modulators, small molecules that either rescue the misfolded mutated CFTR protein (correctors) or improve its function at the cell surface by increasing the gating of the protein (potentiators) has been a more successful strategy and led to the first approved treatments targeting the basic CF defect. Stop codon read through drugs are explored for premature stop codon mutations. Modulating ion channels other than CFTR is another possible strategy.

In parallel with this drug discovery pipeline, it was obvious that the clinical phase of drug development needed refinement. Optimal clinical trial protocols relevant for the patients and feasible within certain timelines needed to be developed, using outcome measures that are reliable and standardized between clinical trial centers. Also, it is important to identify sufficient numbers of patients with specific characteristics who are motivated and empowered to participate in clinical trials.

## Clinical trial networks for cystic fibrosis

The Cystic Fibrosis Foundation (CFF) in the USA [<http://cff.org/>] was the first to develop a CF disease-specific clinical trial network. They partnered with biotech companies so that they would take an interest in developing drugs for patients with CF. For the clinical phase of drug development, they saw the importance of developing a Therapeutic Development Network (the CFF-TDN). The therapies or drugs under development were grouped according to their place in the pathophysiological cascade as well as the phase of clinical development: the therapeutic pipeline for cystic fibrosis was born and the progress over time could be monitored and easily visualized [<http://www.cff.org/research/DrugDevelopmentPipeline/>].

The CFF-TDN was founded in 1998. Several national European research initiatives came later, as well as a large Australian CF working group [<http://www.arestcf.org/>]. In 2009, the European Cystic Fibrosis Society (ECFS) [<https://www.ecfs.eu>], a learned society dedicated to CF from research to care and education, decided to set-up an ECFS—Clinical Trials Network (ECFS-CTN) [<https://www.ecfs.eu/ctn>] to further boost efficient clinical research and speed up the clinical phase of CF drug development. Know-how and support by the CFF-TDN greatly boosted the success and rapid growth of the ECFS-CTN.

The steps needed to start a disease-specific clinical trial network can certainly be followed by other learned societies or patient organizations. Therefore, we further describe how we started, how we work at present, and what have been our successes and challenges.

### Steps in the set-up of a disease specific network

#### *Assess the feasibility of starting a clinical trial network*

The learned society ECFS communicated the idea of starting a disease specific clinical trial network to all of its members and inquired whether sites in charge of a sizeable numbers of patients were interested in working together in a clinical trial network. Of 139 replies, 127 were positive and 95 centers with more than 100 CF patients under their care were identified. Hereby, feasibility was established.

Given the many candidate sites, criteria for site participation and site ranking were set up. These included patient potential, meeting the ECFS standards of care for patients with CF [11], having experience with clinical trials, having the available staff and infrastructure, know-how on specific measurement techniques for use in clinical trials, having a detailed CF patient database, agreeing to reserve the patient population for clinical trials run by the network, and demonstrating institutional support for working in this network. When the call for joining the clinical trials network was launched, 29 applications were received from candidate sites. From these, 18 sites

in 8 different countries were selected according to the predefined criteria by an independent committee including scientists experienced with other disease specific clinical trial networks.

Apart from learned societies for CF, several countries, including many European countries, have one or more patient/parent support group. From the conception of the idea of a disease-specific network, the learned society ECFS informed the patient organizations (grouped in CF Europe [<http://www.cf-europe.eu/>]) about this plan and sought their cooperation as a partner to develop this plan.

