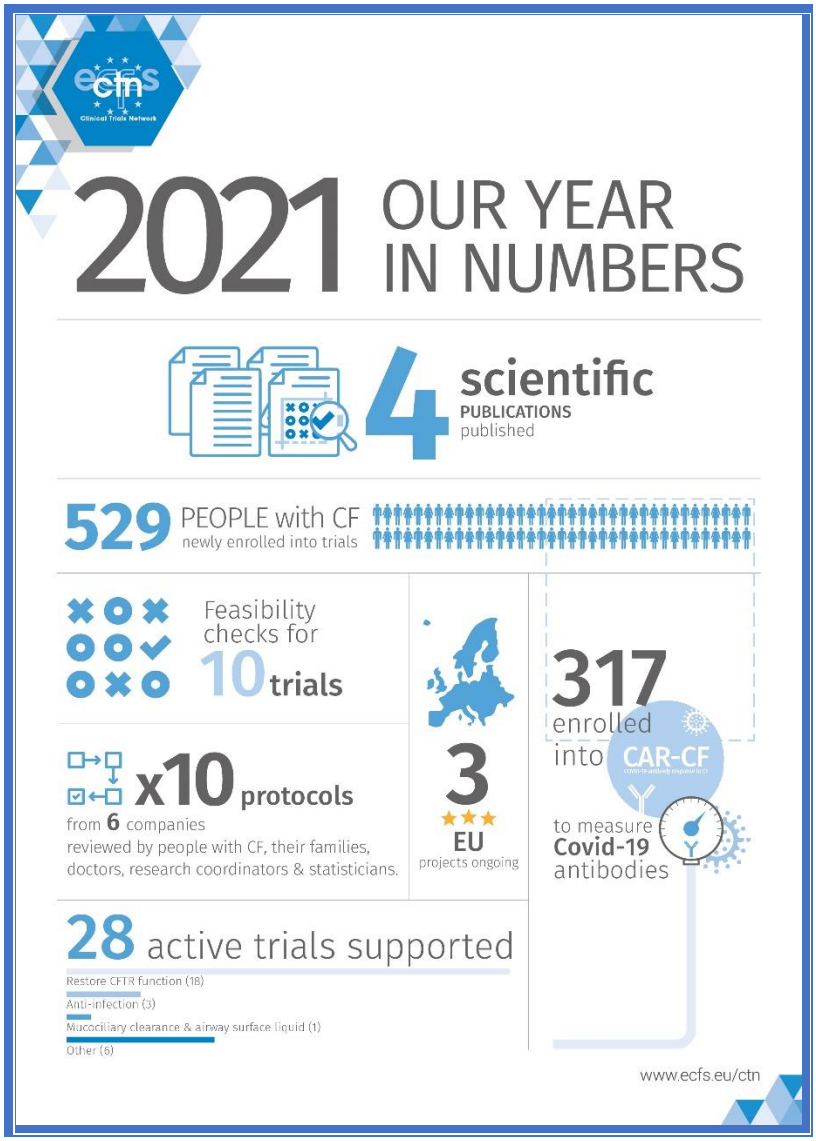
ECFS Clinical Trials Network

Information for companies



V13, May 2022

Content

Quick guide for companies 3
Contact information 4
CTN Organigram 4
CTN Executive Committee 5
CTN Sites 6
Introduction: CTN history and mission 9
ECFS-CTN Services 11
Role of the CTN Coordinating Centre 11
Optimizing patient recruitment for CTN studies 11
Protocol review 12
Feasibility Assessment 17
Follow up of trials conducted in CTN sites 18
Standardization, certification and central reading 20
Quality and training 20
Fees for services 21
Fees Protocol review (not optional) 21
Fees Eligibility assessment (not optional) 21
Fees for other services 21
Partnerhips 22
Questions and Answers 24
Acknowledgements 25
Quick guide for companies 26

Quick guide for companies

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This means that CTN sites will selectively recruit patients for studies that are accepted as "CTN studies", therefore improving recruitment.

Tips for a smooth process:

- Contact the CTN coordinating centre (ECFS-CTN@uzleuven.be) when the first draft protocol is available (or even earlier) and before contacting individual CTN sites with feasibility requests

- The ECFS-CTN can provide advice on country and site selection and will conduct the feasibility check in cooperation with the sponsor

- When contracting a CRO, inform them about the ECFS-CTN, so a communication plan between the 3 actors can be set up

- Consider use of the ECFS-CTN independent Data Safety Monitoring Board (DSMB) also in early stage, so the review processes can run in parallel

- Consider use of the ECFS-CTN Standard Operating Procedures for main outcome parameters, as well as expert advice, certification of centers and central reading during the trial

