" When I first decided to participate to the protocol review process I thought maybe this will be just a check that obvious things are addressed. Going through the first protocol I was submitted with I realized that IT IS USEFUL for a patient to provide comments because what it is obvious for a patient is not necessarily obvious for a protocol writer. E.g. the time it takes to perform routine checks during the testing period and the consequent impact on your life's quality. There are many aspects that you realize are important while going through the protocol and may be you don't even consider otherwise.
I'm glad to have entered into the network for the protocols review and I hope to have provided a useful contribution into this process. "

Roberto Vimercati, Italy

" As a patient I review research proposals mostly because I contribute to better treatment and finding a cure for cystic fibrosis. No matter how my condition is, my mind works fine and what is in my power to do, I gladly do. I'm pleased to know that my opinion is valued. In addition to that, it complements my education as research master student. I learn from the academic foundation that build a proposal and try to understand the biochemical or statistical content. Finally, it is nice to be informed about the development of new drugs or treatments.
In my experience, the protocols are of high quality and the topics are very relevant. Researchers are aware of the patient population: they take their regular treatment schedule and safety in consideration. I'm able to give some practical advices and share my opinion as patient, but I never had major concerns. It is clear that the studies are carefully designed by qualified experts. Knowing that people care about cystic fibrosis and that patients, doctors and researches join efforts, gives me hope for the future. "

E The Netherlands

- **Running and supporting academic investigator-initiated trials**

  Some important treatment questions are not answered by trials run by pharmaceutical companies, and it is important that CTN both develops and supports academic investigator initiated multicenter multinational clinical trials in cystic fibrosis.

- **Supporting the study conduct in the sites that are part of the network**

  - A toolbox is available for network sites to support study setup, conduct and close-out.
  - During the study, the coordination centre follows-up on recruitment and other study metrics.
  - The voice of the network can be used in case of unresolved issues with the sponsor or CRO for clinical trials run in ECFS-CTN sites. For example, recently the ECFS-CTN has campaigned to ensure that European patients have a fair chance to participate in potentially desirable worldwide studies

by agreeing paced enrollment plans. These plans should allow enough time for European patients to have the opportunity to volunteer before all the spaces on the trial have been filled up.

- **Standardizing research procedures and outcome parameters**

  When trying to standardize new or existing working methods (for example to measure lung function or to perform a sweat test), it is important to have an international dialogue. If everybody works the same way, there is less variation in results, which means that less patients have to participate in a clinical trial to prove the same effect and results will be available quickly. Standardization working groups have been set up for respiratory function, electrophysiological measurements, microbiological explorations, lung imaging, nutritional evaluation and inflammatory markers.

- **Providing training to the sites' staff**

  - Follow-up on "Good Clinical Practice" training and certification (this is the ethical foundation to protect the rights and welfare of all volunteers in clinical trials).
  - Yearly training sessions for investigators and study coordinators.
  - Training and certification process on outcome measures such as Nasal Potential Difference, Lung Clearance Index and chest-CT scans.
  - Quality assessment and online improvement programme: in 2013, some pilot sites have tested an online self-assessment and quality improvement programme provided by the US network, the CFF-TDN. The process was discussed and made available to all CTN sites in 2014.

- **Communicating towards patients**

  From the start, the ECFS-CTN has actively developed different materials including information for patients related to clinical trials and the development of medicines:

    - Information brochure on clinical trials in cystic fibrosis
    - Posters: "where does my current medication come from"

  In 2013, new materials have been made available :

    - Children's leaflet on cystic fibrosis research
    - Posters to inform patients that their site belongs to the ECFS-CTN

  These documents have been translated into different European languages and have been grouped into 1 section on the ECFS-CTN website https://www.ecfs.eu/ctn: "Information for People with CF".

4. What is the direct and potential benefit to patients?

Due to the standardization of routine care across countries, CF patients live longer with better quality of life. However, CF is still a severe and threatening disease. The only way to defeat this difficult disease is to find new and better treatments. Clinical research is necessary to develop new and more effective treatments so that patients with CF have a prolonged survival and a better life. But clinical research is a complex undertaking, all the more for a relatively rare disease such as CF: many patients have to get involved in trials with the highest scientific merit and priority.

The existence of a European network for CF clinical research such as ECFS-CTN allows such trials to run in the most effective way and maximize chances that effective new drugs are made available to all patients as soon as possible. Indeed, the network gathers large and selected centres all over Europe and ensures an adequate coordination, quick patient recruitment and high standards of performance.