#### *Outline the global network structure*

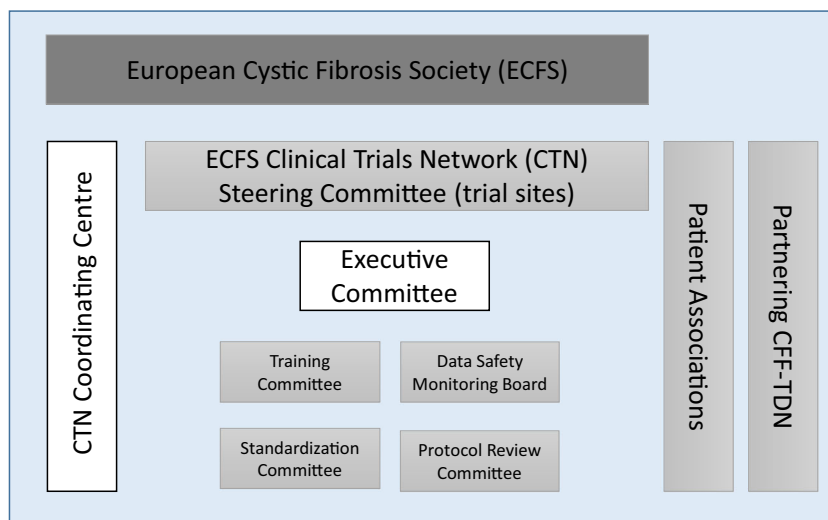
With many partners involved, the setup of an executive committee that steers the activities via a coordinating center was considered crucial. The need for additional committees in charge of specific tasks was also anticipated (Fig. 1).

The executive committee develops and adapts the global strategies of the network. It is chaired by the CTN director who presides the two weekly teleconferences with a preplanned agenda. Members of the executive committee are elected for 3-year terms and represent different European countries. The CTN director is also appointed for 3 years. He or she is a CF physician from one of the participating sites. The CTN director is assisted in his function by the co-chair and the additional personnel at the coordinating center. The latter is responsible for the day to day activities of the network. The coordinating center manages the continuous contact with all CTN sites: feedback, requests, etc. Executive committee meeting minutes are prepared at the coordinating center and sent to all investigators as well as to CF patient organization representatives.

Twice a year, all partners in the network meet face to face. This steering committee includes one investigator from every participating site, all members of the executive committee, leaders of the additional committees, and representatives of national CF patient organizations. Updates on all network activities are provided. Prior to this meeting, new policies or action plans are prepared. These are then discussed, if necessary amended and agreed upon. A representative of the American CF network (CFF-TDN) is also invited to these meetings. This is an enormous boost to keep both networks aligned, to avoid duplication, to use all expertise available.

Financially, the network is supported by the ECFS and by some national patient parent organizations united in CF Europe. A small income is also derived from companies through the review of protocols or feasibility checks. Specific funding is asked for specific projects. For example, a funding from the CFF was received to assess and improve the quality of the network.

**Fig. 1** Structure of the European Cystic Fibrosis Society—Clinical Trials Network (ECFS-CTN)



### *Mission and core tasks of a disease specific clinical trial network*

The ECFS-CTN has a mission to speed up and improve the quality of the clinical phase of drug development. This is done by striving for optimal clinical trial protocols, experienced clinical research practice in every participating site, rigorous standardization of outcome measures, and access to large patient cohorts familiar with clinical research. ECFS-CTN does not work as a contract research organization (CRO) and is as such not responsible for the actual running or quality control in individual sites. It is however important to critically review candidate studies assessing the study design, choice of outcome parameters, feasibility, and priority. It is also of the utmost importance to standardize how the CF-specific outcome measures will be assessed and to offer and monitor site training in clinical trials.

Below, we describe the core tasks. Specific committees are responsible for specific tasks: protocol review, standardization, training, and networking. There is an independent data safety monitoring board (DSMB). Teleconferences of individual committees are organized at regular intervals. Wherever possible, we align our strategy with that of the CFF-TDN in the USA.

### **Protocol review**

All clinical trials that are intended to run within the network are first reviewed via the protocol review committee. To facilitate a swift process, this work is performed by four permanent review groups all including CF specialists, a study coordinator, a statistician, and a CF patient or parent. All score the protocol for scientific merit, feasibility, study design, and strategic fit. A summary report is written by the primary reviewer. There is a possibility to have a combined review with the American network (CFF-TDN) for clinical trials that are planned to be conducted in Europe as well as in North America. After protocol

review, the executive committee votes on the acceptance of the protocol to be run within the network.