Contact information

CTN Coordinating Centre

Veerle Bulteel – Anne Verbrugge – Katia Reeber

UZ Gasthuisberg

Herestraat 49

3000 Leuven

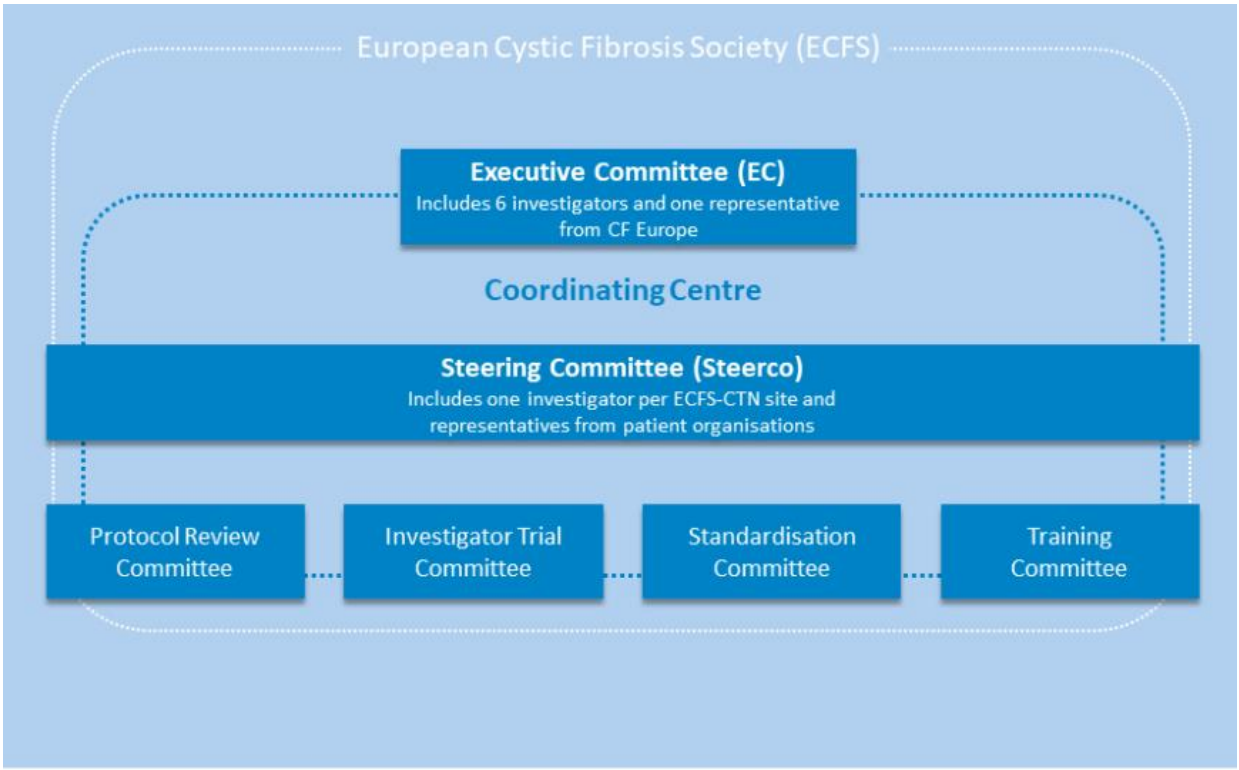
Belgium

Tel.: **+32 479 98 38 39**

Email: ECFS-CTN@uzleuven.be

Website: http://www.ecfs.eu/ctn

CTN Organigram



CTN Executive Committee

ECFS-CTN Director

Damian Downey

Belfast, UK

ECFS-CTN co-Director

Lieven Dupont

Leuven, Belgium

Executive Committee members

Nicholas Simmonds, London, UK
Philippe Reix, Lyon, France
Dario Prais, Petah Tikva, Israel
Jutta Bend, Bonn, Germany (Patient Organization representative)

