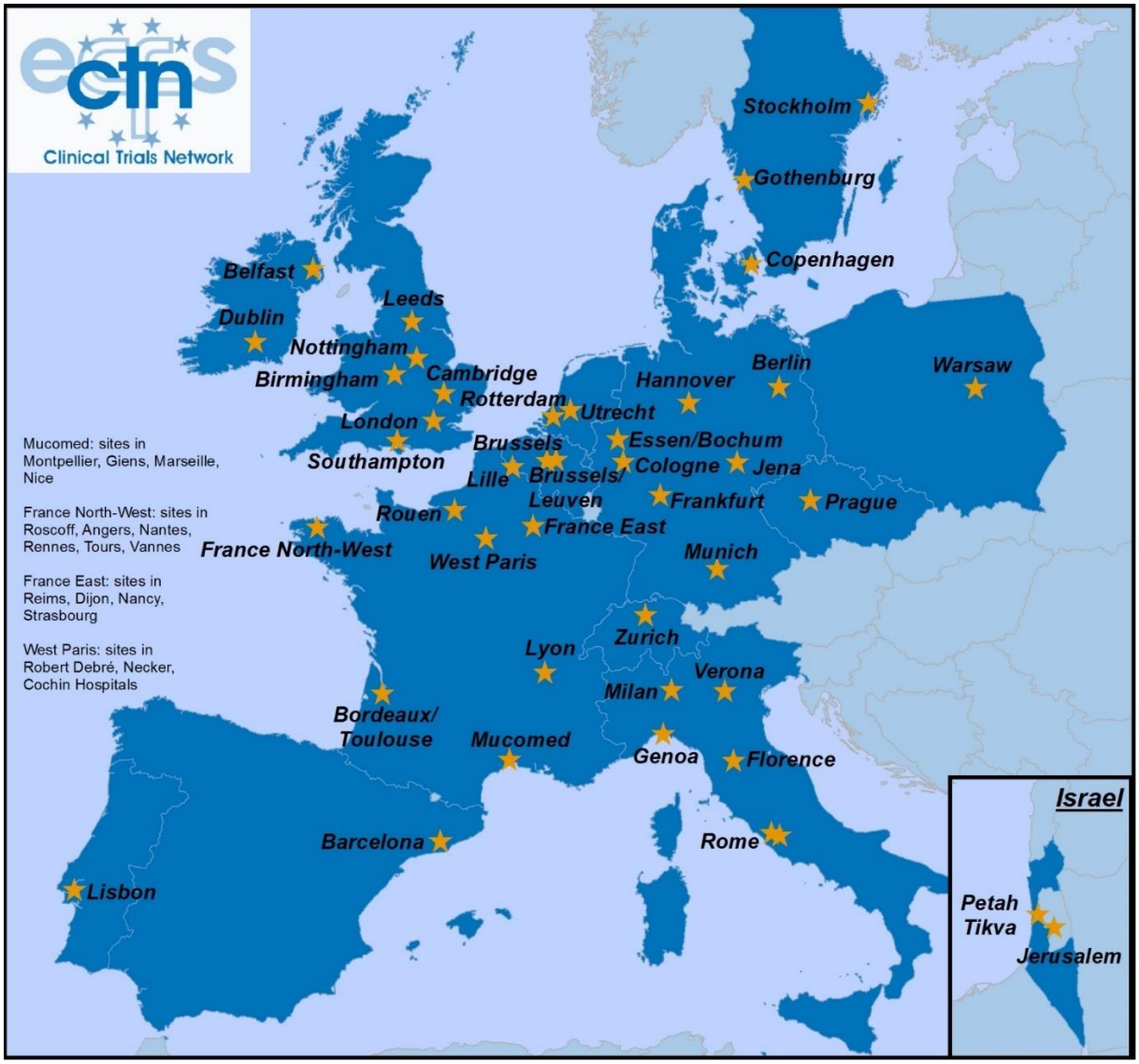

ECFS-CTN

Annual report 2017

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Message from the CTN Executive Director

Dear Friends,

Our mission within the European Cystic Fibrosis Clinical Trial Network (ECFS-CTN) is “to intensify clinical research in the area of CF and to bring new medicines to the patients as quickly as possible.”