As a network policy, the sites agree that by being part of the ECFS-CTN, they only conduct international industry-sponsored studies that have been reviewed and approved by the ECFS-CTN. Since 2009, 57 protocols have been reviewed, 54 have been industry-sponsored, and 3 were investigator-initiated trials.

As years evolve, we notice that protocols are submitted to CTN at an earlier stage and that the ECFS-CTN impact on protocol development is increasing. Sponsors more frequently provide a revised protocol for a second review step, implementing suggestions from the initial review and gaining a better score on the scientific merit and strategic fit.

The number of active studies in the network has increased with every consecutive year and now fluctuates around 15 active studies running simultaneously.

### **Protocol feasibility assessment**

The ECFS-CTN has disease-specific knowledge and can help companies develop a relevant feasibility questionnaire. The clinical sites will provide an accurate count of the number of patients meeting specific study eligibility criteria by consulting their patient databases, which will help the company for appropriate site selection. This way, useless and complex administrative questions are left out so that sites are not burdened unnecessarily.

Since 2011, the network provides this service that is centralized by the CTN coordinating center and can take place in parallel with the protocol review. This service has been performed for 28 protocols since then.

### **Standardization of clinical trial outcome parameters**

In addition, by harmonizing how an outcome measure is used in different centers via unambiguous standard operating

procedures, there will be less variability in results and, therefore, treatment benefit can be evaluated in a more reliable way. In addition, a lower patient number will need to be included in the clinical trial to reach the same statistical power. The standardization committee has put a great effort in standardizing measurement of outcome parameters via separate working parties, each specific to one type of outcome and standardized operating procedures (SOPs) have been written for all CF-specific outcome measures. The SOPs are available upon request at the coordinating center and are of great interest for pharmaceutical companies. Moreover, all sub-committees have worked via a similar, effective method by inventorizing all available information on the clinimetrics of CF-specific outcome parameters, identifying gaps in knowledge, and publishing the findings in major journals [6, 9, 10].

The European Medicine Agency (EMA) has expressed interest in this work. In 2012, it organized a workshop on outcome measures for clinical trials in CF [[https://www.ecfs.eu/files/webfm/webfiles/File/documents/EMA\\_Workshop2012.pdf](https://www.ecfs.eu/files/webfm/webfiles/File/documents/EMA_Workshop2012.pdf)]. This discussion was urgently needed because the only surrogate outcome parameter currently approved (forced expiratory volume in 1 s or FEV<sub>1</sub>) is no longer a sensitive endpoint in a population with a continuously improving long-term outcome [5]. Therefore, the ECFS-CTN is rolling out two new endpoints and, in addition, has organized central reading for these: multiple breath washout with as main readout the lung clearance index (a more sensitive lung function technique especially useful in early or mild lung disease) and an imaging endpoint (chest computed tomography). A procedure for centralized reading is also available for CFTR biomarkers.

Again, all work on outcome parameters has been made easier by the work already done by the CFF-TDN, and the ECFS-CTN has worked in harmony and close collaboration with the CFF-TDN.

### Training committee

The training committee is promoting the improvement of knowledge and skills in clinical research of all investigators and research coordinators. This is achieved by organizing a yearly training session. Different topics are approached every year, and a mixture of ex cathedra and interactive sessions is used. To maximize interest and learning, topics suggested by investigators or research coordinators are included. New themes are approached like preparing for an audit, site trial cost calculation, etc. Making sure all members have up to date Good Clinical Practice (GCP) certification and listing/promoting learning sources are other tasks.

### Other committees and activities

Networking with other learned societies, relevant clinical trial networks, regulatory authorities, and other possible partners is

the ongoing task of the networking committee. The ECFS-CTN is part of the coordinating group of the EMA's network for pediatric research (EnprEMA) [[http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000303.jsp&mid=WC0b01ac05801df74a](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a)].

A data safety monitoring board (DSMB), working independently from the network, is available upon request of pharma companies.