ECFS Representative

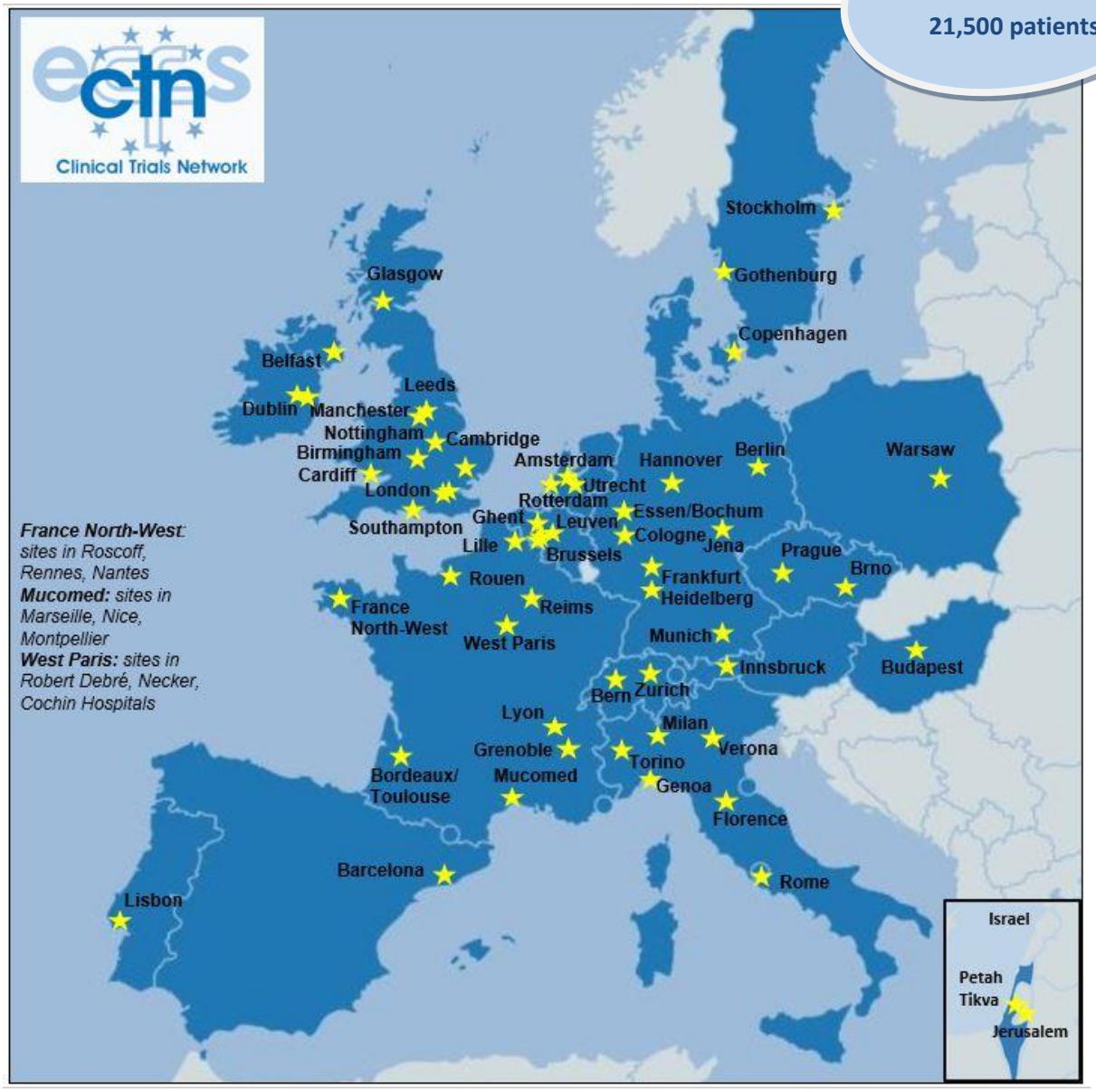
Christine Dubois, Karup, Denmark

Liaison with CFF-TDN

Damian Downey, Belfast, UK

CTN Sites

17 countries
57 sites
21,500 patients



Site list part 1

COUNTRY	CENTER	PI	Co-Investigators
Austria	**Innsbruck**	H. Ellemunter	J. Eder
Belgium	**Brussels (ULB)**	C. Knoop	L. Hanssens
	Brussels (UZB)	E. De Wachter	E. Vanderhelst, S. Vincken
	Ghent	E. Van Braeckel	S. Van Biervliet
	Leuven	L. Dupont	M. Proesmans, F. Vermeulen, M. Boon,
			N. Lorent, P. Van Bleyenbergh
Czech Republic	**Brno**	L. Homola	E. Pokojová
	Prague	P. Drevinek	L. Fila, V. Skalicka
Denmark	**Copenhagen**	T. Pressler	M. Skov
France	**Bordeaux/Toulouse**	S. Bui	M. Fayon, J. Macey, M. Murris-Espin,
			M. Mittaine, L. Roditis
	France North-West	S. Ramel	
	(Nantes, Rennes, Roscoff)		
	Grenoble	R. Hamidfar	C. Llerena
	Lille	O. le Rouzic	N. Wizla-Derambure
	Lyon	Ph. Reix	I. Durieu
	Mucomed	R. Chiron	J-C Dubus, N. Dufeu, C. Piccini-Bailly,
	(Marseille, Montpellier, Nice)		S. Leroy
	Reims	M. Abély	K. Bessaci, B. Ravoninjatovo
	Rouen	Ch. Marguet	S. Dominique
	West Paris	I. Fajac	V. Houdouin, I. Sermet
	(Robert Debré, Necker, Cochin hospitals)		
Germany	**Berlin**	M. Mall	M. Stahl
	Essen-Bochum	S. Sutharsan	F. Stehling, F. Brinkmann, M. Welsner
	Frankfurt	G. Rohde	S. Zielen, O. Eickmeier, W. Gleiber
	Hannover	A.M. Dittrich	F. Ringshausen
	Heidelberg	O. Sommerburg	S. Wege
	Jena	M. Lorenz	A. Moeser
	Cologne	S. van Koningsbruggen-	E. Rietschel
		Rietschel	
	Munich	S. Nährig	M. Griese, M. Kappler
Hungary	**Budapest**	A. Halász	I. Laki
Ireland	**Dublin**	N.G. McElvaney	P. Greally
	(Beaumont + National Children's)		
	Dublin	E. McKone	D. Cox, P. McNally
	(St. Vincent' s + Our Lady's Children's)		