We also bring safety benefits for patients who volunteer to participate in clinical trials. We take care to select the protocols with good preclinical and early phase records, and train centres about informing patients regarding the risks – in terms of obtaining consent, continuously monitoring for side effects, and helping patients to decide on withdrawal from a study, when appropriate.

As a result of high standards in the carrying out of clinical trials, the pharmaceutical industry will be willing to invest in CF research and to work in partnership with CF clinicians and researchers.

5. ECFS-CTN Financial Support

The ECFS-CTN is financially supported by grants from the ECFS and seven national CF-organisations (UK CF-Trust, Vaincre La Mucoviscidose (France), Mukoviszidose e.V. (Germany), Lega Italiana Fibrosi Cistica, Belgian CF Organisation, NCFS (Netherlands), CF-CH (Switzerland). Most recently, in addition, ECFS-CTN has received a grant from the US Cystic Fibrosis Foundation (CFF). CTN is also financed through fees for services (for example protocol review, feasibility checks, etc.) by the pharmaceutical industry. As an important role of ECFS-CTN is to advocate the best interests of people with CF in Europe and beyond having access to effective and improved treatments as quickly as possible, it is important that financial independence from Sponsors is maintained by this mixed funding model. ECFS-CTN increases the opportunity for European CF patients to be involved in clinical trials by bringing more studies to Europe that would otherwise be performed in other parts of the world. As a result of the mixed funding model the ECFS-CTN in conjunction with international partners such as the North American Cystic Fibrosis Foundation Therapeutics Development Network (CFF-TDN) can act without conflict of interest to prioritise studies that are most likely to be of benefit to CF patients. Such prioritization would be more difficult in a

wholly Pharma funded model, emphasising the importance and CTN's appreciation of the valued support of the national CF patient organisations.

6. Why does the ECFS-CTN need your support and what can you do to support ECFS-CTN?

EU collaboration of all stakeholders is needed to conduct high quality clinical research in CF and patients are clearly a key element in this endeavor. Patient organisations can promote a positive attitude towards clinical research. Without their commitment, clinical trials are impossible to conduct. Moreover, their insight into the disease adds specifically to the scientific opinion provided by clinicians. Therefore, patient reviewers are regularly helping to assess new clinical trial protocols. They pay special attention to patient-relevant characteristics of the trial protocol that may either support or jeopardize patients' preparedness to join the trial and to adhere to the protocol. On a more strategic level, national patient associations are key partners for ECFS-CTN. They help to underpin the importance of clinical research in the patient community. This may again support enrolment in clinical trials. Patient organisations also inform patients about regulations that are applied in clinical research in order to ensure efficiency and safety. As part of their routine work, patients organisations provide fair and balanced information about upcoming treatments and most recent scientific progress. While new treatments may have the potential to improve patients' daily life, they still need to be carefully evaluated even after marketing authorisation has been granted. This is because when new drugs are approved and licensed for clinical use, usually safety and effectiveness has only been proven over 2-3 years in the clinical trials. Further real-life long term monitoring is necessary to ensure that this safety and effectiveness continues for patients in the long term. This again is becoming a very crucial field for the co-operation between patient organisations and the ECFS.

Patients organisations can also increase awareness of what ECFS-CTN is doing. Moreover, as no "EU funds" are directly available for such networks as ours, financial support from national associations is essential for the sustainability and independent advocacy role of the ECFS-CTN. Patient organisations can convince donors of this need and promote the importance of allowing money "to go over the borders" for EU collaborative projects.

- **Patient stories: clinical trial participants comment on their experiences:**

"The advantages of participating in the trial were that I liked the idea I took part in research to treat the 'faulty gene' and the results will hopefully help develop a 'cure' for CF."

"The disadvantages were travelling to the hospital, 2 hours from home while studying for exams!"

"I have gained better understanding of my CF. I take medications and taking the study drug wasn't a big deal. My lung functions have improved with the assistance and persistence and encouragement of my research nurse"

Sean Hamilton, aged 18, UK

"The first advantage of taking part in this drug trial is feeling a lot better physically."

"I am not as frightened as I used to be about my years ahead."

"feeling so well means I really cannot be bothered with my nebulisers and physio anymore, I still do them but find it hard to keep motivated."