Another action point is to convince companies to supply placebo arm data from previous CF clinical trials so that the natural variability of outcome parameters can be described. This information is useful for planning of future studies, especially for power calculations and deciding on number of patients needed to include in a trial. It is encouraging that pharmaceutical companies increasingly see the value of sharing data with academic investigators and works towards more openness and even full disclosure of research results [8].

The ECFS-CTN sites have access to a yearly report on study performance including patient enrolment in clinical trials, other clinical trials metrics, and site responsiveness to various ECFS-CTN queries. The scores are given in an individual anonymized way allowing sites to benchmark their performance against the other sites. Those assessments are intended to help sites identify areas to target for improvement. An online quality improvement program was developed by the CFF-TDN and shared with the ECFS-CTN. It consists of several steps, from self-assessment to identification of areas of improvement and tools to drive changes at site level.

### Partnership with national patient organizations

The European National CF Associations provide a small financial support to the network. They are represented in the executive and steering committees. The network tries to involve patients and patient organizations as much as possible because active clinical trial enrolment is only possible via empowerment of the patients. During protocol review, patients (or parents of patients) give their view on aspects that they are the expert on. They answer questions on the acceptability of the burden of the experimental protocol, check if the visit schedule is acceptable to patients who will be recruited in the study, and whether the planned procedures are familiar to the study population. Also, they are asked for suggestions on how to make the protocol procedures more feasible for potential subjects. The patient reviewers are trained on clinical trial regulations, study design, and study protocol rules.

Patient empowerment is also promoted via a brochure explaining different aspects of clinical trials. Leaflets specific for children about participation in clinical trials are available. In addition, the interest in clinical trials is boosted by educational leaflets explaining how their current medications have

been developed. All mentioned documents are freely available on the ECFS-CTN website [<https://www.ecfs.eu/ctn/patient-brochures>]. In the near future, it is planned to setup an advisory group for young persons with CF.

## Successes and challenges

### Successes

The ECFS-CTN was quickly successful and popular. The motivation to join was very high, and already in 2012, the network expanded to include an additional 12 sites out of 37 further applicants. A new expansion (wave 3) has become operational in 2016. The network now counts 34 sites in 15 countries grouping 17,500 patients. An up-to-date list of centers and investigators who participate in the network is publicly available on the ECFS-CTN website [<https://www.ecfs.eu/ctn/list-ctn-centres>].

The ECFS-CTN have achieved much in a short time period. The ECFS-CTN has become very operational and productive despite having limited financial resources. This was possible thanks to a head-start by the CFF-TDN allowing us to use all of their expertise. The enthusiasm of investigators and research coordinators within the network has been the catalyzer of this fast progress. Every member feels involved because responsibilities are rotated on a pre-defined basis. Many new activities have started involving new partners so that all feel imbedded and active in the network. All partners feel that their expertise and experience in clinical trials has improved noticeably. All strive for optimal quality delivery.

The network provides specific expertise and advice to companies conducting CF clinical trials. The network also offers high quality in clinical trials via the work done in experienced and well trained sites. Investigators and patients are aware that the clinical trials conducted via ECFS-CTN have been reviewed and meet certain standards. During trial startup and conduct of a trial, the ECFS-CTN central office stays in close contact with all sites. The network can therefore identify issues for improvement and can act as a single point of contact to sponsors until resolution of problems.

It has never been the intention of the ECFS-CTN to monopolize clinical trials in the field of CF in the network sites. The aim is to improve the quality of CF trials and to intensify clinical research in the area of CF. However, because the network now provides access to 17,500 patients in 15 countries (more than half of known subjects with CF in Europe), bypassing the network becomes difficult for any international CF-related clinical trial.

We have been able to standardize outcome measures and we had fast recruitment for CF studies, especially for trials with CFTR modulators.

