CLINICAL INVESTIGATION

Developing an international network for clinical research: the European Cystic Fibrosis Society – Clinical Trials Network experience

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Clinical trial networks provide a centralized resource for the successful execution of a clinical trial. For diseases with relatively small populations, such as cystic fibrosis, the most appropriate action is to form a larger operational group. The rationale for setting up a European Clinical Trials Network for cystic fibrosis is to bring new medications to the patients faster. A centralized protocol review will improve the quality and feasibility of clinical studies. Standardization of outcome parameters will help to decrease variation of results and therefore the sample size needed. Motivating patients to take part in research and promoting the safety of participants in clinical trials are of great importance.

Keywords: clinical trials • cystic fibrosis • learned society • registry • research network

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Cystic fibrosis: a rare, life-shortening disease in need of more efficient therapies

Cystic fibrosis (CF) is a life-shortening hereditary disease. Relentless lung infections and poor digestion are the main symptoms. Symptomatic treatments have improved the outcome but current median age at death is still only 26–28 years [1]. As the patient's health declines, the complexity and the cost of the treatment increase and the quality of life decreases. The disease occurs worldwide in males and females and is the most common life-threatening genetically inherited disease affecting Caucasians. Still, it is classified as a rare (or 'orphan') disease. Across 27 EU countries, the prevalence is 0.74 per 10,000 and approximately 30,000 CF patients are registered in 35 European countries [2].

The genetic cause of the disease has been known for 20 years and consists of errors on both copies of the gene coding for the CFTR protein. Knowledge on how the error in the gene leads to absence or dysfunction of the protein opened up a new era of research. Several small chemical compounds have been identified that are able to overcome the basic defect of CF in cell cultures. These new strategies are now being evaluated in patients.

The Clinical Trials Network as an initiative of a learned society (European CF Society)

The development of new drugs for CF has led to an increase in the number of clinical trials in the last 10 years. Unfortunately, this has not usually been associated with improvements in the quality of clinical research [3]. One of the problematic design factors in many published studies is the small patient sample size. For diseases with a relatively small pool of patients, setting up multicenter trials instead of single-center trials will increase the number of eligible patients, and therefore statistical power

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and speed of recruitment. Other important factors for quality design of clinical trials are the selection of appropriate in- and exclusion criteria, use of meaningful and reliable outcome measures, appropriate data analysis and adherence to regulatory guidelines. To optimize study design quality and protect patient safety, a close cooperation is needed between pharmaceutical sponsors and experienced CF centers, with optimal facilities for the conduct of clinical trials.

In the USA, the CF Foundation (CFF), a patient parent organization, supported the development of the CFF Therapeutics Development Network (TDN) [4]. This network, with the coordinating center in Seattle, started activities in 1998 with eight selected centers, and expanded stepwise to 77 centers by 2009. The success of both the CFF Therapeutics Development Program for drug discovery and the activities of the TDN has led to a growing pipeline of new therapeutics under development [101].

The first initiative to form a European Clinical Trials Network for CF came from the former European CF Society (ECFS) presidents, Gerd Döring and Marie Johannesson, in 2006 [5]. Consequently, the project received full support from the current ECFS president, Stuart Elborn. A workpackage titled 'Coordination of Clinical Research' was included in the FP6 funded European Coordination Action for Research in CF (EuroCareCF) project in 2006 and finally led to the creation of the ECFS-Clinical Trials Network (ECFS-CTN) [6,102].

The aim of the ECFS-CTN is to optimize the development and evaluation of new and approved treatments for CF through efficient clinical studies in Europe. A network of clinical trial sites according to state-of-the-art quality criteria needs to be maintained, as well as appropriate structures supporting the network in the acquisition, planning and conduct of clinical trials. As a first step, the ECFS-CTN focused on the review and conduct of trials initiated by pharmaceutical companies. In the future, this will be extended to projects in cooperation with nonprofit organizations and academic centers.

Key steps in the formation of the ECFS-CTN

Site selection

The site selection process was preceded by a feasibility assessment. In 2007, the ECFS sent out a survey to CF center directors in Europe, inquiring about patient availability for clinical trials and about their interest to join a research network. Consequently, an extensive evaluation form was sent to the 95 sites showing interest, each caring for more than 100 CF patients. The following criteria were predefined:

- Patient potential according to different age classes;
- Meeting the ECFS standards for standard of care [7];
- Experience of site director and staff in conducting clinical trials;
- Good clinical practice (GCP) accreditation of staff;
- Availability of specific measurement techniques, staff and infrastructure;
- Presence of interactive patient database;
- Proof of institutional support.

The 29 received applications were ranked by the ECFS president and an external research specialist. After careful review, 18 sites were selected in eight countries (Belgium, France, Italy, Germany, Portugal, Sweden, the UK and The Netherlands).

