CLINICAL INVESTIGATION

The European Cystic Fibrosis Society–Clinical Trials Network: an international network to optimize clinical research for a rare disease

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The European Cystic Fibrosis Society–Clinical Trials Network was established in 2009 as an initiative of the learned European Cystic Fibrosis Society. Its aim is to optimize the development and evaluation of new and approved treatments for cystic fibrosis through efficient clinical studies in Europe. The European Cystic Fibrosis Society–Clinical Trials Network is composed of 30 selected sites across 11 European countries. Its activities are supported by a coordinating center, steering and executive committees and committees for protocol review, standardization, training, networking and data safety monitoring board. The current projects are to set up an investigator-initiated trial, to implement central laboratories for outcome measures, to move new surrogate end points forward and to facilitate quality within the network through providing a quality-improvement program. A new expansion is planned in the near future.

Keywords: clinical trial • cystic fibrosis • learned society • outcome measure • rare disease • research network

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Challenges for clinical research in cystic fibrosis

Cystic fibrosis (CF) is a life-shortening, autosomal recessive disorder affecting 70,000 individuals worldwide. It is caused by mutations in a gene called *CFTR*, which encodes a chloride channel [1]. The disease is dominated by pulmonary disease with persistent bacterial bronchitis and pancreatic maldigestion and malabsorption. Over the last 75 years, CF-projected life expectancy has increased from months to nearly 38 years thanks to a holistic approach to care and intensive symptomatic treatment, both prophylactic and in response to acute events [2]. Moreover, due to the intensive basic and clinical research that followed the identification of the *CFTR* gene in 1989, new therapies have been developed and a pipeline of potential new therapies is being evaluated in patients.

Despite this progress, new therapies are badly needed since the current median age at death is still only 26–28 years [3]. Developing these therapies is challenging. CF is a rare disease with a relatively small pool of patients. New molecules need to be evaluated in pivotal Phase III trials that require several hundreds of subjects. Moreover, new medicines aimed at correcting the CFTR protein are being developed and these new personalized medicines are likely to be beneficial to very specific subsets of patients, mainly defined by their *CFTR* mutations. This means that Phase III trials for these CFTR-modifying drugs are even more difficult to conduct since only a subset of CF patients can be enrolled. With this issue about numbers, it is critical that patients only participate in clinical trials that are meaningful, both in terms of the molecule being tested and of the quality design of the trial. Another challenge lays

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in the outcome measures used to detect the treatment effect. With pulmonary insufficiency as the main cause of morbidity and death, forced expiratory volume in 1 s is still the gold-standard outcome measure in clinical studies and in the regulatory approval of CF respiratory therapies [101]. However, with overall improvements in CF care, the yearly decline in forced expiratory volume in 1 s varies greatly with the characteristics of the CF population and might be very low, especially in children [4]. New and more sensitive outcome measures need to be validated.

2009: the set-up of a European network for CF clinical research

These issues of numbers of patients, numbers of trials and new outcome measures cannot be resolved at a national level but need the gathering of international CF experts. In 1998, the US CF patient parent organization launched a CF clinical research network, the CF Therapeutics Development Network (CF–TDN), which has made major contribution to CF clinical research [5]. In 2009, the European Cystic Fibrosis Society (ECFS), a learned society aiming at advancing knowledge about CF throughout Europe and beyond, took the initiative to form an ECFS Clinical Trials Network (ECFS–CTN) to optimize the development and evaluation of new and approved treatments for CF through efficient clinical studies in Europe [102].

The CF centers making up the ECFS–CTN were chosen by means of site selection process based on predefined criteria: patient potential according to age-classes, proof of meeting the ECFS-consensus for standards of care, experience of site-director and staff in clinical trials, proof of Good Clinical Practice accreditation of principal investigator and staff, availability of study personnel and specific measurement techniques, presence of an interactive database to quickly check inclusion and exclusion criteria for clinical trials and proof of institutional support for participation in the CTN. In total, 18 sites in eight countries were selected out of 29 applications. The network expanded in 2012 after a similar selection process where 12 applications were selected among 37 received. The ECFS–CTN is now composed of 30 sites in 11 countries and is responsible for 13,500 patients (Figure 1).

The basic structure of the ECFS–CTN was established (Figure 2) and a 'code of conduct' about the responsibilities of partners was agreed by all sites. The steering committee is the main governing body of the network. It meets twice a year with a representative of each site being present. An update of the network and of all the working groups is provided and action plans are discussed and agreed. An executive committee composed of six ECFS–CTN principal investigators from six different countries, a representative of patient parent organizations and a representative of ECFS is the decision-making body. It meets every 2 weeks by teleconference. The other working groups are a protocol review committee to evaluate all potential studies to be conducted through the network; a standardization committee to harmonize clinical outcome parameters used in clinical trials; a training committee to build further research expertise; an independent data safety monitoring board and a networking committee to interact with other stakeholders.

These activities are supported by a coordinating center composed of a coordinator, a secretary and a part-time standardization coordinator. Financially, the network is supported equally 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 required for specific projects. For example, funding from the US patient parent organization, the CF Foundation, was received to assess and improve the quality of the network.

2009–2013: ECFS–CTN core activities & achievements

Clinical trials

Between the start of the network in 2009 and 2013, 30 protocols have been reviewed by the protocol review committee. Most of the protocols are industry-sponsored studies. However, three protocols are investigator-initiated trials. As the ECFS–CTN becomes more known in the CF community, companies sponsoring clinical trials in Europe submit their protocols to the ECFS–CTN at an earlier stage, taking advantage of the expert comments about the study design and the scores indicating the feasibility, scientific merit and priority of the protocol. Since 2012, it has become common practice to have companies submitting revised protocols for a second review. Indeed, the European Medicines Agency has noted the benefit of companies submitting their proposed clinical trial protocols after a review by the relevant expert CTN. In parallel, since 2011, the ECFS–CTN offers feasibility check along with protocol review and this service has been provided six times. Again, this feasibility check within the ECFS–CTN allows the company to get an early feedback on the protocol and its feasibility from CF experts.

From its start, the number of studies running in the network has grown steadily (Figure 3) and to date, 26 clinical trials have been, are being or are planned to be conducted within the ECFS–CTN. All ECFS–CTN sites have participated in at least one to nine trials during the past 5 years. For each study, the ECFS–CTN coordinating center follows up on recruitment and timelines. For six out of the eight completed studies carried

Figure 1. European Cystic Fibrosis Society–Clinical Trials Network site location: 30 sites in 11 countries.
Some sites are composite sites with several cystic fibrosis centers acting as one site for the network.

out in the ECFS–CTN, the number of enrolled patients per site was higher in ECFS–CTN sites compared with other participating sites outside of the ECFS–CTN.

Outcome parameters

Standardization of outcome parameters is necessary for efficient trials; it reduces variability in results and hence allows for smaller patient sample sizes. The ECFS–CTN allows international CF experts to share their expertise and groups have been set up to write standardized operating procedures for CFTR function, nutrition, respiratory function, microbiological explorations, chest imaging and inflammatory markers. In the spring of 2010, a consensus conference on outcome parameters in CF was organized by the ECFS and the ECFS–CTN. One of its goals was to work on CF outcome parameters, mainly to inventorize all available information on clinimetrics of specific CF outcome measures and identify gaps in knowledge. The first manuscript on CFTR biomarkers has been published [6] and the one on inflammatory markers is in press [7]. Besides providing useful information to researchers and pharmaceutical companies, these documents allow discussion of the value of specific outcome parameters with health authorities. In September 2012, the European Medicines Agency held a workshop on end points for CF clinical trials and representatives of all stakeholders, including representatives of the ECFS–CTN and pharmaceutical companies, were present [103]. Current clinical end points and alternative clinical end points such as lung clearance index (LCI) and chest computed tomography (CT) were discussed. The meeting has laid the ground for revising the current European Medicines Agency Guideline on the "clinical development of medicinal products for the treatment of CF" [101].

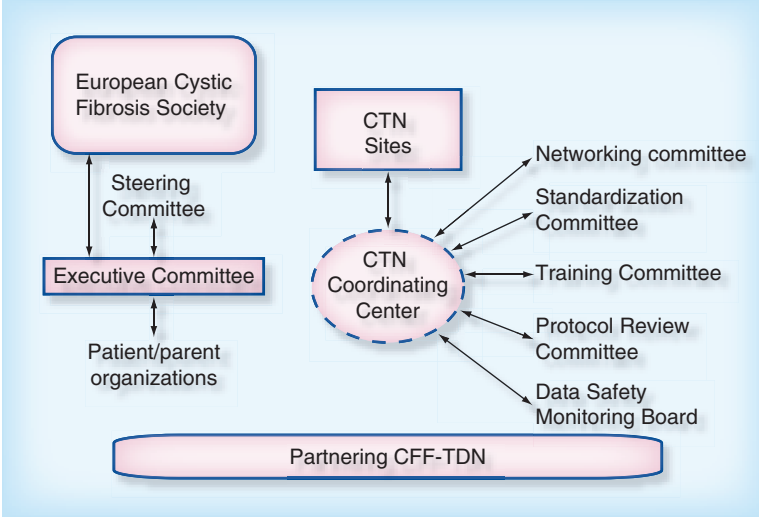

Figure 2. Current structure of the European Cystic Fibrosis Society–Clinical Trials Network.
CFF-TDN: Cystic Fibrosis Foundation Therapeutics Development Network; CTN: Clinical Trials Network.

■ Training

The training status of investigators at each ECFS–CTN site is monitored, online Good Clinical Practice courses are provided and an annual half-day training course is organized for investigators and research coordinators.

■ Cooperation with patient parent organizations

The CF patient is at the heart of the ECFS–CTN project and an active involvement of patient parent organizations from the start was critical to make this project successful. One representative of patient parent organizations is a member of the executive committee; representatives of patient parent organizations are invited to the steering committee meetings twice a year and meet the executive committee at a face to face meeting once a year. Several patient parent organizations have gathered together to help and financially support the ECFS–CTN. A report to patient parent organizations on ECFS–CTN activities was written in 2013 and it is planned to be repeated yearly. Patients are also directly involved in ECFS–CTN activities such as the review of protocols. They pay special attention to the feasibility and potential acceptability of the protocol by patients and their families. To inform and motivate patients to take part in research, a brochure on clinical trials has been written as well as a leaflet with drawings for children and posters showing that all current CF medications are available due to the completion of clinical trials. All those documents are available on the ECFS–CTN website in several languages.

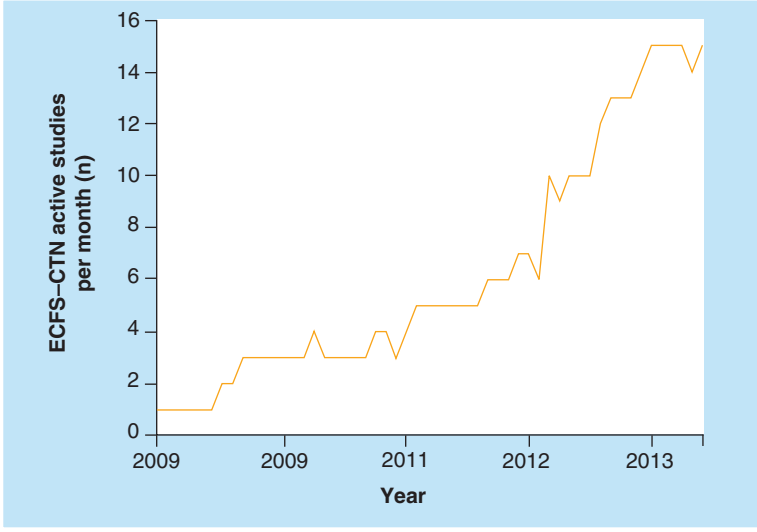

Figure 3. Number of active studies per month in the European Cystic Fibrosis Society–Clinical Trials Network since its start in 2009.
ECFS-CTN: European Cystic Fibrosis Society–Clinical Trials Network.

■ Networking

Active links with key partners have been built. Mostly, the Cystic Fibrosis Foundation Therapeutics Development Network (CFF TDN), the US counterpart of the ECFS–CTN, has been a major partner from the start of the EFCS-CTN, freely sharing its experience of more than 10-year [5]. The ECFS–CTN is in contact with learned societies such as the European Respiratory Society, regulatory bodies such as the European Medicines Agency and other relevant networks. For example, the ECFS–CTN belongs to the coordinating group of the European Network of Paediatric Research–European Medicines Agency. Its aim is to foster high-quality ethical research on quality, safety and efficacy of medicines to be used in children. A meeting between the European Network of Paediatric Research–European Medicines Agency and members of the European Parliament was held in February 2013 to discuss pediatric research in the context of the revised clinical trial directive under discussion in the European Parliament [8].

ECFS–CTN projects

■ Set up an investigator-initiated trial

After 3 years of existence, it was felt that the ECFS–CTN was ready to set up an investigator-initiated trial that would answer questions critical for CF care but was unlikely to be promoted by pharmaceutical companies. A structured process was put in place: sites were asked to name topics of interest for an investigator-initiated trial. Two topics were then selected during the next steering committee meeting and working groups began to draft protocols while feasibility checks were run in the

network. The topic that was most favored by sites was selected and a steering group of experts wrote a full protocol. The next steps are to have the protocol reviewed by the US CF clinical research network, the CFF TDN, and the budget drafted to apply for funding.