## Challenges

### *Running an investigator-initiated clinical trial*

The network feels that all elements are in place to start an investigator-initiated trial. There is a need: the many unanswered CF treatment questions including trials in the area of comparative effectiveness that will unlikely be evaluated by an industry sponsor. There is the necessary network capacity: patient numbers, expertise for appropriate protocol design, standardized outcome parameters, the investigators' willingness to perform these types of trials.

Although in the past years, an orderly process was followed for the topic selection and protocol development, so far no ECFS-CTN investigator-initiated study has started. This is mainly because of complexities associated with different regulations in different countries, and with feasibility. Also, it is a challenge to find the necessary budget for an Europe wide study.

### **Regulations and administrative burden surrounding clinical trials**

We are very enthusiastic about the response of the European Medicine Agency to our network. We had a successful meeting on outcome parameters, and all were convinced that a new and modernized view on outcome parameters is needed. However, so far, this has not resulted in specific actions by the EMA. The Pediatric Investigation Plan is a good initiative but sometimes leads to unrealistic requests for trials that are not feasible.

We do see that there is overregulation for low-risk clinical trials such as academic studies of comparative effectiveness. This is an obstacle. Overregulation also moves the focus away from patient safety to an overload of administrative work [7]. It unnecessarily increases cost for these trials. In many countries trials in the comparative effectiveness area require that drugs are supplied to the patient via the study budget. This is unreasonable since the patient would also be treated if not included in the trial.

### **Finances**

Although the national patient organizations support the network intellectually, very little financial support is brought in. This is to some level understandable because the patient organizations raise money on a national level and very little of this money is allowed to cross the border. Still for research and clinical trials in a rare disease such as CF, the solution is really at a multinational level. The American network does not have that particular challenge.

The ECFS-CTN actively chooses not to be financially dependent on pharmaceutical companies, CROs, and other commercial vendors. Our motivation to invest in drug development is to improve patient outcome via faster access to new and better treatments. We therefore do not want to make a great profit from working with companies. On the other hand, we do realize that the ECFS-CTN does facilitate their work. Still, we have absolutely no influence on pharma drug cost setting nor on necessary “easy” to implement safety measures such as the need of cumulative lab results during the conduct of clinical trials. We do not have much influence also on the choice of European countries where a study will run as this is usually decided very early on by a company. This results in having experienced sites underused because they belong to what companies perceive as insufficiently appealing countries for whatever the reason.

In contrast with other networks, sites selected to be part of the ECFS-CTN get no funding because there are insufficient resources in the network. They are involved in a very stimulating collaborative work, and they have more opportunities to run studies which bring some funding. However, they are dependent on their national or institutional clinical research programs and the ECFS-CTN is unable to help selected sites to become even more efficient with additional human resources or to develop some specific outcome measures by helping them acquire the equipment or the expertise.

Access to appropriate research funding is difficult as the competition is stiff. There is also no proper alignment between the setting of priorities in research and the assignment of necessary EU funding, e.g., the European Medicines Agency put out a document listing the research priorities to diminish current unlicensed and off label use of drugs in children [16] [[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2009/10/WC500004017.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf)]. But this work and listing was never followed up by providing the necessary funding to bring this plan forward.

## Conclusion

Disease-specific clinical trial networks are especially important in rare disorders. Clinical trial protocol review and standardization of outcome parameters can form the core towards improved clinical trials with robust outcomes. In addition, an increased level of knowledge by all participants in the network further improves quality delivery. Around the core committees, other activities can be built such as networking, data safety monitoring, quality control, and self-evaluation. Thanks to a lean but very performant central coordination team much can be achieved at a limited cost. Acquiring better funding for investigator-initiated trials is one of the priorities of the network.

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**Author contributions** Veerle Bulteel is a coordinator of the ECFS-CTN since the start in 2009, has written several chapters of the article, and approved the final version. Isabelle Fajac was closely involved in the startup and development of the ECFS-CTN as an executive committee member and director. She has revised and rewritten parts of the article and approved the final version.

**Compliance with ethical standards** This article does not contain any studies with human participants or animals performed by any of the authors.

**Conflict of interest** The authors declare that they have no conflict of interest.

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