



Journal of Cystic Fibrosis Volume 10 Suppl 2 (2011) S67–S74

Journal of  
**Cystic  
Fibrosis**

[www.elsevier.com/locate/jcf](http://www.elsevier.com/locate/jcf)

# Guideline on the design and conduct of cystic fibrosis clinical trials: The European Cystic Fibrosis Society–Clinical Trials Network (ECFS-CTN)

K. De Boeck<sup>a\*</sup>, V. Bulteel<sup>a</sup>, H. Tiddens<sup>b</sup>, T. Wagner<sup>c</sup>, I. Fajac<sup>d</sup>, S. Conway<sup>e</sup>, F. Dufour<sup>f</sup>,  
A.R. Smyth<sup>g</sup>, T. Lee<sup>e</sup>, I. Sermet<sup>d</sup>, B. Kassai<sup>h</sup>, S. Elborn<sup>i</sup>  
on behalf of all ECFS-CTN network partners

<sup>a</sup> University Hospital of Leuven, Leuven, Belgium

<sup>b</sup> Erasmus Medical Centre, Rotterdam, The Netherlands

<sup>c</sup> Johann Wolfgang Goethe-Universität, Frankfurt/Main, Germany

<sup>d</sup> Université René Descartes, Paris, France

<sup>e</sup> St. James University Hospital, Leeds, United Kingdom

<sup>f</sup> Vaincre la Mucoviscidose, Paris, France

<sup>g</sup> Division of Child Health, University of Nottingham, Nottingham, United Kingdom

<sup>h</sup> Epicime, CIC 201, RIPPS, Hôpital Femme Mère Enfant HCL & Université de Lyon, Lyon, France

<sup>i</sup> Belfast City Hospital, Belfast, UK

## Abstract

We describe the rationale for disease specific research networks in general as well as the aims and function of the European Cystic Fibrosis Society–Clinical Trials Network (ECFS-CTN) specifically. The ECFS-CTN was founded in 2009 with the aim of improving the quality and quantity of clinical research in the area of cystic fibrosis (CF) in Europe. A network of 18 clinical trial sites in 8 European countries was established according to uniform state-of-the-art quality criteria. To support the ECFS-CTN in the acquisition, planning and conduct of clinical trials, the network is equipped with a coordinating centre, steering and executive committees, and committees for protocol review, standardization, training and networking as well as a data safety monitoring board. A strong partnership with European CF patient parent organizations aims to increase awareness of the need for efficient clinical research and the participation of patients in clinical trials.

© 2011 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

*Keywords:* Research network; Clinical trials; Cystic fibrosis

## 1. Introduction

The Clinical Trials Subgroup of EuroCareCF Workpackage 3 (Coordination of Clinical Research) held meetings to discuss the best strategy to design and implement clinical trials in the area of new therapies for cystic fibrosis (CF) patients. These discussions endorsed the need for a disease specific clinical trials network in Europe. This document explains the need for and formation of the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN).

### 1.1. Rationale for a CF Clinical Trials Network

A recent review lists all studies on survival and mortality reported from CF registries [1]. Even with the best possible care, the median survival of subjects with CF is only about 36 years of age. It should be emphasized that the median age of survival is a statistical prediction made for a specific birth cohort. In all CF patient registries the current median age at death is at least 10 years younger than the calculated median life expectancy so that the current median age at death is only about 25 years. This crude reality is insufficiently reported. Against such a background of premature mortality it is obvious that research into new treatments and especially treatments with “disease modifying drugs” might bring major improvement in life expectancy and quality of life for CF subjects.

\* Corresponding author: Kris De Boeck, Department of Pediatrics, University of Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 343831; fax: +32 16 343842.

*E-mail address:* [christiane.deboeck@uzleuven.be](mailto:christiane.deboeck@uzleuven.be) (K. De Boeck).

Lung function decline relates to mortality [2] and most patients die from respiratory insufficiency. Therefore, research aimed at preventing lung function decline should receive highest priority.

### 1.2. Challenges for CF trials

In the last decades, the number of clinical trials in the field of CF has increased [3]. In the period 1961–2002, eight hundred and five trials were identified, but 63% of these were performed in the last 5 years. This increase in number was not paralleled by an increase in the number of multicentre large size trials. Therefore, many if not most clinical trials conducted in CF patients have not conclusively answered the research question posed. The clinical phases of CF drug development face challenges related to the disease, the organization of care in CF centres, the CF patient population and regulatory authorities [4].

CF is a complex genetic disease of a progressive nature. The wide variation in causal mutations is in part responsible for the type and severity of the disease process [5]. But even in subjects with the same mutation, the severity of organ involvement varies [6]. Between subject differences considerably influence the outcome of drug testing.

CF study design needs to take into account evolving aspects of the disease process. At present about 50% of patients with CF are children. With the advent of newborn screening the need for clinical research in this young age group is highlighted since many aspects of standard CF care in the young are not evidence based [7]. Even with the current best standards of care and despite good nutritional status and preserved lung function, 50–80% of children with CF identified through newborn screening develop bronchiectasis by the age of 5 years [8,9].

Centralized care in appropriately staffed dedicated CF centres leads to improved outcomes [10,11]. However, not all CF care centres have the appropriate staff, expertise and structure to conduct clinical trials [12]. Even if the infrastructure is excellent, there are a limited number of CF patients in individual CF care centres. Hundreds of patients are needed to assess drug efficacy in phase III studies. There are competing clinical trials and the availability of patients is further reduced by limitations related to age and disease status in specific study protocols.

Even if premature mortality is a reality, this is often not consciously considered by individual CF patients and their parents. Improved outcomes, especially maintained lung function in young CF children, have changed the face of the disease. Most children with CF live active “relatively normal” lives despite the burden of treatment. The current course of the disease with typical lung function decline in later adolescence and young adulthood is a reality better appreciated by experienced CF clinicians than by CF patients and their parents. Regretfully, subject participation in CF clinical trials is only 5–10%. Reasons for CF patients declining to participate in trials include lack of time and fear of side effects. The need for CF research should be explained

when parents are informed of their child’s diagnosis. In addition, physicians should find a better balance between the dual message of current better outcome, but the still nearly uniformly life shortening nature of CF.

Research in children is more complex from an ethical and regulatory perspective. To determine treatment efficacy, disease stage is likely to be as important as subject age. Still pharmacokinetics of drugs must be evaluated separately in children.

Regulations such as the EU Directive on clinical trials ensure high standards and patient safety. But, increasing bureaucratic demands pose a barrier for orphan disease research where the financial profit of drug development is limited. Assigning orphan drug status [13] and specific task forces to boost progress in the treatment of orphan diseases are therefore of paramount importance. As an example, the seventh framework program (FP7) of the European Commission will support projects for “clinical development of substances with clear potential as orphan drugs”.

Due to the challenges enumerated, the most appropriate action in CF research is to form larger operational groups and to focus on both study quality and quantity. Multicentre trials improve statistical power, enhance external validity and through rapid recruitment, give more timely results. On the other hand, additional coordination is needed to cope with practical difficulties such as logistics, costs and inter-centre communication and standardization of procedures.

### 1.3. History of clinical trial networks

The first clinical trial networks were developed in the field of cancer research, for example the Cancer and Leukemia Group B (“CALGB” – 1956 – US) or the European Organization for Research and Treatment of Cancer (“EORTC” (initially named “GECA”) – 1962 – EU).

The “Greenberg Report” written in 1967 and published in 1988 describes the organization, review and administration of cooperative studies as well as the basic components required for a research network [14]. It explains the crucial role of the coordinating centre to continually maintain communication between all participants. It also highlights the importance of critically reviewing candidate studies to judge scientific quality, feasibility, design and potential benefits.

Since the 1960’s, several disease specific clinical trial networks have been developed, which have successfully developed new treatments for specific patient groups (e.g. The Asthma Clinical Research Network (“ACRN” – 1993) or the Acute Respiratory Distress Syndrome Network (“ARDSnet” – 1994). Examples specific to Europe are the Pediatric European Network for Treatment of AIDS (“PENTA” – 1991) and the European Myeloma Network (“EMN” – 2003).

The old fashion point of view that research in children is unethical has led to the off label use of many drugs in children. In Europe as well as in the USA there is increasing awareness that research in the paediatric age group should be promoted. In Europe this is the role of the Paediatric Committee (PDCO) of the European Medicines

Agency (EMA). As a result, several paediatric networks have been established (e.g. the European Society for Paediatric Nephrology (ESPN) and the Paediatric Rheumatology European Society (PRES)). Other welcome initiatives are the obligation to have a Pediatric Investigation Plan (PIP) for every new investigational drug application and the creation of an association of paediatric networks. For additional information, we refer the Reader to <http://www.ema.europa.eu/htms/human/paediatrics/regulation.htm> and <http://www.ema.europa.eu/htms/human/paediatrics/network.htm>.

#### 1.4. Goals, advantages and disadvantages of clinical trial networks

For diseases with relatively small patient populations such as CF, clinical trial networks provide a centralized resource and adequate access to patient populations for the successful execution of clinical trials [15]. In this way, adequately powered clinical trials can be conducted and drug development for orphan diseases is facilitated. Also the quality of medical science at participating sites is enhanced by the combined expertise of multiple participants and the training opportunities that are offered. A significant reduction in the enrollment period can be obtained as a result of the larger patient pool.

By using standard operating procedures to measure outcome parameters and increasing the expertise of personnel at CF centre, variability in results will decrease. As a result, fewer patients will be required to demonstrate clearly a significant effect of the investigational product [16–18]. Improved knowledge about the natural course of the disease through analyses of data in patient registries will help to define the most important research questions leading to more evidence based study design and sample size calculation [18].

Possible disadvantages are the cost, the more complex decision-making process and the inadequate recognition of individual investigators in multicentre research [15].

#### 1.5. CF specific networks in the US and Europe

Established in 1998, the US Cystic Fibrosis Foundation-Therapeutics Development Network (CFF-TDN) has proved highly effective at accelerating clinical trials of new therapies for CF. Uniting CF patient parent organizations and academia establishes powerful alliances for CF patient care and therapy development. Patient parent organizations provide finances, academia provide scientific expertise and both provide expert leadership. Although countless excellent people have been involved in the success of the CFF-TDN, the visionary leadership of Robert Beall and Bonnie Ramsey is recognized by all. The CFF-TDN started its activities with 8 centres selected by competitive application. The network expanded to 18 sites in 2004 and more recently to 77 centres. This expansion is necessary since more than 30 different therapies are currently under development (see <http://www.cff.org/research/DrugDevelopmentPipeline/>). Together, the 77 centres provide a pool of 19,000 CF patients for clinical trials.

The centres are supported by a central coordinating centre at Seattle Children's Research Institute and 7 reference centres each specializing in the standardization and interpretation of a major CF outcome measure. The success of the CFF-TDN in the US has been remarkable. For this reason, the NIH plans to exploit the CFF-TDN organization and develop a therapeutic pipeline similar to that of CFF as a generic model to improve research efficacy for rare diseases [19].

Initiatives to organize CF clinical research have been underway in Europe for some time. Examples include the Scandinavian CF Study Consortium, the German CF research organization (<http://muko.info/Mukoviszidose-Institut.1835.0.html?&L=0>) and the UK CF gene therapy consortium (<http://www.cfgenetherapy.org.uk/>). But many studies surpass the capacity of national patient groups. Hence, the need for a pan-European initiative. The ECFS-CTN is the European answer to the CFF-TDN. Many research ideas have been pioneered by European researchers including application of antibiotics via inhalation to treat CF lung disease, defining an eradication strategy for early *Pseudomonas aeruginosa* lung infection, highlighting the parallels between diffuse panbronchiolitis in Japan and CF lung disease which led to the use of macrolides to treat CF lung disease, developing ursodeoxycholic acid treatment for CF liver disease and recognising the importance of polyunsaturated fatty acids (PUFA) in CF pathophysiology [20–26]. But in Europe national borders have often hindered the formation of larger operational networks to definitely settle research questions

#### 1.6. Conclusion

The rationale for setting up the ECFS-CTN is to optimize the development and evaluation of new and approved treatments for CF in pan-European clinical studies. This includes advising on optimal study design, identifying the most appropriate target population, improving sample size calculations by using real life data and decreasing sample size by standardizing outcome parameters. Besides study design, other important roles of the ECFS-CTN are to motivate patients to take part in research and promote the safety of participants in clinical trials. The example of the CFF-TDN is inspiring and proves this can be achieved

## 2. Network function

### 2.1. Establishment of the ECFS-CTN

ECFS presidents Gerd Döring and Marie Johannesson took preparatory steps to form a European clinical trial network [4]. The ECFS leadership of Professor Stuart Elborn continued in the same spirit but the EuroCareCF program was the catalyst for this project, leading to the creation of the ECFS-CTN, which commenced its activities in January 2009.

A structured process had taken place to ensure a just and solid basis for the ECFS-CTN. A feasibility questionnaire was sent to all European CF physicians known to the ECFS. This questionnaire asked CF centre directors whether they



were interested in participating in a European clinical trials network as well as to report the number of CF patients under their care. Of 139 replies, 127 were positive and 95 centres responsible for the care of more than 100 CF patients were identified. A second in depth questionnaire was sent to the directors of these 95 centres. Centres were asked to report patient potential according to age-classes, verify that they complied with the ECFS consensus for standards of patient care, report the experience of site-director and staff in clinical trials, provide proof of Good Clinical Practice (GCP) accreditation of principal investigator and staff, report the centre's track record in performance of clinical trials, availability of study personnel and specific measurement techniques, presence of an interactive database to quickly check inclusion and exclusion criteria for clinical trials and provide proof of institutional support for participation in the ECFS-CTN. Preference for sites with both paediatric and adult CF patients was specified. Neighbouring CF centers were allowed to group themselves into one operational unit provided one principal investigator would oversee the operation of the group and communication within and outside the group. Stuart Elborn and a cancer research specialist then ranked the applications. Figure 1 shows the 18 centres from 8 different countries selected to form the first wave of the ECFS-CTN. There is no hierarchy between centres; all are equal partners in the ECFS-CTN.

## 2.2. Aims

The aim of the ECFS-CTN is to improve the quality and quantity of clinical research in the area of CF and to bring new medicines to patients faster. This is achieved by establishing a network of clinical trial sites according to uniform state-of-the-art quality criteria, by setting-up an appropriate structure

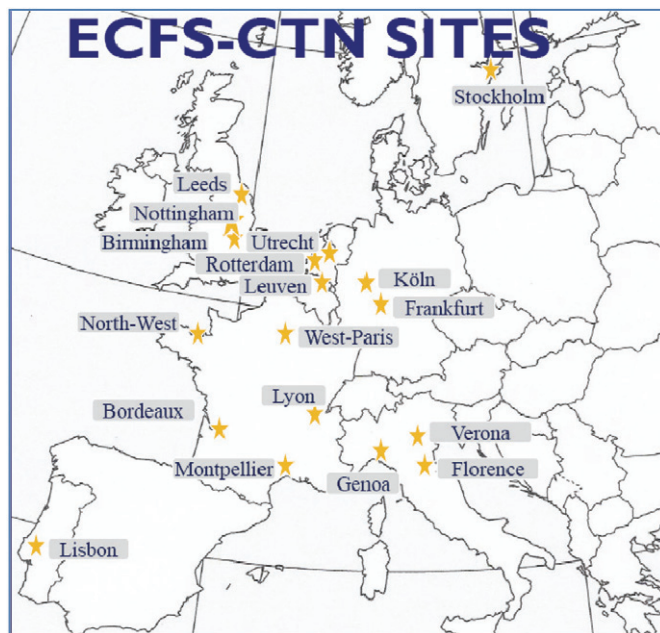


Fig. 1. ECFS-Clinical Trials Network site locations: 18 sites in 8 countries.

supporting the network in the acquisition, planning and conduct of clinical trials and finally by attracting projects in cooperation with non-profit organisations, academic centres and pharmaceutical or medical-device companies.

### 2.2.1. Overall function and agreements between ECFS-CTN members ("Code of conduct")

Only studies that are evaluated by the protocol review committee are potential studies to be conducted through the network. All ECFS-CTN partners refer requests by pharmaceutical companies or clinical research organisations (CROs) for participation in CF studies to the ECFS-CTN coordinating centre. The code of conduct also provides directions on confidentiality, conflict of interest, publication policy, financial agreements and communication. The sites agree to comply with the European clinical trials directive (GCP-compliance) and to meet and maintain the requirements for membership in terms of patient numbers, staff structure, capabilities, competencies, accreditations, continuous education and processes required by the ECFS-CTN. Other responsibilities of membership are recruitment of patients according to agreed timelines and number, timely protocol review and replies to feasibility requests, commitment to share clinical trial expertise with other centres within their region and swift communication with the coordinating centre.

### 2.2.2. Building a positive partnership with patient parent organisations

When the ECFS-CTN was established, it was realized that the active involvement of patient organizations is critical to the network's success. Therefore one member of the ECFS-CTN's Executive Committee represents patient parent organizations. Patients need to be informed about why clinical research is important. They also need the right information to promote better participation in clinical trials. To keep patient parent organizations fully informed about the activities of the ECFS-CTN, a newsletter is distributed regularly. Hopefully these actions will boost patient participation in clinical trials.

### 2.2.3. Building a positive partnership with pharmaceutical companies

The ECFS-CTN seeks to interact with pharmaceutical companies at an early stage in the design and development of clinical trials, at a time when it can actively influence protocol design. The protocol review committee provides feedback on a proposed protocol and suggests changes in the general protocol design, the choice and the frequency of assessing endpoints as well as inclusion and exclusion criteria. At the request of pharmaceutical companies, CF centres can assess feasibility by consulting their databases to determine how many of their subjects meet certain inclusion and exclusion criteria. In addition the protocol review committee will give a priority score to a trial. Because so many competing trials need to be performed, this is of great relevance. By interacting early with pharmaceutical companies and by providing advice about protocol design, patient recruitment is improved. Also correct delineation of responsibilities and

timing of interactions between pharmaceutical companies, CROs and CF centres is needed.

### 2.3. Structure

During the first business meeting of the ECFS-CTN which was held in Leuven in November 2008 and funded by EuroCareCF, the basic structure of the ECFS-CTN was established (Fig. 2). The 'code of conduct' on how to share information and the responsibilities of partners was agreed by all partners.

#### 2.3.1. Executive committee

The executive committee (EC) consists of 5 ECFS-CTN principal investigators from 5 different countries and a representative of patient parent organizations. During biweekly teleconferences time is devoted to implement the policy that was agreed during the business meeting. A delegate from the ECFS and the ECFS-CTN Coordinator also participate in these meetings. Meeting minutes are distributed to Primary Investigators and Co-Investigators in all ECFS-CTN sites.

In any European Network, it is important to have enough member states participate and to rotate principal responsibilities through the different partners. For this reason, ECFS-CTN Executive Committee members are appointed for 2 or 3 year terms and are then replaced by other members to allow fresh ideas to emerge and to make sure all partners have a feeling of building, sharing and belonging.

#### 2.3.2. ECFS-CTN coordinating centre

ECFS has committed itself to prime the network by funding a clinical trial network coordinator and a part-time secretary for 3 years. At the beginning of May 2009, the network coordinator was recruited. The coordinator functions as the daily contact person for the ECFS-CTN and interacts with partners, industry, patient parent organizations and other interested partners. The coordination centre also follows up the decisions of the ECFS-CTN Executive Committee and

other working groups, and coordinates the protocol review process. A second part time coordinator has recently been recruited.

#### 2.3.3. Steering committee

Twice a year, a face to face meeting is organized of the executive committee, the network coordinator, a representative from each ECFS-CTN site, the leaders of the different network committees, a representative of the ECFS, a representative of European patient parent organizations and an invitee from the CFF-TDN.

During these meetings, an update is provided by all working groups, the financial plan is discussed, and action plans for the next year are agreed. At the 2010 steering committee meeting, the ECFS expressed its continued support for the operation of the ECFS-CTN and several European patient organizations agreed to provide additional support for the network. Furthermore the need for a second coordinator was endorsed as were plans to modestly expand the ECFS-CTN.

#### 2.3.4. Other committees

The *Protocol Review Committee* consists of a leader, deputy and CF specialists with expertise in different domains. The protocol review process is based on the one used by the CFF-TDN with modifications to adapt to the European experience. Prior to initiation of protocol review a contract is set up between the pharmaceutical company and the ECFS-CTN. For every protocol submitted detailed feedback about the study design is provided and a score is calculated reflecting the priority and feasibility of the research question posed. Only protocols with the highest priority scores are candidates for acceptance by the network.

The ECFS-CTN coordinator oversees the process and timelines from first contact with a company, until delivery of the final report and follow-up communication.

Diverse companies have been in close discussions with the ECFS-CTN to have their protocols reviewed. By July 2010, 11 protocol reviews had been finalized. In response to requests

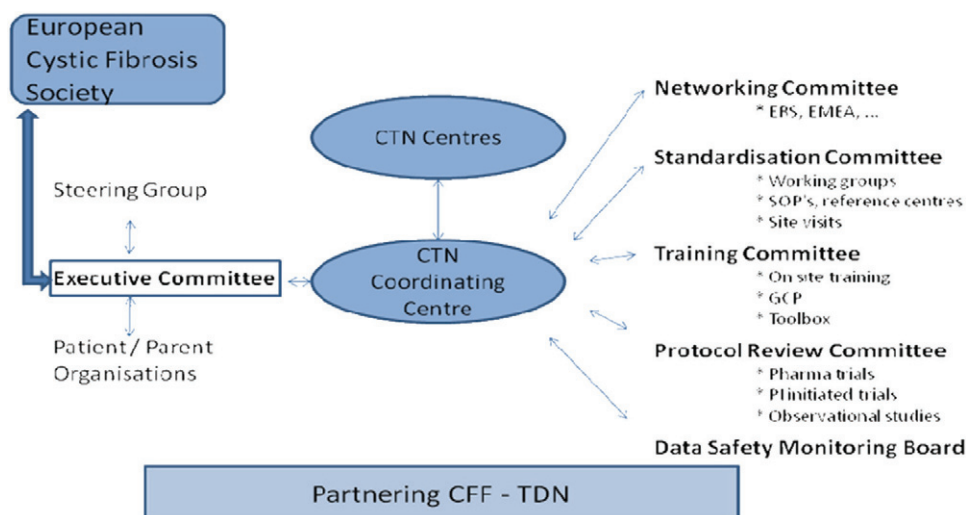


Fig. 2. Current structure of the ECFS-Clinical Trials Network. For further information, see text.

for transatlantic clinical trials, a process for joint reviews with the CFF-TDN has been set up.

The *Standardization Committee* is tasked to create high quality standard operating procedures. It comprises several sub-committees: Respiratory Function Explorations, Lung Imaging (CT), Microbiological Explorations, Inflammatory Markers, Nutritional Status Evaluation, Nasal Potential Difference, Intestinal Current Measurements and Sweat Test. Individuals outside the ECFS-CTN are invited to contribute their expertise to these working groups.

The standardization subcommittees are preparing consensus documents on outcome parameters. For this purpose, the subcommittees will work in close contact with their counterparts in CFF-TDN reference centres. A concluding consensus meeting to finalize the work was held in March 2010. The main goals of the consensus documents will be to achieve agreements on aspects of outcome parameters in clinical trials (inside and outside the ECFS-CTN), to compose an inventory of literature data and to agree on standard operating procedures. It is hoped that the consensus documents will be of use for authorities such as the EMA.

The *Training Committee* will build further research expertise. As a first step the possibility to follow online GCP training has been provided to all sites and key people were certified in early 2010 (financed by CFF). ECFS-CTN training sessions for centre personnel covering different aspects of clinical trial conduct, will also take place at ECFS meetings. The first ECFS-CTN Training and Development meeting was held at the 33rd European CF Conference, Valencia, Spain (16–19 June 2010).

The independent *Data Safety Monitoring Board* (DSMB) service is offered upon request. The cost for convening the necessary expertise will be covered by individual pharmaceutical companies or by the appropriate trial budget.

The aim of the *Networking Committee* is to interact with existing organizations such as ECFS working parties, National (generic) Networks, the EMA, the European Respiratory Society, other scientific organizations etc. In this way existing resources and available expertise is used, policies are streamlined and impact is increased.

Teaming up with the ECFS Registry will be extremely valuable and has already been anticipated. With the advent of mutation specific CF trials, knowing the geographic prevalence of individual mutations is crucial. In addition, other relevant clinical data will become available from this pan-European CF Patient Registry developed by EuroCareCF and the ECFS, which will assist in realistic protocol design. The registry data report from the year 2006 can be found at [http://www.ecfs.eu/files/webfm/webfiles/File/ecfs\\_registry/ECFRreportA2006.pdf](http://www.ecfs.eu/files/webfm/webfiles/File/ecfs_registry/ECFRreportA2006.pdf), while the EuroCareCF report on the demographics of CF in Europe has been published recently [27].

### 2.3.5. Partnering with the CFF-TDN

As much as possible the ECFS-CTN aims to mirror TDN structure and function. To ensure communication and cooperation remains maximally efficient between the ECFS-

CTN and the CFF-TDN, monthly teleconferences have been instituted. There are however major differences between the ECFS-CTN and the CFF-TDN. The CFF-TDN has an established track record, the ECFS-CTN is emerging; the sponsor of the CFF-TDN is the parent organization (the CFF), the initial sponsor and initiator of the ECFS-CTN is a scientific society, the ECFS; the central organization of the CFF-TDN has a large full-time staff, whereas the ECFS-CTN has recruited 1.5 coordinators and has a part-time secretary.

### 2.3.6. Relationship with European non-ECFS-CTN centres

The ECFS-CTN's standardization committee currently welcomes input from experienced researchers outside the network. This will further promote universal acceptance of standard operating procedures. The ECFS-CTN aims to expand its network to include a larger number of centres by 2012. Input from non ECFS-CTN members is also necessary in the data safety monitoring board. The ECFS-CTN seeks to create an open spirit towards non-ECFS-CTN sites.

## 2.4. Communication

The coordinating centre is the central contact point for receiving internal and external questions and for sending out requests, meeting minutes, newsletters etc. The coordinating centre is located in Leuven, Belgium and can be reached by email (ECFS-CTN@uzleuven.be) or telephone (+32 479 983839).

The ECFS-CTN publishes and distributes regular newsletters as well as a special newsletter for patients. General information about the ECFS-CTN, information specific for companies and newsletters are available from: <http://www.ecfs.eu/ctn>. A password protected online file repository for internal use is available.

## 3. Evaluation of Clinical Trials Network

### 3.1. Short term

One of the priorities of the ECFS-CTN is to improve the quality of CF clinical trials by standardizing methods (writing Standard Operation Procedures) and by obtaining a reduction in variability of outcome parameters (consensus outcome parameters). Also input from the protocol review committee on draft protocols might impact on the schedule for patient visits and procedures, leading to more patientfriendly study design, greater patient satisfaction and increased patient recruitment.

Research quantity can be expressed as for example the percentage of patients enrolled and the percentage of target enrollment.

Research efficiency can be calculated as for example the time from regulatory packet receipt to first patient enrolled and time from enrollment approval to first patient enrolled.

The quality delivered by the ECFS-CTN for one specific study might also be measured by keeping track of the number



of major protocol violations and by sending a questionnaire to the sponsor that calculates a “quality score”.

### 3.2. Medium term

When sites are involved in multiple ECFS-CTN studies, the parameters described above might be used to make a combined analysis (e.g. yearly) that provides more information about how sites are performing individually. This information might also be used to tackle problems at specific sites and if necessary to exclude sites from further participation in the ECFS-CTN.

In the medium term, the operation of the ECFS-CTN as a whole might be examined by analyzing the total number of studies undertaken and the number of subjects coming from ECFS-CTN sites participating in different clinical trials.

At this stage it will also be important to provide feedback (study reports) to the scientific community and to CF patients (via the website newsletters and conference presentations).

### 3.3. Long term

By analysing quantity, quality and efficiency as described above, the goal is to reduce the time required to bring new effective medicines to the patient. This is of course whilst maintaining optimal research quality and safety.

## 4. Other aspects

### 4.1. Funding

The ECFS has committed itself to further support the network financially. The network activities will bring in some money (e.g. fees for protocol reviews or feasibility checks), but it is clear that these fees will never be sufficient to sustain the ECFS-CTN.

We strongly believe that patients with CF and their parents will play a crucial role in the success of the network, with the result that effective new drugs are made available to all patients as soon as possible. We therefore are thankful that patient parent organizations in several participating countries contribute to network costs (personnel and activities). Parent organizations – united by CF Europe – agreed a memorandum of understanding with the ECFS-CTN. This will likely be the start of wider involvement of patient organizations in the clinical trials network.

Efforts will be directed at accessing funds from the European Union for network operation and for running CF clinical trials especially with drugs licensed for indications outside of CF treatment. Often drugs used in CF are not profitable to pharmaceutical companies and thus unlikely to be studied. In concert with other scientific organizations the ECFS-CTN will list research priorities [28], work out a scientifically sound and practically feasible protocol and apply for EU funding.

### 4.2. Ethics

By grouping expertise and means in major European centres research quality and patient safety will be improved thereby contributing to ethically sound research.

Of course all clinical research has to comply with European as well as country specific laws and guidelines. Work undertaken by the Ethical/Legal/Social Issues Workpackage of the EuroCareCF project has produced a roadmap of all governing European as well as country specific legislation regulating paediatric clinical trials [29,30].

## 5. Conclusion

EurocareCF Workpackage 3, with its aim to investigate the best strategy to design and conduct CF research facilitated the formation of the ECFS-CTN.

At this moment, 18 centres in 8 countries are actively involved in this network. The establishment of an executive committee, steering committee, a coordinating center and different subcommittees guarantee a solid organizational structure with several links to different stakeholders.

The modalities for interaction between centres have been described in a code of conduct to be adhered to by network sites. Information about how the ECFS-CTN operates has been provided to pharmaceutical companies.

Protocol review will improve the quality and feasibility of clinical studies taken up by the network. Standardization of outcome parameters will lead to uniform conduct and improve quality performance in clinical trials undertaken by the network.

A strong partnership with CF patient parent organizations will increase awareness of the need for efficient clinical research to identify better therapies faster and likely improve patient participation in clinical research.

In conclusion, quite some work has already been undertaken relating to the establishment and operation of the ECFS-CTN. A firm foundation has been built to continue on the multiple tasks that await attention in the years to come.

## Acknowledgements

Christine Dubois from ECFS and the entire ECFS Board; national CF patient and parent organizations and CF Europe; ECFS-CTN Principal Investigators and Co-Investigators and their site personnel; Bonnie Ramsey, George Retsch-Bogart and Jill Van Daltsen and their staff at the CFF-TDN; Robert J. Beall, Preston W. Campbell, III, Bruce C. Marshall and their staff at CFF; CF parents and patients. This work was supported by the European Union Sixth Framework Programme (contract no. LSHM-CT-2005-018932, EuroCareCF).

## Conflicts of interest

S. Conway is on the Advisory Board for Gilead, Novartis and Vertex. K. De Boeck is or has been on the Advisory

Board for Gilead, Novartis, Vertex and PTC and has done consultancy for Eurand, Pharmaxis and Inspire.

## References

- [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* 2009;8(4):229–37.
- [2] Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr* 1997;131(6):809–14.
- [3] Briggs TA, Bryant M, Smyth RL. Controlled clinical trials in cystic fibrosis – are we doing better? *J Cyst Fibros* 2006;5(1):3–8.
- [4] Doring G, Elborn JS, Johannesson M, et al. Clinical trials in cystic fibrosis. *J Cyst Fibros* 2007;6(2):85–99.
- [5] Zielenski J. Genotype and phenotype in cystic fibrosis. *Respiration* 2000;67(2):117–33.
- [6] Decaestecker K, Decaestecker E, Castellani C, Jaspers M, Cuppens H, De Boeck K. Genotype/phenotype correlation of the G85E mutation in a large cohort of cystic fibrosis patients. *Eur Respir J* 2004;23(5):679–84.
- [7] Marshall C. Clinical practice guidelines for the care of infants identified through cystic fibrosis newborn screening. *J Pediatr* 2009;155(Suppl. 4):S71–116.
- [8] Linnane BM, Hall GL, Nolan G, et al. Lung function in infants with cystic fibrosis diagnosed by newborn screening. *Am J Respir Crit Care Med* 2008;178(12):1238–44.
- [9] Claire Wainwright: plenary session 3 of the North American CF conference, Minneapolis, USA, Oct. 15–17 2009 (<http://www.nacfconference.org/plenaryarchive.asp>).
- [10] Lebecque P, Leonard A, De Boeck K, et al. Early referral to cystic fibrosis specialist centre impacts on respiratory outcome. *J Cyst Fibros* 2009;8(1):26–30.
- [11] Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2005;4(1):7–26.
- [12] Elborn JS, Hodson M, Bertram C. Implementation of European standards of care for cystic fibrosis – provision of care. *J Cyst Fibros* 2009;8(5):348–55.
- [13] Binns R, Driscoll B. New European rules on orphan drugs. *Pharm Sci Technol Today* 2000;3(7):218–9.
- [14] Organization, review, and administration of cooperative studies (Greenberg Report): a report from the Heart Special Project Committee to the National Advisory Heart Council, May 1967. *Control Clin Trials* 1988;9(2):137–48.
- [15] 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* 2002;54(11):1505–28.
- [16] Standaert TA, Boitano L, Emerson J, et al. Standardized procedure for measurement of nasal potential difference: an outcome measure in multicenter cystic fibrosis clinical trials. *Pediatr Pulmonol* 2004;37(5):385–92.
- [17] Corey M. Power considerations for studies of lung function in cystic fibrosis. *Proc Am Thorac Soc* 2007;4(4):334–7.
- [18] Goss CH, Mayer-Hamblett N, Kronmal RA, Williams J, Ramsey BW. Laboratory parameter profiles among patients with cystic fibrosis. *J Cyst Fibros* 2007;6(2):117–23.
- [19] Francis S. Collins: plenary session 1 of the North American CF conference, Minneapolis, USA, Oct. 15–17 2009 (<http://www.nacfconference.org/plenaryarchive.asp>).
- [20] Hoiby N, Frederiksen B, Pressler T. Eradication of early *Pseudomonas aeruginosa* infection. *J Cyst Fibros* 2005;4(Suppl 2):49–54.
- [21] Hoiby N. Diffuse panbronchiolitis and cystic fibrosis: East meets West. *Thorax* 1994;49(6):531–2.
- [22] Jaffe A, Francis J, Rosenthal M, Bush A. Long-term azithromycin may improve lung function in children with cystic fibrosis. *Lancet* 1998;351(9100):420.
- [23] Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. *Lancet* 2002;360(9338):978–84.
- [24] Colombo C, Setchell KD, Podda M, et al. Effects of ursodeoxycholic acid therapy for liver disease associated with cystic fibrosis. *J Pediatr* 1990;117(3):482–9.
- [25] Strandvik B, Gronowitz E, Enlund F, Martinsson T, Wahlstrom J. Essential fatty acid deficiency in relation to genotype in patients with cystic fibrosis. *J Pediatr* 2001;139(5):650–5.
- [26] Touw DJ, Brimicombe RW, Hodson ME, Heijerman HG, Bakker W. Inhalation of antibiotics in cystic fibrosis. *Eur Respir J* 1995;8(9):1594–1604.
- [27] Mehta G, Macek M, Mehta A. European Registry Working Group. Cystic fibrosis across Europe: EuroCareCF analysis of demographic data from 35 countries. *J Cyst Fibros* 2010;9(Suppl 2):S5–21.
- [28] Smyth A, Barbato A, Beydon N, et al. Respiratory medicines for children: current evidence, unlicensed use and research priorities. *Eur Respir J* 2010;35(2):247–65.
- [29] Pinxten W, Dierickx K, Nys H. Diversified harmony: Supranational and domestic regulation of pediatric clinical trials in the European Union. *J Cyst Fibros* 2011;10(Suppl 2):183–98.
- [30] Pinxten W, Dierickx K, Nys H. Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. *Eur J Pediatr* 2009;168(10):1225–34.