This aim is truly ambitious and can only be reached by a team-effort with the engaged input of all of us: patients, families, patient organisations, clinical trial teams and clinical trial networks. We all have worked very hard in 2017 and have accomplished milestones of our mission: we have intensified clinical research in CF and we have brought new medicines to our patients! Let´s keep this successful path - many new effective treatments and new therapeutic approaches are yet to come!

2017 has been a very busy year for ECFS-CTN: 31 studies have been performed in our network comprising 43 sites within 15 countries. Most studies were Phase 2 or 3 studies on CFTR modulator therapies, 30 new protocols were reviewed by our protocol review teams, 14 feasibility services were managed and 3 new European projects for CF were started in which ECFS-CTN is a major partner, etc.

How can we communicate all this information in a way that is both attractive and understandable to read? Patients and patient representatives have often told us that our year report was too long or not focused on the most relevant topics.

Therefore we are pleased to share with you this annual patient report of 2017 which not only comes in a new design showing the detailed information about the activities with the ECFS-CTN; it also is the first report based on the detailed and critical input of individual patients, families, patient reviewers and patient organisations. Thank you very much for all your constructive criticism, comments and ideas we have received to improve this report. So this also is an important accomplishment reflecting a real team approach! Do let us know what you think!

The management of complex data and the development of such a report takes a considerable amount of work. Thank you to the ECFS-CTN team for putting together this new version of the patient report.

Please contact us if you have any items you would like to have included in future annual reports.

Yours sincerely,

Silke van Koningsbruggen-Rietschel

Director ECFS-CTN

2017

ECFS-CTN year in numbers

A new ECFS-CTN director

(Silke van Koningsbruggen-Rietschel, Germany)

30 protocols from 13 companies reviewed by people with CF, their families, doctors, research coordinators and statisticians

Work started on the **PROMS**

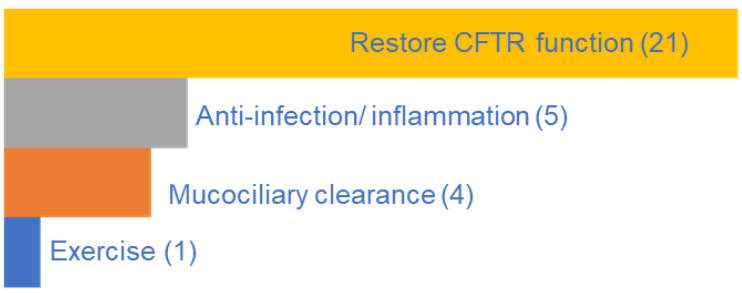
Patient reported outcome measures project

New research staff funded in **19** sites

3 new EU projects funded

Feasibility checks performed for **14** trials

31 active trials supported



300 patients newly enrolled into trials (249 adults and 51 children)