Tom Purdon, aged 17, UK

2014 Annual reporting

1. Participating sites, governance, committees

1.1. ECFS-CTN sites 2014:

	Center	PI	Co-Investigators
Belgium	Leuven / Brussels	K. De Boeck	L. Dupont, M. Proesmans, P. Lebecque, T. Leal
Czech Republic	Prague	P. Drevinek	L. Fila
Denmark	Copenhagen	T. Pressler	M. Skov
France	Bordeaux / Toulouse	M. Fayon	J. Macey, M. Murris-Espin, F. Brémont
	France East*	M. Abély	F. Huet, J. Derelle, L. Weiss
	Mucomed*	R. Chiron	L. Méziane, L. Mély, J-C Dubus, M. Reynaud-Gaubert, M. Albertini
	France North-West*	G. Rault	L. Guéganton, A. Magnan
	Lyon	P. Reix	I. Durieu
	West Paris*	A. Munck	I. Fajac, M. Lebourgeois, D. Hubert, I. Sermet
Germany	Berlin	D. Staab	N. Derichs
	Frankfurt	T. Wagner	S. Zielen
	Hannover	B. Tümmler	T. Köhnlein
	Köln	E. Rietschel	S. Van Koningsbruggen
	Münich	S. Nährig	M. Griese, R. Huber, M. Kappler
Italy	Florence	C. Braggion	G. Taccetti
	Genova	L. Minicucci	A. De Allesandri, R. Casciaro
	Milan	C. Colombo	G. Pizzamiglio
	Rome	S. Quattrucci	S. Bertasi
	Verona	M. Cipolli	S. Volpi
Portugal	Lisbon	C. Barreto	P. Azevedo, L. Pereira
Spain	Barcelona	S. Gartner	J. de Gracia Roldan
Sweden	Göteborg	A. Lindblad	M. Gilljam
	Stockholm	L. Hjelte	F. Karpati
The Netherlands	Rotterdam	H. Tiddens	M. Bakker
	Utrecht	K. van der Ent	I. Bronsveld, J. Lammers
UK	Belfast	S. Elborn	J. Bradley, A. Reid
	Birmingham	E. Nash	J. Whitehouse
	Leeds	T. Lee	K. Brownlee, C. Etherington, D. Peckham
	London	J. Davies	D. Bilton, E. Alton, I. Balfour-Lynn
	Nottingham	A. Smyth	A. Knox

*:

France East:	Dijon, Nancy, Reims, Strasbourg
Mucomed:	Giens, Marseille ped, Marseille Adult, Montpellier, Nice
France North-West:	Roscoff, Rennes, Angers, Vannes, Nantes, Tours
West Paris:	Robert Debré, Necker, Cochin hospitals

2015 Update:

13 additional sites have been selected during 2015 to join the ECFS-CTN from 1st January 2016. These are: Brussels, Rouen, Lille, Essen-Bochum, Jena, Dublin, Jerusalem, Petah-Tikva, Rome, Warsaw, Zurich, Southampton, and Cambridge. As a result four new countries are involved (Ireland, Israel, Poland and Switzerland) and in total the CTN now covers around 17500 adult and pediatric CF patients in 15 countries and 43 sites.

1.2. Coordinating centre:

The coordinating centre streamlines communication between CTN sites, working groups, patient and parent organizations, industrial companies, etc.

The coordinating centre is located in Leuven, Belgium and is staffed by a full time coordinator and a half-time secretary since 2009. An additional half-time administrative assistant joined in September 2012.

Tasks of the coordinating centre:

- Central hub internal/external communication
- Coordination of protocol review and feasibility checks
- Repository documents/information
- Keep internal overview of studies that are in review, in conduct or in the pipeline
- Follow up on patient recruitment for ongoing studies
- Developing agreements, templates, forms, ...
- Writing brochures, newsletters, articles
- Update public website with ongoing CTN studies
- Follow-up/implement decisions executive committee
- Pharma contacts: info, negotiations, protocol reviews
- Logistics: face to face meetings, teleconferences, meeting minutes

A part time coordinator for standardization activities, located in Belfast, worked for ECFS-CTN until July 2014. A new coordinator has been appointed to start in January 2015.

2015 Update:

Kate Hayes commenced her role as Standardisation Co-ordinator in January 2015 and has progressed the output of the Standardization Committee chaired by Professor Isabelle Sermet.

1.3. Governance:

- Executive committee (EC)

The EC consists of 6 investigators from different sites and different countries, as well as a patient organization representative. 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 and to the national patient organizations supporting the ECFS-CTN.