Site list part 2

Israel	**Jerusalem**	M. Cohen-Cymberknoh	M. Wilschanski
	Petah Tikva	D. Prais	M. Mei-Zahav, H. Mussaffi
Italy	**Florence**	G. Taccetti	S. Bresci, A.S. Neri, V. Terlizzi
	Genoa	C. Castellani	R. Casciaro, F. Cresta
	Milan	C. Colombo	G. Pizzamiglio
	Rome	A. Fiocchi	F. Alghisi
	(Bambino Gesù)		
	Torino	B. Messore	I. Esposito
	Verona	M. Cipolli	P. Melotti
Poland	**Warsaw**	D. Sands	K. Walicka-Serzysko
Portugal	**Lisbon**	C. Barreto	P. Azevedo, L. Pereira
Spain	**Barcelona**	S. Gartner	A. Alvarez
Sweden	**Gothenburg**	M. Gilljam	A. Lindblad
	Stockholm	I. de Monestrol	F. Karpati
Switzerland	**Bern**	Ph. Latzin	R. Fischer
	Zurich	A. Moeller	A. Jung, M. Schuurmans
The Netherlands	**Amsterdam**	S.W.J. Terheggen-Lagro	J. Altenburg
	Rotterdam	H. Janssens	M. Bakker
	Utrecht	K. van der Ent	H. Heijerman
United Kingdom	**Belfast**	D. Downey	J. Bradley, A. Reid
	Birmingham	J. Whitehouse	M. Desai
	Cambridge	Ch. Haworth	A. Floto
	Cardiff	J. Duckers	J. Forton
	Glasgow	G. MacGregor	L. Thomson
	Leeds	T. Lee	D. Peckham, P. Whitaker, I. Clifton,
			C. Etherington, A. Adams, E. Guy, C. Edwards
	London	G. Ruiz	P. Macedo
	(King's College)		
	London	J. Davies	N. Simmonds, A. Jones, R. Dobra
	(Royal Brompton)		
	Manchester	P. Barry	A. Horsley, A. Maitra
	Nottingham	A. Smyth	H. Barr
	Southampton	M. Carroll	G. Connett, T. Daniels, J. Legg

Introduction: CTN history and mission

History of the ECFS-CTN

The ECFS and EuroCareCF (EU Framework 6 Program) worked together to launch the ECFS-Clinical Trials Network (ECFS-CTN) in 2008.

The network originally provided access to 18 large and experienced CF centres, located in 8 different countries throughout Europe. Twelve more sites were added in 2012. In 2015, 13 additional sites were selected, who were fully involved in 2016. That brought us to a total of 43 sites in 15 countries. In 2018, we launched another call for new member sites to join CTN. After carefully evaluating the applications we selected 15 new sites from 11 countries, who became official CTN member sites from January 2020.

That brings us to a total of **57 sites in 17 countries**.

All centres fulfill a certain set of criteria such as number of patients, human resources, experience in clinical trials and infrastructure support.

Aims of the ECFS-CTN

Clinical trial networks provide a centralized resource for the successful execution of a clinical trial. For diseases with relatively small populations such as CF, the most appropriate action is to form a larger operational group and to focus on both study quality and quantity.

The aim of the European Cystic Fibrosis-Clinical Trials Network is to intensify clinical research in the area of cystic fibrosis and to bring new medicines to the patients as quickly as possible. This is done by:

1. **Maintaining a network of clinical trial sites dedicated to CF care and with a long standing experience in clinical trials**
2. **Keeping appropriate structures supporting the network in the selection, planning and improvement of clinical trials**
3. **Attracting projects in cooperation with non-profit organizations, academic centres and pharmaceutical or medical-device companies**

The CTN centres have agreed to preferentially perform trials that are selected by the Network. The pharmaceutical company can be assured that high standards will be maintained in all centres. CTN centres limit the numbers of studies in their centre thereby optimizing patient inclusion in chosen trials. This can be translated in cost saving for companies.

The CTN is of course not a Contract Research Organization (CRO). The running and follow-up on the study remains in the hands of the pharmaceutical company and the CRO of their choice.

The CTN has centres in Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Israël, Italy, Poland, Portugal, Spain, Sweden, Switzerland, The Netherlands and the UK. It is possible that a company will not run a particular study in all countries included in the network. The CTN partners understand and accept this fact. Likewise a company is free to include CF centres outside the ECFS-CTN or cooperate with existing national clinical trial networks.

ECFS-CTN Services

Role of the CTN Coordinating Centre

The coordinating centre (based in Leuven, Belgium) serves as the central point of contact for all internal and external communication.

The Coordinator, Project Manager and Administrator are easy to contact and will handle your questions within a short timeline.

The coordinating centre will also help companies with the different steps of the protocol review process and feasibility check

ECFS-CTN@uzleuven.be

Optimizing patient recruitment for CTN studies

Individual CTN sites will refer companies who approach them for study performance to the CTN coordinating centre.

They have agreed to **preferentially participate in CF studies which have been reviewed by the CTN Protocol Review Committee** and which have received sufficient priority scoring. This helps to select protocols in such a way that the (limited) CF study population is involved more efficiently in clinical trials.

This means that CTN sites will selectively recruit patients for these studies that are accepted as "CTN study", improving the recruitment to these studies substantially.

Protocol review

Apart from reviewing the scientific design and safety aspects, the protocol review committee will also evaluate the protocol for feasibility. Where possible, advice will be provided on what adjustments could make the protocol more attractive for patients and for sites, again leading to better recruitment.

Providing protocols as draft design, will give the companies the advantage that some feedback from the protocol review committee can still be incorporated in the final study design.

In the long term, improvement of CF protocol quality and feasibility will bring efficient medicines faster to the patients.

Protocol review: Procedure and Timing

See also the schematic overview hereafter.

1. Sponsors are advised to contact the CTN coordinating centre as early as possible (preferably six weeks before protocol submission) to start the administrative preparations of the review process. This will save valuable time once the protocol is available.
2. The confidentiality agreement according to the companies should be sent to the CTN Director for signature, followed by the (draft) protocol. At this point, a protocol synopsis would also be sufficient.
3. A Study Evaluation Agreement will be setup between the sponsor and the CTN coordinating centre, describing the services and associated fees.
4. A protocol review group is assigned to review the protocol. This group consists of 3 MD CF experts, an experienced study coordinator, a statistician and 2 trained patient (or parent of patient) reviewers. Ad hoc reviewers with specific expertise can be added if needed. The sponsor will be provided with the list of involved people to arrange confidentiality agreements.

5. The CTN coordinating centre will check with reviewers if there is no conflict of interest.

6. The timeline (4 to 6 weeks depending on the agreement) starts when

   a. The Company has arranged confidentiality agreements with all reviewers AND
   b. The Study Evaluation Agreement has been signed by both parties AND
   c. The protocol has been provided to the CTN coordinator

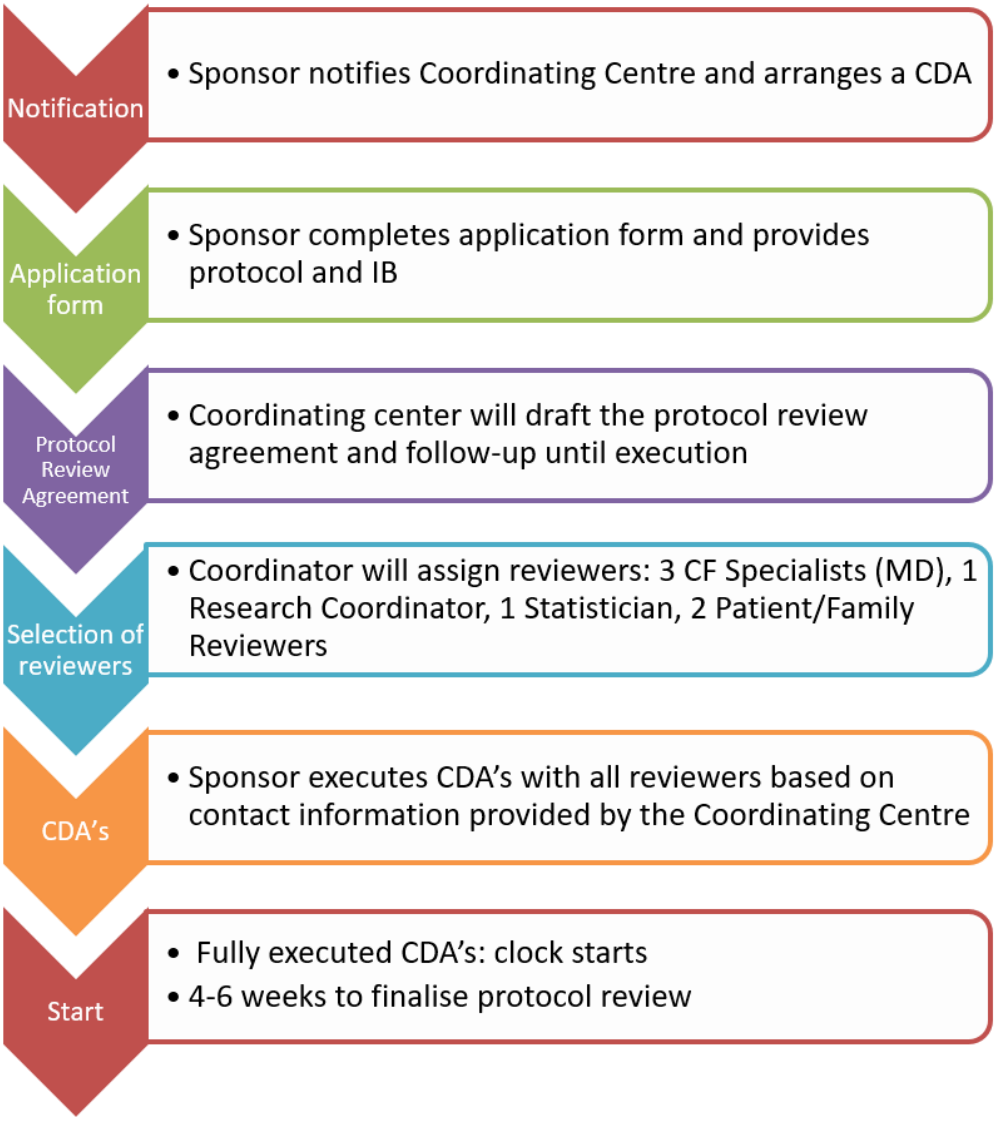
7. **The protocol review group provides detailed comments and rates the protocol for Feasibility, Scientific Merit, Study Design and Strategic Fit.** The patient/parent reviewers answer a specific questionnaire aiming at giving the CF patient/parent perspective on the study. The CTN Executive Committee will use this information to prioritize the protocol. Afterwards, all information is provided to the sponsor.

8. The sponsor can choose to resubmit a revised protocol (1 time).

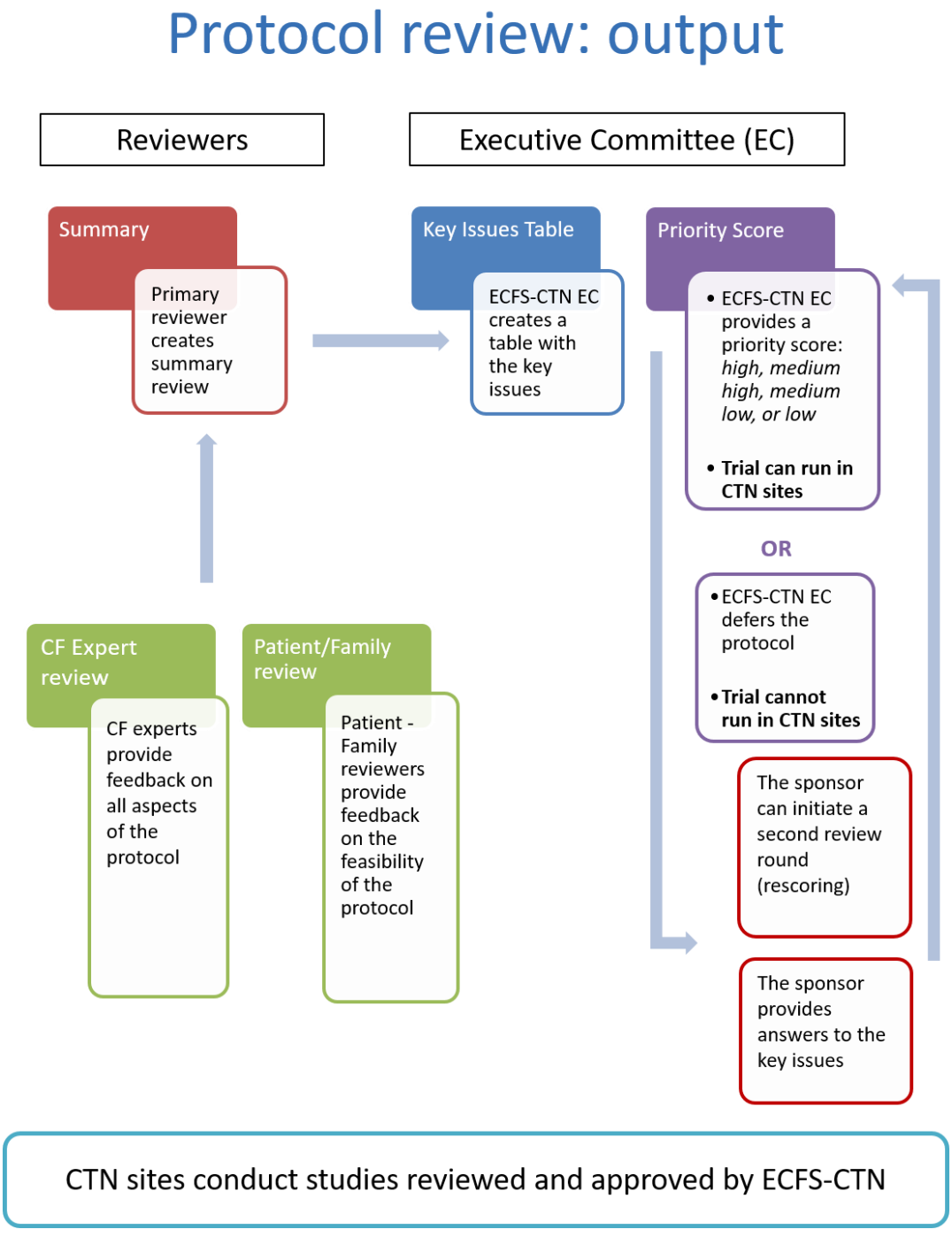
9. Clinical trials in CF often include participants across different cities, countries and even continents. For trials planned to run in Europe, US, and/or Canada, a joint **"global" protocol review** is sometimes performed with our partner clinical trial networks in the US and Canada. All three networks are collaborating to improve and streamline this process.

CTN Protocol review process Part 1:
From sponsor notification till start of review

Protocol review: preparation



CTN Protocol review process Part 2:
From start of review to final report



Protocol Assistance

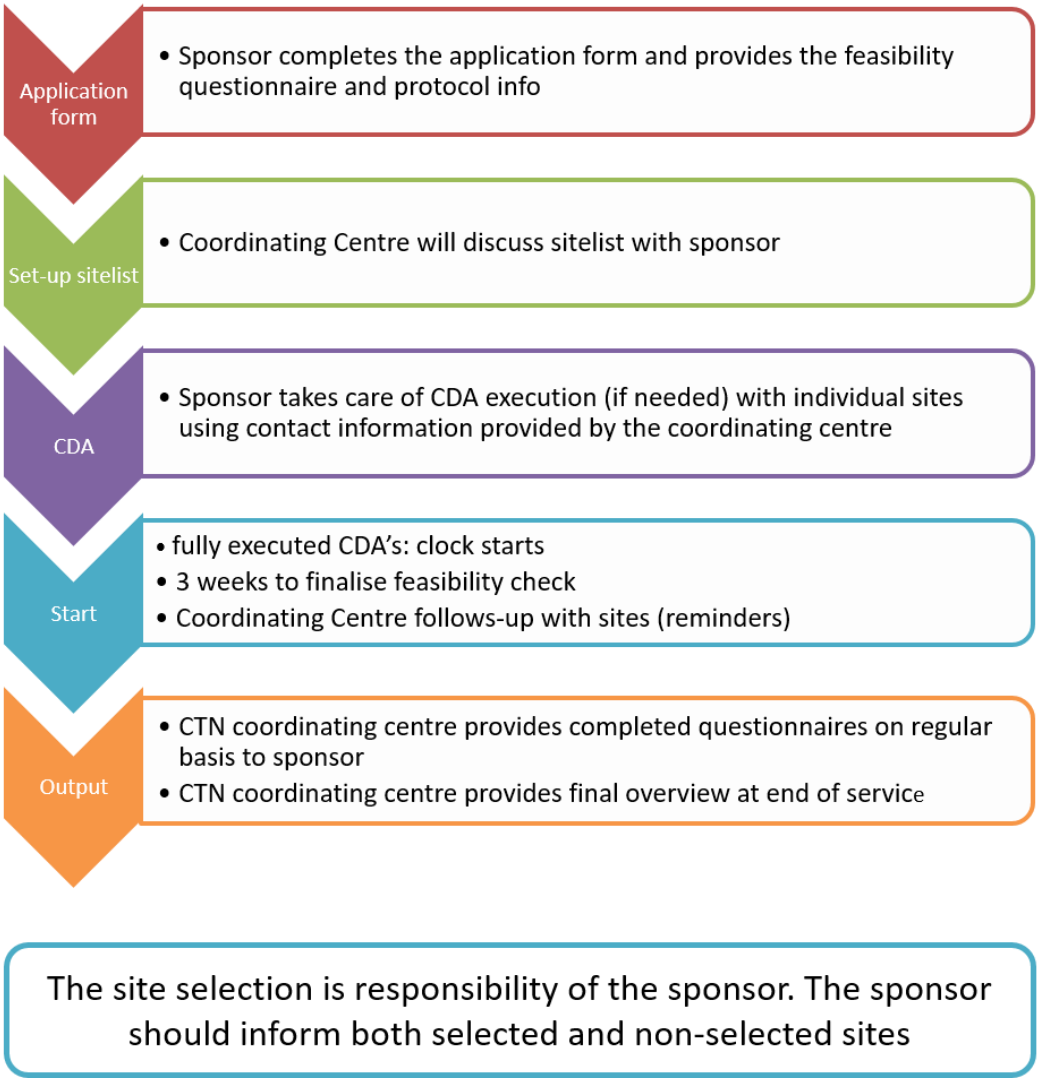
ECFS-CTN experts can provide help in the early phase development of study design. For more info please contact ecfs-ctn@uzleuven.be

Feasibility Assessment

ECFS-CTN will assist with providing an accurate count of the number of patients meeting study eligibility criteria by consulting the patient databases in the ECFS-CTN clinics. This process is centralized by the CTN coordinating centre. Individual CTN sites will refer companies who approach them with feasibility requests to the CTN coordinating centre.

The ECFS-CTN can help with the design of the feasibility questionnaire. The coordinating center sends the questionnaires to the sites selected by companies and for which a confidentiality agreement has been signed. The coordinating center follows up on responses, provides updates to companies and provides all questionnaires and a summary to companies. See below for applicable fees. Companies can also consult the ECFS Registry data for mutation / population specific questions (ecfs-pr@uzleuven.be).

Feasibility Service



The site selection is responsibility of the sponsor. The sponsor should inform both selected and non-selected sites

Follow up of trials conducted in CTN sites

A close liaison between the ECFS-CTN coordinating centre and CTN sites and sponsors ensures that any issues arising during the conduct of a study or at a particular site are quickly shared across the network. This info will optimize the effective running of a trial and an appropriate recruitment.

DSMB

The ECFS-CTN can provide assistance for the setup of an independent Data Monitoring Safety Board with CF experts. This service is optional. The CTN will bring you in contact with the DSMB coordinator (based at the University of Lyon in France), who will setup an agreement, arrange the fees, and execute services independently from CTN. An information brochure is also available on the website https://www.ecfs.eu/sites/default/files/images/DSMB.pdf.

For global studies a global DSMB can be setup in cooperation with CFF-TDN.

Standardization, certification and central reading

- Assistance in the setting of CF-specific outcome parameters such as lung clearance index, nasal potential difference, sweat test etc. and contact with experts can be provided along with ECFS-CTN **Standard Operating Procedures**.
- A **reference center** within the network can also be in charge of **certification** of the sites selected for the trial (inside or outside ECFS-CTN) and of **central reading** during the trial itself
    - Lung Clearance Index
    - Imaging
    - Nasal Potential Difference

Companies who would like to use one of these outcome parameters in a clinical trial, are encouraged to ask the ECFS-CTN for advice in the early stages of set-up.

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 meeting of site investigators.

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

Fees for services

Fees Protocol review (not optional)

Detailed feedback about study design and priority rating for the study:
10,000 to 12,000 €.

Fees Eligibility assessment (not optional)

Accurate count of the number of patients meeting study eligibility criteria by consulting the patient databases in the ECFS-CTN clinics:
500 to 750 € per responsive site.

Fees for other services

An individual offer will be issued based on the specific service to the client.

Partnerships

Active links are built between CTN and key partners involved in clinical trials in CF. This way existing resources and available expertise is used, policies are streamlined and impact is increased.

- The network discusses gaps or issues in CF research with representatives of the **EMA**. For example : Medicines for Children, the need for defining appropriate outcome parameters, etc.

  The objective is to improve the context for regulatory decisions in the field of CF drug development in Europe. This is achieved by providing scientifically sound and convincing information to the EMA and applicable national competent authorities thereby helping these institutions to set up appropriate guidance documents and to discuss specific applications for marketing authorization related to CF.

- The ECFS-CTN is also a voting member of the coordinating group of the EMA's European Network of Pediatric Research which is called **EnprEMA**.

  More info:
  http://www.ecfs.eu/ctn/enprema-self-assessment-form

- **National and European CF Patient Organizations**
- **National Research networks** in Europe, US, Canada, Australia
- The US CF Foundation Therapeutics Development Network (**CFF-TDN**). There are two yearly face to face meetings and monthly teleconferences with the CFF-TDN.
- The **learned societies** such as the European Respiratory Society (ERS).
- The ECFS-CTN is partnering in **EU funded projects** (European Reference Network, IMI, H2020):
  - http://www.ern-lung.eu/
  - https://www.hitcf.org
  - http://www.conect4children.org
  - https://www.oligogpivotalcf.eu

Questions and Answers

Q1: Is the ECFS-CTN a CRO?

- The ECFS-CTN is not a Contract Research Organization. The running and the follow-up of the study remains in the hands of the pharmaceutical company and the CRO of their choice.

Q2: What are the options if a protocol is not accepted by the ECFS-CTN?

- The company can provide responses to the critiques questions and / or resubmit a revised protocol. The Protocol Review Committee will check if scores can be updated based on these revisions.
- In general, the ECFS-CTN is open for discussion, for example on the reason why a protocol received a certain priority rating.
- The ECFS-CTN can help to refer companies to national networks.

Q3: Will a study need to run in all ECFS-CTN countries or sites?

- It is possible that a company will not run a particular study in all countries included in the network. The CTN partners understand and accept this fact. Likewise a company is indeed free to also include CF centres outside the ECFS-CTN.

Q4: Is there a risk that comments from the ECFS-CTN protocol review committee will be in contradiction with regulatory requirements?

- The ECFS-CTN is not a regulatory agency. Comments should be considered as advice to add quality and improve recruitment. There is always room for discussion if comments are in conflict with the views of regulators or other advisors.

Q5: Will ECFS-CTN review delay the start of the study?

- The ECFS-CTN wants to encourage companies to contact the coordinating centre as early as possible in the study startup procedure (preferably 6 weeks before protocol submission and not in a late stage of site selection). A draft protocol or synopsis can be sufficient to start the review. This way timelines will not be endangered and the company will receive valuable information at a moment where the protocol can still be updated.

Q6: How is conflict of interest avoided?

- All individuals involved with protocol review or DSMB will sign a disclosure form. If there is any significant conflict of interest, the person will be excluded to work on that specific protocol.

PLEASE DO NOT HESITATE TO CONTACT US WITH YOUR OTHER QUESTIONS OR DOUBTS!

Acknowledgements

With special thanks to:

- The ECFS for their trust and support
- The CF Patient Organizations and people with CF for their support and participation
- The CFF-TDN, national networks and pharma companies for believing in the CTN
- The CTN investigators, site personel and committee members for ongoing effort and work done
- All others that shared knowledge or provided logistic help for their valuable input to build the network

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