Formation of the executive committee

The first executive committee (EC) was set up at a business meeting at the end of 2008, this can be considered as the starting point of the ECFS-CTN activities.

At this meeting, the aims were formulated and a business plan to achieve these goals was developed. The network structure (Figure 1), responsibilities, cooperation of the different partners and communication plan were described. The code of conduct and a financial plan were outlined.

One director and one co-director have been appointed. They have the final responsibility for setting the agenda, making decisions and for the global functioning of the network.

The EC consists of five site investigators from five different countries, as well as a patient organization representative. As planned, three members have been replaced after 2 years, and the maximal term for each mandate is 3 years, so both variation and continuity are guaranteed. The EC is a decision-making body and meets every 2 weeks by teleconference. They develop the network policies and steer actions to the different committees. The EC also decides whether a protocol that has been reviewed by the protocol review committee can run in sites that are part of the CTN. Meeting minutes are provided to all network investigators.

Code of conduct

A code of conduct has been approved by the network members, describing the following internal rules:

- CTN sites need to relay requests of pharmaceutical companies for CF clinical trials to the CTN coordinating center;

- CTN sites run studies that are reviewed and approved by the CTN;
- Each CTN site devotes time to the functioning of the network.

Steering committee

Twice a year, one investigator from each CTN site meets with the EC, the working committee chairpersons and the patient organization representatives, to discuss current CTN activities, financial plans, as well as future strategies and action items.

Coordinating center

A network coordinator and half-time secretary were appointed to act as a central point of contact and to streamline communication between CTN sites, committees, patient and parent organizations, industrial companies and so forth. The coordinating center follows up on the decisions generated by the EC and other working groups, and coordinates the protocol review process. Other tasks include organization of meetings and teleconferences, creation of newsletters, brochures and other publications, maintaining information that is posted on the public website [103] and in an internal CTN file repository. The coordinating center also follows up on patient recruitment for studies that are ongoing in the network.

A second part-time coordinator was hired 1 year after the start of the ECFS-CTN to coordinate the activities of the standardization committees.

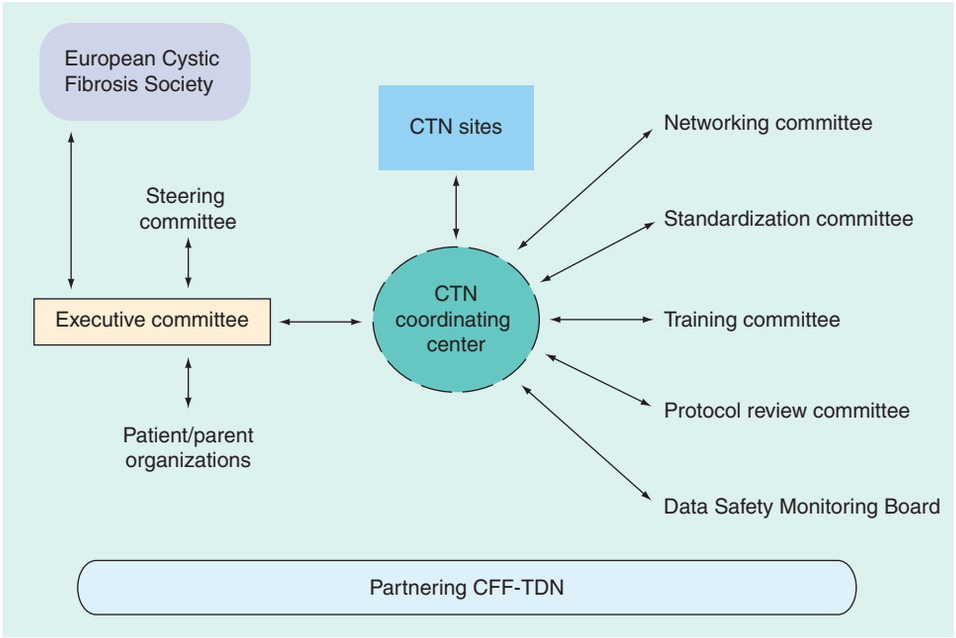

Figure 1. European Cystic Fibrosis Society Clinical Trials Network organogram.
CFF: CF Foundation; CTN: Clinical Trials Network; TDN: Therapeutics Development Network.

ECFS-CTN core activities & achievements

In 2 years, the core activities described below helped to achieve the review of 16 protocols in cooperation with different pharmaceutical companies. Eight protocols were implemented in CTN sites and several more are in the preparatory phase.