Clinical trials and CTN

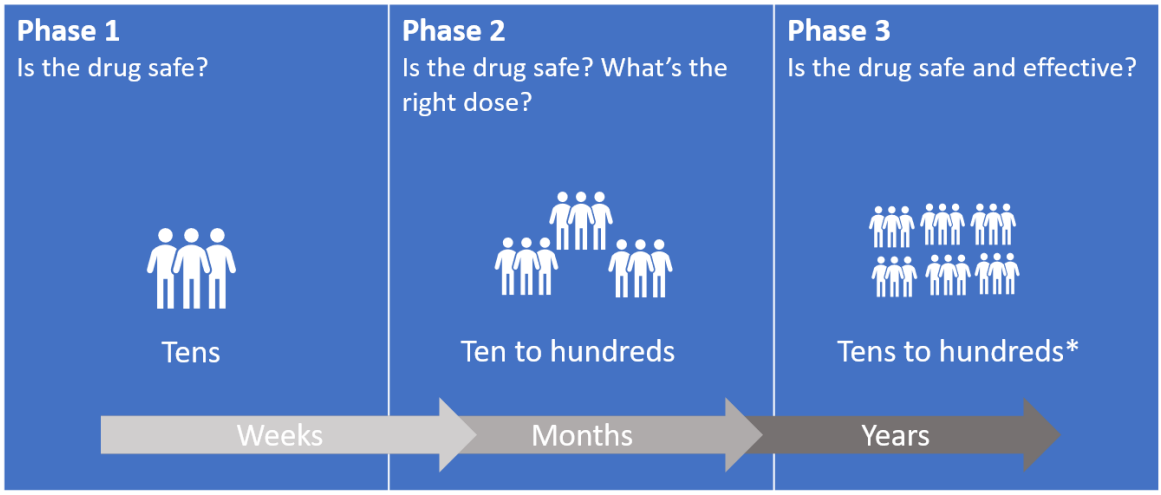
What are clinical trials?

In clinical trials, healthy people and/or patients take a new medicine to help researchers assess whether the medicine is safe and effective at treating the disease in question.

All medicines, including those for CF, are tested in several clinical trials from phase 1 to phase 3. Once licensed, "real world" safety testing continues in Phase 4 trials. We work with the ECFS Patient Registry for Phase 4 trials.

Where can I find out more about clinical trials?

Check out this leaflet from the CF Trust in the UK: https://www.cysticfibrosis.org.uk/get-involved/clinical-trials/taking-part-in-clinical-trials



*As trial designs for rare diseases improve, fewer patients are needed to test the drug

How does a European network streamline research?

The aim of ECFS-CTN is to intensify clinical research in the area of CF and to bring new medicines to patients as quickly as possible.

Increase cooperation between the whole CF community (patients, patient organisations, pharmaceutical industry and academic researchers)

Share expertise across countries to standardise research procedures and measures

Give a stronger voice to member sites in case of issues with clinical trials

Encourage high quality research by training staff and monitoring site performance

When was ECFS-CTN founded?

ECFS-CTN was founded in 2008 by ECFS and EuroCareCF, a project funded by the EU. The Cystic Fibrosis Foundation (CFF) in the USA had already set up a successful therapeutic drug development network (CFF-TDN) and they gave us a lot of help in setting up procedures.

CTN structure and governance

What sites are involved and why?

There are 43 CTN sites across 15 countries in Europe. Member sites have a good track record in clinical trials, highly trained staff and good infrastructure. Check the map on the cover of this report to see which sites are involved.

What if my city isn't on the map? Can I still participate in trials?

Ask your CF care team about clinical trials happening in your area

Plans started in 2017 for the third CTN expansion and the application process is due to finish in late 2018 and will be announced in 2019.

How does CTN work?

ECFS-CTN is an ECFS project and is run by:

- the Executive Committee (6 doctors from different countries and 1 patient organisation representative) who meet by teleconference twice monthly. They develop network policies, steer actions to different committees and approve clinical trials to add to the CTN portfolio following protocol review
- the Steering Committee (Steerco) is made up of 1 doctor from each member site, a representative from each of the funding patient organisations, executive committee members and CTN staff. Steerco members meet in person twice yearly to discuss CTN activities, strategies and common challenges.

The CTN Coordinating Centre has 5 staff members who organise the daily activities of CTN and support the various committees in carrying out their tasks.

Funding

ECFS-CTN is funded by a grants and by charging fees for scientific services to pharma companies.

CTN helps pharma companies improve the design of clinical trials. It is important that CTN is not financially dependent on pharma companies so that we have no conflict of interest when giving scientific advice on clinical trials. Therefore we limit our earnings from services to pharma, and rely on the generous support of ECFS and patient organisations to make up the shortfall.

ECFS-CTN is grateful to the following organisations for funding our work in 2017: ECFS, CFF, European patient organisations (from France, Germany, UK, Italy, Belgium, the Netherlands, Luxemburg, and Switzerland).

You can find our 2017 financial report at the end of this document.

CTN activities

Protocol review

A clinical trial should answer a scientific question (e.g. is the medicine safe and effective?), should be well planned so that hospital staff can work efficiently and should ask only what is reasonable from patients.

Our protocol review system gives patients a voice in setting the research agenda and makes sure that trials take into account the patient experience.

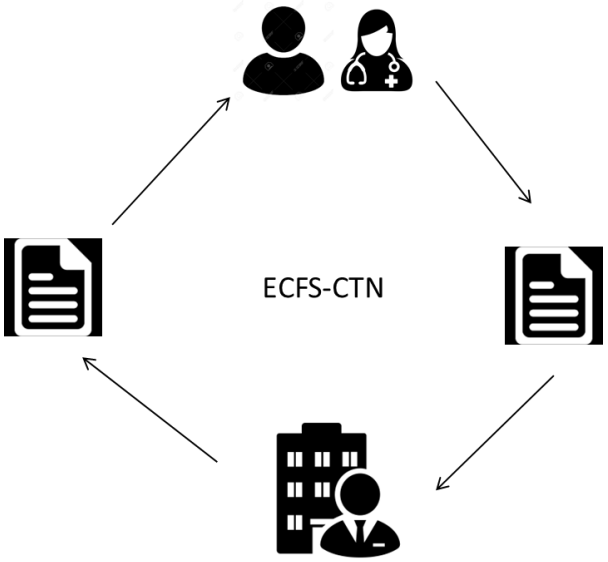
The protocol is the “handbook” for a clinical trial and describes in detail how the medicine will be tested, how patients will be involved and how the data will be analysed. The pharmaceutical company developing the medicine is responsible for designing the clinical trial and writing the protocol.

Designing a good clinical trial is a team game and needs input from all the main players involved – that is from doctors, research coordinators, statisticians, and of course people with CF and their families.

At ECFS-CTN, we coordinate the review of new clinical trial protocols by expert groups of CF doctors, research coordinators, academic researchers and people with CF and their families.

They check that the research question is worthwhile, the practical plan is well thought out and that the demands of participation in the trial are reasonable for patients.

ECFS-CTN strongly encourages sponsors to update the protocol based on the advice provided by the review.



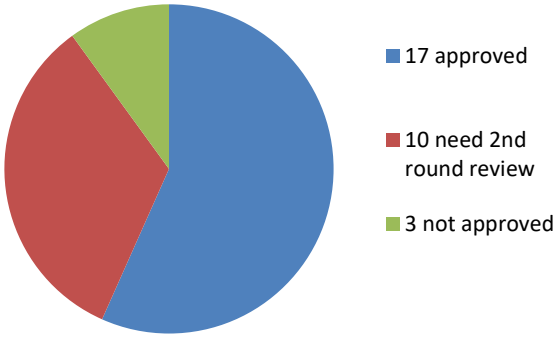
Clinical trials in CF often include patients across different cities, countries and even continents. For trials planned to run in Europe and the USA, a joint “global” protocol review is sometimes performed with our American counterparts in the CFF-TDN.

CTN activities

Protocol review

With 30 protocol reviews, 2017 was our busiest year to date (up from our previous record of 17 reviews in 2015).

When a protocol is reviewed and approved, we tell all the sites in ECFS-CTN that the protocol had a successful review.



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

Roberto, Italy

"As a patient I review research proposals mostly because I contribute to better treatment and finding a cure for cystic fibrosis. Not 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 a research masters student. I learn from the academic foundation that build proposal and try to understand the biochemical or statistical content. Finally it's nice to be informed about the development of new drugs or treatments.

Martine, the Netherlands

"As a person with CF born in the fifties of the last century, when there was neither any knowledge about CF nor any evidence based treatment, I am fascinated by the speed with which the process quality in CF research develops, aiming at conducting exclusively quality approved clinical studies. I highly appreciate that the patients' view on trials is an integral part of this system.
In my opinion, the patients' review process is well organised. There is always the possibility of contacting the scientific experts if any questions occur. The training the patient reviewers received at the beginning provided valuable insight into clinical studies and was this a good preparation. It is exciting to experience how clinical trials work and to be able to actively contribute to a god study design."

Birgit, Germany

CTN activities

Standardisation of procedures and clinical trial measures

In research, it is important that we all work in the same way, so that the results from clinical trials are reliable and so that we can compare results from different clinical trials.

ECFS-CTN brings together experts from all over Europe to agree the best way to perform clinical tests and measurements in clinical trials. We also work jointly with our American and Canadian colleagues on some projects.

The standardisation committee has produced 37 standard operating procedures, 9 peer reviewed publications in scientific journals (see www.ecfs.eu/ctn/publications), a patient and carer information leaflet about sweat testing (available in 16 languages) and a paediatric advice leaflet for sputum induction (available in 4 languages).

The ECFS-CTN also trains and certifies site staff in the following measurements for clinical trials: multiple breath washout, spirometer-controlled chest CT scanning, nasal potential difference, sweat test and intestinal current measurement.

NEW in 2017: patient reported outcomes

In 2017, ECFS-CTN started a project to develop patient reported outcome measures (PROMs), in collaboration with patient organisations.

PROMs cover issues of concern to patients and the data can often be collected by self-administered questionnaires. These are important because they supply patient-reported information about daily life which cannot be captured by usual measures. This can include quality of life measures such as patients' resilience, coping strategies, and perception of their future and disease. In clinical trials they can provide a reliable way to gain the patients' perspective regarding the benefits and limitations of a specific treatment.

ECFS-CTN surveyed over 100 French and Swedish patients to assess their views on the Cystic Fibrosis Questionnaire. The patients said they wanted more questions about treatment burden, impact on social and leisure time, peer acceptance of CF, mood and quality of sleep, family planning and impact of disease on family life.

ECFS-CTN is now working with our patient organisation partners through CF Europe to explore patient priorities and to look more deeply into the issues identified by patients.

We are always looking for enthusiastic and motivated patients and carers to help guide our research, if you would be interested in getting involved in this patient-centred project, please get in touch with Kate Hayes, one of our CTN staff (k.hayes@qub.ac.uk)

CTN activities

Quality and training

We monitor sites participating in ECFS-CTN approved clinical trials to check that trials are set up and run efficiently. We provide feedback to sites throughout the year and we discuss site quality and performance at our twice yearly Steerco meeting of site investigators.

The ECFS-CTN training committee organises a yearly training day for research coordinators.

Feasibility services

After a protocol has been approved to run in the ECFS-CTN, we help the pharmaceutical company identify appropriate sites to participate in the trial. The clinical trial protocol includes a checklist of which patients should be enrolled.

ECFS-CTN then helps pharmaceutical companies contact sites to see if they can participate in trials. We encourage companies to contact all eligible sites and to give all sites a chance to participate.

In 2017, we coordinated 16 feasibility checks (a big increase from the 7 checks we performed in 2016).

Example

A clinical trial needs to enrol girls and boys with CF aged 11-17 with the G551D mutation. Sites must be trained to do a measurement called multiple breath washout (also called LCI).

We shortlist the sites fulfilling these criteria and encourage the sponsor to approach all the shortlisted sites

We send a questionnaire to ask if these sites want to participate, and send the answers back to the sponsor

CTN activities

Expert advice to regulators

ECFS-CTN members give expert advice to the regulatory agencies that decide whether or not to license new medicines. In 2017, the ECFS-CTN gave expert advice to the European Medicines Agency (EMA) about the design of clinical trials in children with CF.

Safety monitoring in trials

In some clinical trials, data is shared with an external committee who independently monitor data as the trial is ongoing. If they notice any safety problems, this committee can stop the trial. Companies can use the ECFS-CTN affiliated “data safety monitoring board”, based in Lyon, France.

Increasing research capacity

A 2016 survey of ECFS-CTN sites found that lack of research staff was a major barrier to participating in clinical trials. The CFF generously offered to partially fund extra research staff at qualifying sites. In total, 19 ECFS-CTN sites were awarded funding to hire research staff. We are very grateful to the CFF for supporting research capacity in Europe, in the spirit of our shared vision to bring new treatments for CF to patients.

Active trials in ECFS-CTN in 2017

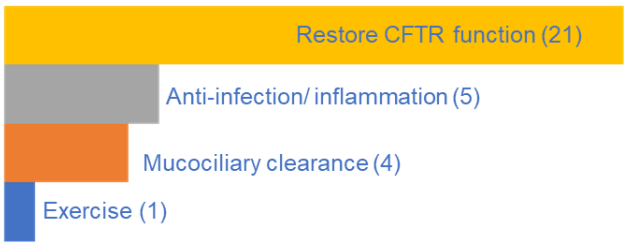
Find details of all trials we support (and results) at:
www.ecfs.eu/ctn/clinical-trials

There were 31 active clinical trials in ECFS-CTN in 2017.
Trials were mostly Phase 2 and 3 trials of CFTR modulators.

In total, 300 patients were newly enrolled into clinical trials in 2017 (249 adults and 51 children).

Number of trials

By type of medicine



By trial phase

Active clinical trials in ECFS-CTN in 2017

	RESTORE CFTR FUNCTION
	Phase 3 testing of VX-661 in people aged 12 years and older with 2 ΔF508 mutations (VX14-661-106)
	Testing VX-661 in people aged 12 years and older with 1 ΔF508 mutation and 1 other mutation (VX14-661-108) Testing VX-661 in people aged 12 years and older with 1 ΔF508 mutation and 1 other mutation responsive to ivacaftor (VX14-661-109) Long term rollover testing of VX-661 in combination with ivacaftor in people aged 12 years and older with 1 or 2 ΔF508 mutations (VX14-661-110) Long term rollover testing lumacaftor in combination with ivacaftor in people aged 6 years and older with 2 ΔF508 mutations (VX15-809-110)
	Phase 3 testing of ivacaftor in people aged 3-5 years with a CFTR gating mutation (VX15-770-123)
New!	Phase 3 testing of ivacaftor in children with CF aged <2 years with a gating mutation (VX15-770-124)
New!	Phase 3 testing of ivacaftor in children with CF aged <2 years with a gating mutation (VX15-770-126)
	Phase 2 testing of VX-371 in people aged 12 years and older with 2 ΔF508 mutations and being treated with Orkambi (VX15-371-101)
New!	Phase 2 testing of VX-440 combination therapy in people aged 12 years and older (VX15-440-101)
New!	Phase 1 early testing of VX-659 in people with and without CF (VX16-659-001partD)
New!	Phase 2 testing of VX-659 combination therapy in adults (VX16-659-101)
New!	Early testing of VX-445 in people with and without CF (VX16-445-001)
	Early safety testing of QR-010 in adults with 2 ΔF508 mutations (PQ-010-001)
	Long term testing of ataluren (PTC124) in people with nonsense mutation (PTC124-GD-021e-CF)
New!	Phase 2 testing of GLPG2222 in people with 1 ΔF508 mutation and 1 gating mutation, being treated with ivacaftor (GLPG2222-CL-201)
New!	Phase 2 testing of GLPG2222 in people with 2 ΔF508 mutations (GLPG2222-CL-202)
New!	Phase 2 testing of GLPG2737 in people with 2 ΔF508 mutations being treated with Orkambi (GLPG2737-CL-202)
New!	Early testing of FDL169 in people with 2 ΔF508 mutations (FDL169-2015-04)
	Phase 2 testing of BAY63-2521 in adults with 2 ΔF508 mutations (Bayer 17020)
New!	Early testing PTI-428 in adults with CF (PTI-428-01)
	ANTI-INFLAMMATORY **ANTI-INFECTIVE**
	Optimising eradication of Pseudomonas (Uni. Hospitals Bristol NHS Foundation Trust TORPEDO-CF)
	Phase 2 testing of GS-5745 on lung function of adults (Gilead GS-US-404-1808)
	Phase 3 testing of IgY antibodies to prevent repeated Pseudomonas infection (German MI PsAer-IgY)
	Phase 2 testing of CTX-4430 in adults with CF (Celtaxsys CTX-4430-CF-201)
	Phase 2 testing of (R)-Roscovitine in adults with 1 or 2 ΔF508 mutations and chronic Pseudomonas infection (CHU Brest ROSCO-CF-1)
	MUCOCILIARY CLEARANCE
New!	Inhaled hypertonic saline in preschoolers (UMC Erasmus SHIP-002)
New!	Phase 2 testing of inhaled SPX-101 (Spyryx SPX-101-CF-201)
	Long-term inhaled mannitol in CF adults (Pharmaxis DPM-CF-303)
New!	Early testing of inhaled QBW276 in adults (Novartis CQBW276X2201)
	EXERCISE
	ACTIVATE-CF: exercise programme (Würzburg University Hospital ACTIVATE-CF)

European research projects

ECFS-CTN is a partner in several ongoing EU projects. In 2017, we had the good news that 3 more projects that we are involved in won EU funding.

Personalised Treatment for Cystic Fibrosis Patients with Ultra-rare CFTR Mutations

New!

- Starts January 2018
- Duration: 60 months
- Funded by the EU (Horizon 2020)
  http://www.hitcf.org/

A multinational clinical project to test the orphan drug OligoG CF-5/20 in a pivotal phase 2b clinical trial for the treatment of cystic fibrosis

New!

- Starts January 2018
- Duration: 36 months
- Funded by the EU (Horizon 2020)
  http://www.oligogpivotalcf.eu/

Collaborative network for European clinical trials for children

New!

- Starts May 2018
- Duration: 72 months
- Funded by the EU (Horizon 2020 and EFPIA)
  http://conect4children.org/

European Reference Network-LUNG

- a network of European healthcare providers dedicated to ensuring and promoting excellence in care and research for the benefit of patients affected by rare respiratory diseases.
  https://ern-lung.eu/

"Clinical proof of concept for a RNA-targeting Oligonucleotide for a Cystic fibrosis-F508del MEDication"

- 2 clinical trials were conducted in ECFS-CTN sites
- Funded by the EU (Horizon 2020)
  http://pro-cf-med.eu/

Financial report 2017

Reflects book-keeping year 1 Jan – 31 Dec 2017:

ECFS Projects		Audited Accounts (01Jun2018)		2017
ECFS Clinical Trials Network	EUR			EURO
Income	100.000	ECFS Support		
	309.258	Protocol Income / Feasibility Studies		
	117.499	National Associations		
			Income total	526.756
Expenses	305.128	Personnel Expenses		
	42.190	Travel/Meetings (includes 13,906 Euro support to RC)		
	7.881	Teleconference/Office Equipment /Misc		
	41.035	Software Upgrade		
	10.267	CTN Server		
	12.534	Lawyer fees		
	2.051	Publication		
			Expenses total	421.085
	105.671		RESULT 2017	105.671
		Assets		
		Net capital 1 January 2017		727.850
		Result 2017		105.671
				833.521
		Committed 2018		
		Warranty fund		18.815
		Salaries 2018		305.000
				323.815

CFF grant for Additional Research Capacity ("ARC")

The US Cystic Fibrosis Foundation granted support to the ECFS-CTN for the period 2017-2019 for the following:

1. Partial funding to hire additional research personnel for maximum 22 selected sites
2. Funding of an administrator at the CTN coordinating centre
3. Support to sites for entering data in the Trial Management System (2600€ per year)

In 2017 the maximum amount for this grant was $1,225,800