2014 Executive Committee:

ECFS CTN Director

Isabelle Fajac (Paris)

ECFS-CTN Co-Director

Tim Lee (Leeds)

ECFS-CTN Executive Committee members

Nico Derichs (Berlin)
Pavel Drevinek (Prague)
Silke Van Koningsbruggen (Köln)
Giovanni Taccetti (Florence)
Andreas Reimann (Bonn, Patient Organization representative)

ECFSPR Representative

Anil Mehta (Dundee)

Liaison with CFF-TDN

Nico Derichs (Berlin)

ECFS representative

Christine Dubois, ECFS

2015 Update:

The following executive committee members have stood down at the end of their three year terms: Isabel Fajac, Pavel Drevinek, Nico Derichs, and Andreas Reimann. Tim Lee (Leeds) is now Director; Silke Van Koningsbruggen (Köln) is Co-Director; and joining the Executive Committee are Damian Downey (Belfast), Lieven Dupont (Leuven) and Michael Fayon (Bordeaux) as investigators and Paola De Carli from the French patient organisation.

- **Steering committee**

Twice a year, one investigator from each CTN site meets face to face with the Executive Committee, the working committee chairpersons and the patient organization representatives, to discuss current CTN activities, financial plans, as well as future strategies and action items. Meeting minutes are provided to the national patient organizations supporting the ECFS-CTN.

Steering committee meetings 2014:

Leuven, Belgium: January 23-24th
Gothenburg, Sweden: June 11th

Meeting minutes have been provided to the patient organization representatives

1.4. Committees:

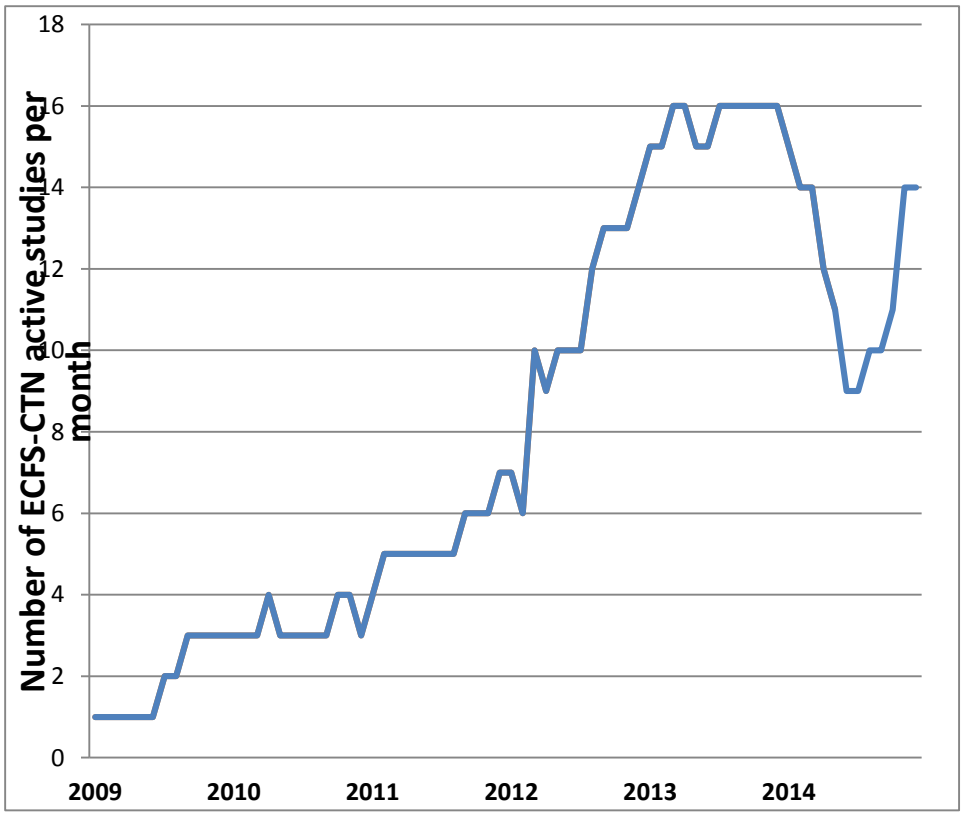
- Committees have been established for protocol review, training, networking and standardization, as well as a Data Safety Monitoring Board*.

(A Data Safety Monitoring Board is a committee of independent clinical research experts who review data in ongoing clinical trials, ensuring that participants are not exposed to undue risk)*

2. Activities of ECFS-CTN in 2014

2.1. Studies (clinical trials):

a) Evolution active studies per month since start of the ECFS-CTN:



b) *Protocol reviews*

- All protocols reviewed in 2014 included input from 2 patient (or parent-) reviewers.
- 12 protocol reviews were executed or ongoing in 2014. 8 of these were performed in cooperation with the TDN ("global review"). (45 protocols have been reviewed since the start of the network in 2009)
- 3 protocols were on CFTR modulating drugs, 2 on drugs that aim to restore the airway surface liquid, 2 on anti-infective agents, 3 on anti-inflammatory agents, and 2 on enzyme replacement therapies.
- 7 of the studies reviewed in 2014 received positive evaluation and have become active or are planned to become active in selected CTN sites (information confidential until study start). For 5 studies the final evaluation is pending.

c) *Feasibility checks*

- This service towards clinical trial sponsors aims to identify sites that have the necessary patients and infrastructure to participate in a certain study protocol. The ECFS-CTN is encouraging sponsors to have this service executed by the ECFS-CTN for studies that are planned to run in ECFS-CTN sites.
- In 2014, 6 feasibility checks were performed or initiated.

d) *Active studies in ECFS-CTN sites*

In December 2014, 14 studies are active in ECFS-CTN sites and 6 started in 2014. The most recent overview with study details is posted on the public website: **http://www.ecfs.eu/ctn/clinical-trials**

21 Studies have been active in 2014:

CFTR Modulation:

- *Vertex VX-809 alone and combined with VX-770 (VX09-809-102)*
- *Vertex VX11-661-101*
- *Vertex VX11-770-108*
- *Vertex VX11-770-09109*
- *Vertex VX12-770-111*
- *Vertex VX12-770-112*
- *Vertex VX12-809-103*
- *Vertex VX12-809-104*
- *Novartis CQBW25X2101*

- *PTC PTC124-GD-021-CF*
- *Bayer 17020*

Anti-Infective

- *Novartis EARLY study (Tobi in children)*
- *Mukoviszidose Institut gGmbH: Efficacy Study of IgY (Antibody Against Pseudomonas) in Cystic Fibrosis Patients (PsAer-IgY) – Part of the IMPACTT EU-funded project (see http://www.impactt.eu/node/3*
- *TORPEDO-CF*
- *Insmed Arikace TR02-110*
- *Novartis CTBM100C2401*
- *Novartis CTBM100C2401E1*

Restore Airway Surface Liquid

- *Pharmaxis DPM-CF-204*
- *Pharmaxis DPM-CF-303*
- *Algipharma SMR2984*

Conditioning program

- *Würzburg University Hospital: ACTIVATE-CF*

e) Outcome of clinical trials – where available (status end of 2014)

Since the start of the network in 2009, 17 studies have been completed:

1. *A Phase 3 Efficacy and Safety Study of PTC124 as an Oral Treatment for Nonsense-Mutation-Mediated Cystic Fibrosis* (Sponsor: PTC Therapeutics)
   - Results of this study are available: http://www.ecfs.eu/ctn/PTC124-GD-009
2. *A Randomized, Double Blind, Parallel Group, Placebo Controlled 28 Day Study to Investigate the Safety, Tolerability and Pharmacodynamics of SB-656933 in Patients With Cystic Fibrosis* (Sponsor: GlaxoSmithKline)
   - Results of this study are available: http://www.ecfs.eu/ctn/gsk-sb656933

3. *A Randomized, Double-blind, Placebo-controlled Parallel Group Study to Investigate the Safety and Efficacy of Two Doses of Tiotropium Bromide (2.5 Mcg and 5 Mcg) Administered Once Daily Via the Respimat Device for 12 Weeks in Patients With Cystic Fibrosis* (Sponsor: Boehringer Ingelheim Pharmaceuticals)

    - Results of this study are available: http://www.ecfs.eu/ctn/boehringer-tiotropium-phase2

4. *A Randomised, Double-blind, Placebo-controlled Parallel-group Trial to Confirm the Efficacy After 12 Weeks and the Safety of Tiotropium 5 Mcg Administered Once Daily Via the Respimat® Device in Patients With Cystic Fibrosis* (Sponsor: Boehringer Ingelheim Pharmaceuticals)

    - Results of this study are available: https://www.ecfs.eu/ctn/boehringer-tiotropium-phase%203

5. *Randomized, Active-Controlled Multicenter Study to Assess the Efficacy, Safety and Tolerability of Arikace™ in Cystic Fibrosis Patients with Chronic Infection Due to Pseudomonas Aeruginosa* (Sponsor: Insmed)

    - Results for this study are available: https://www.ecfs.eu/ctn/arikace

6. *A phase 3, open-label, randomized trial to evaluate the efficacy and safety of MP-376 inhalation solution (Aeroquin tm) versus tobramycin inhalation solution (Tobi) in stable cystic fibrosis patients* (Sponsor: MPEX)

    - Results for this study are available: https://www.ecfs.eu/ctn/mpex-209

7. *A Phase 3 Extension Study of Ataluren (PTC124) in Subjects With Nonsense-Mutation-Mediated Cystic Fibrosis* (Sponsor: PTC Therapeutics)

    - Results for this study are available: https://www.ecfs.eu/ctn/PTC124-GD-009

8. *Study of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-G551D CFTR Gating Mutation (KONNECTION)* (Sponsor: Vertex)

    - Results for this study are available: https://www.ecfs.eu/ctn/vertex-vx12-770-111

9. *Open-Label Phase 2 Trial to Evaluate the Safety and Efficacy of Aztreonam 75 mg Powder and Solvent for Nebuliser Solution/Aztreonam for Inhalation Solution (AZLI) in Pediatric Patients With Cystic Fibrosis (CF) and New Onset Lower Respiratory Tract Culture Positive for Pseudomonas Aeruginosa (PA) (ALPINE)* (Sponsor: Gilead)

    - Results for this study are available: https://www.ecfs.eu/ctn/alpine

10. *Open-label phase 3 trial to evaluate the safety of Aztreonam 75 mg powder and solvent for nebuliser solution/aztreonam for inhalation solution (AZLI) in children with cystic fibrosis (CF) and chronic pseudomonas aeruginosa* (Sponsor: Gilead)

    - Results for this study are available: https://www.ecfs.eu/ctn/pals

11. *A Phase 2, Multicenter, Double Blinded, Placebo Controlled, Multiple Dose Study to Evaluate Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of VX 809 Alone and in Combination with VX 770 in Subjects with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation* (Sponsor: Vertex)

    - Results for this study are available: https://www.ecfs.eu/ctn/Vertex-VX-809-alone-and-combined-with-VX-770

12. *A single arm, open-label, multicenter, phase IV trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with cystic fibrosis* (Sponsor: Novartis)

    - Results for this study are available: https://www.ecfs.eu/ctn/Novartis-CTBM100C2401

13. *Phase 2, multicenter, double-blinded, placebo-controlled, 3-part study to evaluate the safety, efficacy, and PK and PD of VX-661 monotherapy and VX-661/VX-770 cotherapy in subjects with CF who are homozygous for the F508del CFTR gene mutation* (Sponsor: Vertex)

    - Results for this study are pending

14. *A Phase 3, 2-Part, Open-Label Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are 2 Through 5 Years of Age and Have a CFTR Gating Mutation* (KIWI) (Sponsor: Vertex)

    - Results for this study are pending

15. *A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have the R117H-CFTR Mutation (KONDUCT) (Sponsor: Vertex)*

    Results for this study are available:
    https://clinicaltrials.gov/ct2/show/results/NCT01614457

16. *A Phase 3, Randomized, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation* (TRAFFIC) (Sponsor: Vertex)

    - Results for this study are available:
      https://www.ecfs.eu/ctn/vertex-vx12-809-103

17. *A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor Monotherapy and in Combination with Ivacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation* (TRANSPORT) (Sponsor: Vertex)

    - Results for this study are available:
      https://www.ecfs.eu/ctn/vertex-vx12-809-104

2015 Update:

2015 has been a very busy year so far: 14 studies are currently active in the CTN, of which 8 are in the recruitment stage. See https://www.ecfs.eu/ctn/clinical-trials for the most up to date status of ongoing and finalized trials.
18 protocol reviews (involving 10 different pharma companies) and 10 feasibility services have been conducted or are ongoing so far this year (status mid July).

Nine new trials and 2 roll-over studies are expected to start by beginning of 2016.
This means our trial sites are facing an increased study load. Managing capacity is a current action point in the network. Examples of steps taken are the network expansion and the continuing certification of sites for outcome parameters.

2.2. Training

- **5th annual ECFS-CTN training session for CTN Investigators and Study Coordinators (June 11th, 2014, ECFS conference Gothenburg)**

19 investigators and 29 research coordinators attended the morning session. An invited speaker from Quintiles (an international Clinical Trial Organization, CRO) provided advice on how to manage monitoring visits. There was also a session on the challenges of initiating a study protocol.

The other part of the morning was dedicated to a number of interactive workshops, covering the ECFS-CTN online Trial Management System (TMS), the quality management and improvement system (eQUIP-CR) that was designed by the TDN and will be implemented in ECFS-CTN, study budgeting with focus on the timing of procedures and the certification process for Lung Clearance Index measurement (LCI). LCI is a sensitive type of lung function measurement that measures how long it takes for a gas (usually nitrogen) to be washed out of the lungs during normal breathing, that is increasingly being used as an effectiveness measure in CF clinical trials.

An afternoon session was organized especially for the research coordinators. Besides the presentation of specific training topics, this gives them a chance to meet colleagues from other sites and countries and to share experiences.

Colleen Dunn and Zoë Davies, experienced research coordinators at the TDN in the US, assisted by Els van der Wiel (Rotterdam) and Isabelle Vachier (Montpellier) talked about the research coordinators' responsibilities and the study binder contents.

2.3. Standardisation

a) Written standard operating procedures (SOPs) are available for:

1. Measuring weight, height, BMI, head circumference
2. Intestinal Current Measurement
3. Cycle ergometry
4. Modified Shuttle test
5. Infant Pulmonary Function
6. Spirometry younger than 6

7. Spirometry older than 6
8. Bronchoalveolar lavage for Inflammatory markers
9. Sweat test

NEW 2014:

10. Sputum induction
11. Standard measurement of Nasal Potential Difference (NPD)
12. Central reading for NPD
13. Governance SOPs related to clinical trial conduct (to help sites that do not have institutional SOPs)
    - Creation, review and management of SOPs
    - Creation and maintenance of trial masterfile
    - Creation and maintenance of investigator site file
    - Case report form management
    - Project audit
    - Authorship in research
    - Delegation of responsibilities
    - Data collection and storage
    - Data management
    - Informed consent
    - Equipment maintenance
    - Reporting deviations, violations and breaches
    - Management of adverse events

b) Manuscripts on clinimetrics of outcome parameters

The aim of these manuscripts is to review the evidence for the outcome measures we use to test the effect of new therapies for people with CF. They are also a record of expert opinion on how these outcome measures should be used and what further work needs done before the licensing authorities and other researchers feel confident in using them.

2014 publications from the ECFS-CTN standardization committee:

Lung clearance index: Evidence for use in clinical trials in cystic fibrosis.
Kent L, Reix P, Innes JA, Zielen S, Le Bourgeois M, Braggion C, Lever S, Arets HG, Brownlee K, Bradley JM, Bayfield K, O'Neill K, Savi D, Bilton D, Lindblad A, Davies JC, Sermet I, De Boeck K; On behalf of the European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) Standardisation Committee.

J Cyst Fibros 2014; 13(2): 123-138

Clinimetric properties of broncho-alveolar lavage inflammatory markers in cystic fibrosis
Fayon M, Kent L, Bui S, Dupont L, Sermet I; European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) Standardisation Committee.
Eur Respir J 2014; 43(2): 610-26

A complete publication list is available here: https://www.ecfs.eu/ctn/publications

c) Setup of a competence centre for Lung Clearance Index measurement for use in clinical trials.

- The central facility in London provides central reading for studies involving LCI as an outcome measure.
- More than twenty sites in the ECFS-CTN that are equipped with the Ecomedics Exhalyzer® are being trained and the certification process has begun.

d) 9 sites were certified for standardized measurement of Nasal Potential Difference since the start of the certification process in 2013.

e) SCIFI-CF project: The set-up of the chest-CT network for standardization of technique, central reading and storage is ongoing.

In 2013 and 2014 all 15 ECFS-CTN sites that showed interest were visited by the implementation team. At each visit CT scanners were characterized using three age specific phantoms. Furthermore training was given on how to execute a spirometer controlled chest CT scan. The capability of the ECFS-CTN to include chest CT as an outcome measure in clinical studies has been noticed by the pharmaceutical industry.

f) Intestinal Current Measurement (ICM)

A certification process started for sites that can perform intestinal current measurements for clinical trials. 3 ECFS-CTN sites are certified so far.

2.4. Patient involvement

- **ECFS-CTN governance and activities**
  - Andreas Reimann from the German patient organization was the representative of patients organizations in the Executive Committee and a voting member of this Committee for the period 2011-2014. For the period 2015-2017 this role will be taken by Paola De Carli from the French patient organization.
  - Patient Organizations sponsoring ECFS-CTN are invited to steering committee meetings twice a year (Leuven, January 2014; Gothenburg June 2014).
  - Patients are involved in the protocol review process.

- **Information for patients**
  - A public list of ongoing and finalized studies in CTN sites is available: http://www.ecfs.eu/ctn/clinical-trials. Results are posted as soon as available.
  - A patient information brochure on clinical trials is available in 10 languages (http://www.ecfs.eu/ctn/patient-brochures).
  - A leaflet for children has been developed in 2013 and is available in 10 languages: https://www.ecfs.eu/ctn/brochure-children.
  - Posters "where does my current medication come from" are available in different languages: https://www.ecfs.eu/ctn/my-current-medication.
  - Posters informing patients that their site belongs to the ECFS-CTN have been developed in 2013 in different languages.

2.5. Quality program and evaluation of sites

a) Explore and implement eQUIP-CR quality management programme in ECFS-CTN sites

- 5 pilot sites have explored the program that was provided by the US CF network, the CFF-TDN. From their experience a starter package has been made available in 2014 for other sites.

b) Online trial management system (TMS)

- The aim of the TMS is to collect trial information (timelines, patient enrolment numbers and other metrics) every quarter. The information is entered in an online system by the sites. The system allows extracting enrolment reports.
- In 2014, TMS inquiries have occurred in February, May, August and November.

c) Evaluation of site quality and responsiveness

- Sites were evaluated based on study metrics and responsiveness in January 2014, with assistance of an external consultant (quality manage). A general report was written and sites also received individual site quality reports.

2.6. Investigator Initiated Trial

The CTN needs to be able to conduct multicenter academic trials on questions that are not answered by pharma trials.

- 2011-2012: The steering committee looked for topics of interest to start an investigator initiated CTN trial
- Working groups started working on draft protocols and feasibility checks for 2 selected topics. The most feasible program selected at the Steerco meeting in January 2013 was "Comparison of eradication strategies of Methicillin resistant S. aureus"
- A protocol ("METRIC trial") was written by a CTN working group and reviewed by the US network, the CFF-TDN.
- Unfortunately, due to the relatively low rates of MRSA (Methicillin-resistant Staphylococcus aureus) seen in CF patients in Europe, as well as differing availability of the specific antibiotics across European countries, feasibility suggested that this study was not worth pursuing at this time. However the CTN did demonstrate the necessary skills and resources to develop- and run such studies. Going forward, future research priorities for patients and investigators will be determined with a view to collaborating closely with patient organisations in developing a future investigator initiated study.

3. Financial report 2014

- Reflects book-keeping year 1 Jan – 31 Dec 014
- Donations CFF and Ecomedics are one-off and mainly cover costs made in 2013
- Expenses coming years will increase due to network expansion

INCOME	ECFS Support	100.000,00
	National CF associations	126.285,00
	Services to companies	52.835,00
	CFF Donation	83.465,00
	EcoMedics Donation LCI	53.327,00
	Total Income	*415.912,00*

EXPENSES	Travel / Meetings	16.270,44
	HR Coordinating Centre - 1 FTE + 0.5 FTE + 0.5 F	133.774,24
	Leuven Overhead	16.709,40
	HR Standardisation - 0.6 FTE	13.383,87
	Computer & Software/Office equipment	1.959,95
	HR - LCI Competence center 0.6 FTE	28.026,78
	Telecommunication	1.656,85
	Training - Research Coordinators Support	9.365,44
	Expert advice (Legal, statistical, QA, etc)	4.353,46
	Software Development / Maintenance	14.509,88
	EFGCP Membership/ registrations	86,33
	Miscelleanous	24,36
	Total Expenditures	*240.121,00*

4. Short summary of future CTN Projects:

A new business plan for 2015-2017 will be written by ECFS-CTN Executive Committee and discussed with the Patients Organizations. It is foreseen that one of the main projects for 2015 is to plan an expansion of the network with around 10 new sites. The other expected projects are to develop an expert site for LCI and to support the chest-CT network that is being built; to enable ECFS-CTN to develop investigator-initiated trials by setting up a structure dedicated to cross-countries regulatory issues and management of trials (with the help of existing bodies such as ECRIN); and to set up a structure for assessing sites performance and quality. In addition, we do aim to develop a young person's advisory group to enable young people with CF aged 11-18 years to advise on research priorities and be part of the protocol review process. These projects will require more coordination and our coordinating center will need to expand. As for the expert LCI site, it will be supported initially with aim for this site to be sustainable. Finally, the requirement for the IIT support is still to be determined. Due to the careful management of ECFS-CTN budget, some assets are available that will allow these projects to start. Taken together, these developments should increase the ability of the ECFS-CTN to contribute to a strategic and organized approach to developing new and better medicines for CF.