Protocol review

One way of achieving high-quality clinical trials is through the review of study protocols by the CTN Protocol Review Committee. The review process is one of the core activities of the CTN. Companies are invited to involve the CTN in the early stage of their protocol development. Detailed feedback about the study design is provided and a score is calculated that indicates the feasibility, scientific merit and priority of the protocol for acceptance into the network. The protocol review process has been based on the model used by CFF-TDN in the USA and has only been modified where needed to adapt to the European situation. The CTN coordinator overviews the process and timelines from the first contact with a company until delivery of the final report and follow-up communications. An online protocol review system facilitates communication and coordination. A plan has been set up with the CFF-TDN, for the provision of global reviews and a global Data Safety Monitoring Board (DSMB).

From the beginning of 2009 to the end of 2010, 16 pharmaceutical clinical trial protocols have been reviewed, four of which in cooperation with the CFF-TDN.

Follow up of trials conducted in CTN sites

If the protocol review has been successful and the clinical trial is selected by the CTN, it will run in the CTN centers selected by the pharmaceutical company with set-up of individual contracts between the investigators and the company. The CTN coordinating center contacts the sites at regular time intervals to follow up on the recruitment. This allows to identify specific problems or causes for delay and to look for solutions together with the study sponsor.

In March 2011, eight clinical trials were conducted or were ongoing in CTN sites. For the two studies that were completed, the number of enrolled patients per site was higher for CTN centers compared with other participating clinical sites.

Training

The training committee is responsible for monitoring the training status of investigators at each CTN site (e.g., GCP training and informed consent training). In 2009, 36 individuals (at least one person per site) followed an online GCP course (financed by CFF) and obtained certifications.

In addition, the committee organizes an annual training course for investigators of every CTN site. This training course is linked to the ECFS annual conference. Example topics for the face-to-face training sessions in 2010 were:

- Practicalities for setting up a CTN center;
- Perceptions of the pharmaceutical industry (input by two companies);
- Ways to encourage patient recruitment into clinical trials.

It is considered important to liaise closely with other learned societies to ensure that appropriate training resources are shared.

Standardization of outcome measures

The aim of the ECFS-CTN Standardization Committee is to harmonize clinical outcome parameters used in CF clinical research by implementing Standardized Operating Procedures for the main end points used in clinical trials. This will ensure less variation and therefore more reliable results and more efficient trials.

Standardization working groups have been set up for inflammatory markers, lung imaging, microbiological explorations, electrophysiological measurements, nutritional evaluation and respiratory function.

In the spring of 2010, the ECFS and the CTN organized an active and successful consensus conference on 'outcome parameters in CF'. The main goal was to establish a document reflecting European guidelines on aspects of CF outcome parameters for use in clinical trials and to study clinimetrics and feasibility parameters. Experts from the CFF-TDN reference centers in the USA joined the working groups, as well as delegates from different pharmaceutical companies and patient representatives.

Networking

The purpose of the ECFS-CTN Networking Committee is to build active links between CTN and key partners involved in clinical trials in CF. To achieve this goal, the committee is in contact with the following groups:

- Research networks in EU member states;
- National and European CF patient organizations;
- The US CFF-TDN. There are two-yearly face-to-face meetings and monthly teleconferences with the US CFF-TDN;
- The learned societies, such as the European Respiratory Society;
- Regulatory bodies. The network committee discusses with representatives of the EMA gaps in the research of CF-related medicines for children and the need for defining appropriate outcome parameters.

Data Safety Monitoring Board

Guarding the safety of subjects in clinical trials is extremely important. Therefore, the ECFS-CTN can provide assistance for the set up of an independent DSMB with CF experts. The DSMB coordinator (based at the University of Lyon, France) sets up an agreement, arranges the fees and executes services independently from the CTN. For studies conducted in both Europe and the USA, a global DSMB can be set up in cooperation with CFF-TDN.

Future perspective

Enlargement of the network

The ECFS-CTN has started with a limited amount of sites (18), to make sure there was a good overview when implementing the planned structures, communication and activities.

After 2 years of successful activities, it was decided to expand the network with an additional ten sites, with the purpose to include more large, experienced European CF centers.

This additional selection process was started at the end of 2010 by inviting all CF centers in Europe to send in their application form. Similar criteria will be applied for the original selection of sites (see above). The new sites will be selected by mid 2011 and will officially be part of the network by the beginning of 2012.

Cooperation with the ECFS patient registry

The ECFS patient registry [104] is a common platform for data collection on CF patients in Europe. It was initiated in 2006 when funding was awarded under the EU Framework six initiative, as part of the European Coordination Action for Research in CF, titled EuroCareCF.

Purposes of the ECFS patient registry are:

- To measure, survey and compare aspects of CF and its treatment in the participating countries, thereby encouraging new standards of dealing with the disease;

- To provide data for epidemiological research;
- To identify specific patient groups suitable for multicenter trials.

A close cooperation between the CTN and the patient registry (and pharmaceutical companies) can contribute to the quality of design and the effectiveness of clinical trials.