■ Implement the standardized operating procedures for CF outcome parameters

The ECFS–CTN has put great effort in having written standardized operating procedures for most of the outcome parameters used in CF clinical trials. It is now time to ensure this standardization is truly implemented across the network. Processes to have ECFS–CTN sites or operators certified for these outcome parameters are put in place, as well as training for sites wishing to set up new measurement techniques. For some outcome parameters, the ECFS–CTN is also working on providing a central laboratory facility with management and expertise to receive, check quality and score the data. Finally, the aim is to have a unique standardized operating procedure for the main CF outcome parameters and to do so, contacts are established with experts in the US CF clinical research network, the CFF TDN, to merge the EU and US standardized operating procedures.

■ Provide evidence-based knowledge to use new surrogate end points

New outcome parameters to detect early lung disease need to be developed and validated. The LCI and chest CT have been chosen as the most promising new outcome measures in that respect. For LCI, a meeting of ECFS–CTN experts took place to reach a consensus on LCI equipment and centers willing to implement this technique were advised. Moreover, a center for additional training, central reading and expertise is being set up. For chest CT, it was decided that a standardized ECFS–CTN chest imaging framework for Interventions and personalized medicine in CF (SCIFI-CF) be set up. This project aims at setting-up a chest-CT network for standardization of technique, central reading and storage. Following a survey in 2012, 15 ECFS–CTN sites qualified for participation to the SCIFI-CF network. Standardization and training of selected sites has begun. The standardization of both LCI and chest-CT techniques and their implementation within the ECFS–CTN will allow to gather reliable data, obtain the lacking evidence needed to establish their validity as CF end points and get them approved by the European Medicines Agency for use as surrogate outcome parameters in clinical trials. In addition, the ECFS–CTN lobbies with companies to obtain placebo arm data from completed clinical trials. Improved knowledge of the baseline variability of outcome parameters measured under standardized conditions are valuable for the planning of future clinical trials. As such patient data can be used optimally.

■ Enhance quality within the ECFS–CTN through a quality-improvement program

The selection of ECFS–CTN sites was done with a structured process in order to select sites performing clinical research with high-quality. To keep this high-level quality in the ECFS–CTN, it is necessary to evaluate how sites are performing in clinical studies. Moreover, it is of interest for the sites to be able to compare their own performance with that of others in order to help identify areas to target for improvement. A first assessment of study performance was done with some study metrics calculated (such as the mean numbers of patients enrolled per site and per year, the mean number of studies per site and per year, the mean number of days between the site initiation visit and the first patient enrolled) and a report was sent to sites identified by a personal number. In parallel with this evaluation process, it is necessary to provide the sites with a quality-improvement program. Such an on-line program has been developed by the US CF clinical research network, the CFF TDN. It consists of several steps from self-assessment, to identification of areas of improvement and tools to drive changes at site level. The CFF TDN has shared the program with the ECFS–CTN and it is currently being adapted to European sites with different languages, regulatory processes and practices. The yearly quality reports combined with the participation to the quality improvement programs will help to identify possible dysfunctional sites.

Future perspective: expansion of the ECFS–CTN

After the set-up in 2009 and a first expansion in 2012, the ECFS–CTN is currently composed of 30 European sites gathering 13,500 patients. It has established an operational structure and it is recognized as a critical partner for CF clinical research by all stakeholders in the field, such as regulatory agencies, pharmaceutical companies, patient parent organizations and national or international networks. However, at present, it includes only a third of European patients and many new expert sites and investigators could join and add their expertise. Another expansion will be discussed and planned in the near future.

Financial & competing interests disclosure

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Executive summary

- In 2009, the learned European Cystic Fibrosis Society took the initiative to form a European Clinical Trials Network (ECFS–CTN), to optimize the development and evaluation of new and approved treatments for cystic fibrosis through efficient clinical studies in Europe.
- The ECFS–CTN is composed of 30 sites across 11 European countries and is responsible for 13,500 patients.
- To date, 26 clinical trials have been, are being or are planned to be conducted within the ECFS–CTN. Core activities of ECFS–CTN are protocol review, standardization of cystic fibrosis outcome measures, training, networking and data safety monitoring board services.
- The current projects are to set up an investigator-initiated trial, to implement central laboratories for outcome measures, to move new surrogate end points forward and to enhance quality within the network through a quality-improvement program. A new expansion is planned in the near future.

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