A delegate from the registry attends the CTN EC teleconferences and the CTN director is a nonvoting member of the registry steering committee. The basic rules for cooperation have been outlined internally.

Cooperation with CF patient organizations

From the start, it has been clear that ECFS-CTN and the CF patient organizations have a common goal, and that a close relationship is needed.

An important role for ECFS-CTN is to improve clinical trial information to patients. This will be done by the distribution of a patient-information brochure with basic information on clinical trials in CF and by a project that explains to patients how their current medications have been developed. On the public ECFS-CTN website, information is posted about CF studies that are ongoing in sites of the network. Results of studies that have been finished are added if available and in agreement with involved companies.

Patients are involved in the review of patient-orientated documents, training sessions for investigators and a system is being developed for involvement in the protocol review process.

In the USA, the CFF provides a significant amount of direct financial support to the CFF-TDN (counterpart of the ECFS-CTN). In Europe, transferring money from national CF patient organizations to a European network is more challenging, since patient organizations have only legal accountability for patients in their country. This creates a kind of paradox, as the ECFS-CTN is needed for multinational studies. Therefore, a continuous dialogue is engaged to find alternative ways of cooperation and support, such as the formation of a consortium of patient organizations for joined project specific funding.

Involvement in the EMA European Network for Paediatric Research

The European Network of Paediatric Research at the EMA is a network of research, investigators and centers with recognized expertise in performing clinical studies in children [105]. The goals are to enable collaboration between networks and stakeholders to foster high-quality, ethical research on medicines for use in children.

At the beginning of 2011, the ECFS-CTN became part of the coordinating group by fulfilling the following recognition criteria:

- Research experience and ability;
- Network organization and processes;
- Scientific competencies and ability to provide expert advice;
- Quality management;
- Training and educational capacity to build competences;
- Public involvement.

By being part of this group, the ECFS-CTN will help with tasks such as facilitating access of the pharmaceutical industry to paediatric clinical study centers and experts, identifying new networks to include in the European Network of Paediatric Research at the EMA and developing common educational tools for children and parents.

Executive summary

- Multicenter, international clinical trials are needed to develop more efficient therapies for cystic fibrosis (CF).
- A learned society such as the European CF Society (ECFS), can successfully initiate the set-up of a clinical trials network, with the aim to bring new medicines to the patients faster.
- Site selection, formation of an executive committee, steering committee and coordination center, were key elements for the set-up of the ECFS-Clinical Trial Network (CTN).
- Core activities of the ECFS-CTN are protocol review, follow-up of study conduct, training, standardization of outcome measures, networking and DSMB service.
- After a start-up period with a limited number of clinical sites, the ECFS-CTN is ready to involve more CF centers and to develop closer relationships with other actors in the field of CF research, such as the ECFS patient registry, patient organizations and regulatory agencies.

Financial & competing interests disclosure

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Bibliography

1 Buzzetti R, Salvatore D, Baldo E *et al.* An overview of international literature from cystic fibrosis registries: 1. Mortality and survival studies in cystic fibrosis. *J. Cyst. Fibros.* 8(4), 229–237 (2009).

2 McCormick J, Mehta G, Olesen HV, Viviani L, Macek M Jr., Mehta A. Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. *Lancet* 375(9719), 1007–1013 (2010).

3 Briggs TA, Bryant M, Smyth RL. Controlled clinical trials in cystic fibrosis – are we doing better? *J. Cyst. Fibros.* 5(1), 3–8 (2006).

4 Goss CH, Mayer-Hamblett N, Kronmal RA, Ramsey BW. The cystic fibrosis therapeutics development network (CF-TDN): a paradigm of a clinical trials network for genetic and orphan diseases. *Adv. Drug Deliv. Rev.* 54(11), 1505–1528 (2002).

5 Doring G, Elborn JS, Johannesson M *et al.* Clinical trials in cystic fibrosis. *J. Cyst. Fibros.* 6(2), 85–99 (2007).

6 De Boeck K, Tiddens H, Wagner T *et al.* Guideline on the design and conduct of cystic fibrosis clinical trials: the European Cystic Fibrosis Society-clinical trials network (ECFS-CTN). *J. Cyst. Fibros.* 10(Suppl. 1), S53–S66 (2011).

7 Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. *J. Cyst. Fibros.* 4(1), 7–26 (2005).

Websites

101 Cystic Fibrosis Foundation: drug development pipeline www.cff.org/research/DrugDevelopmentPipeline/

102 European Coordination Action for Research in Cystic Fibrosis www.eurocarecf.eu/

103 European Cystic Fibrosis Society: clinical trials network www.ecfs.eu/ctn

104 European Cystic Fibrosis Society: patient registry www.ecfs.eu/projects/ecfs-patient-registry/intro

105 European Medicines Agency www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks