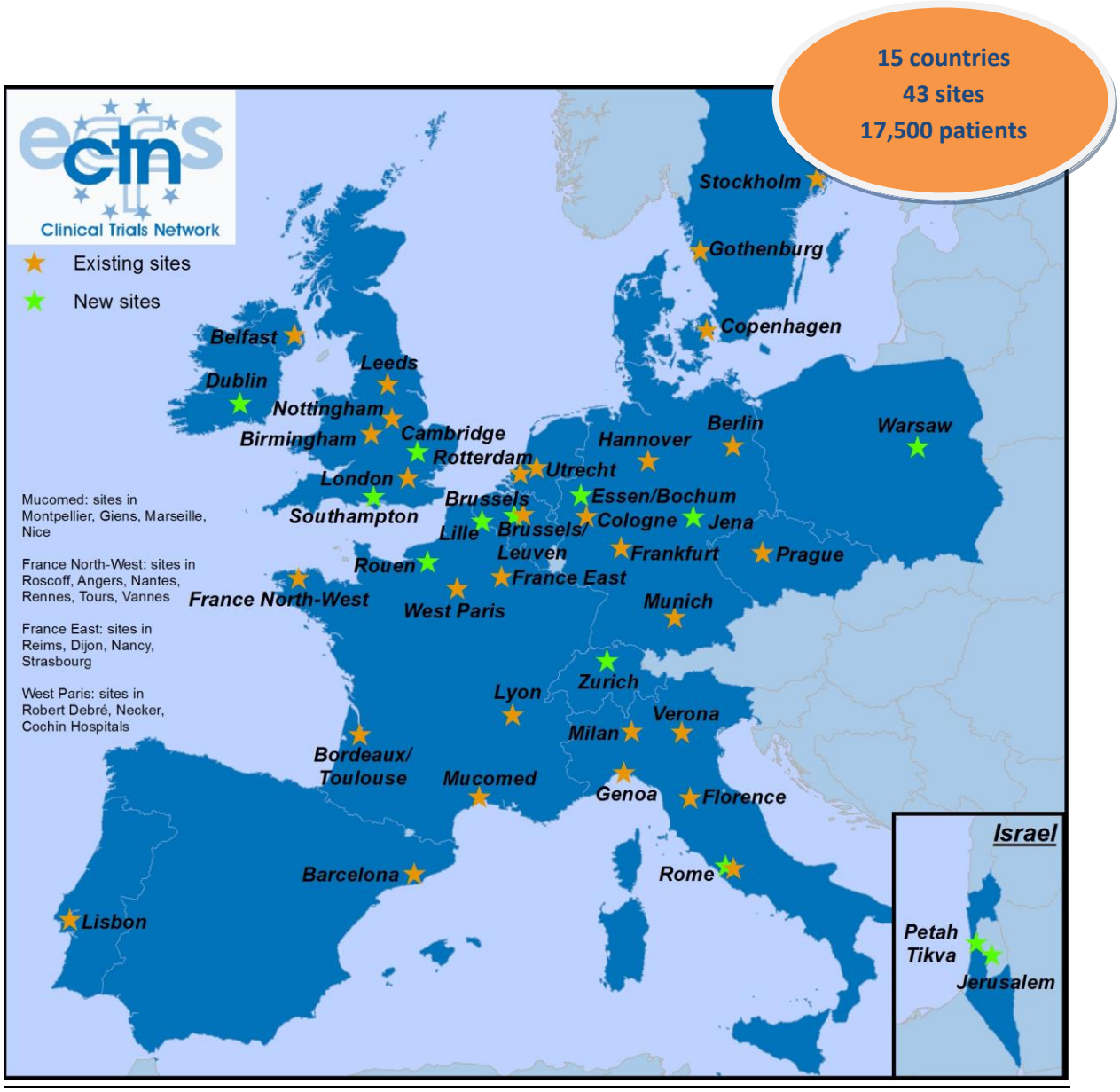
ECFS Clinical Trials Network

Information to companies



V6, 2015

Content

Quick guide for companies

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

Tips for a smooth process:

- Contact the CTN coordinating centre (ECFS-CTN@uzleuven.be) at the time a 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 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

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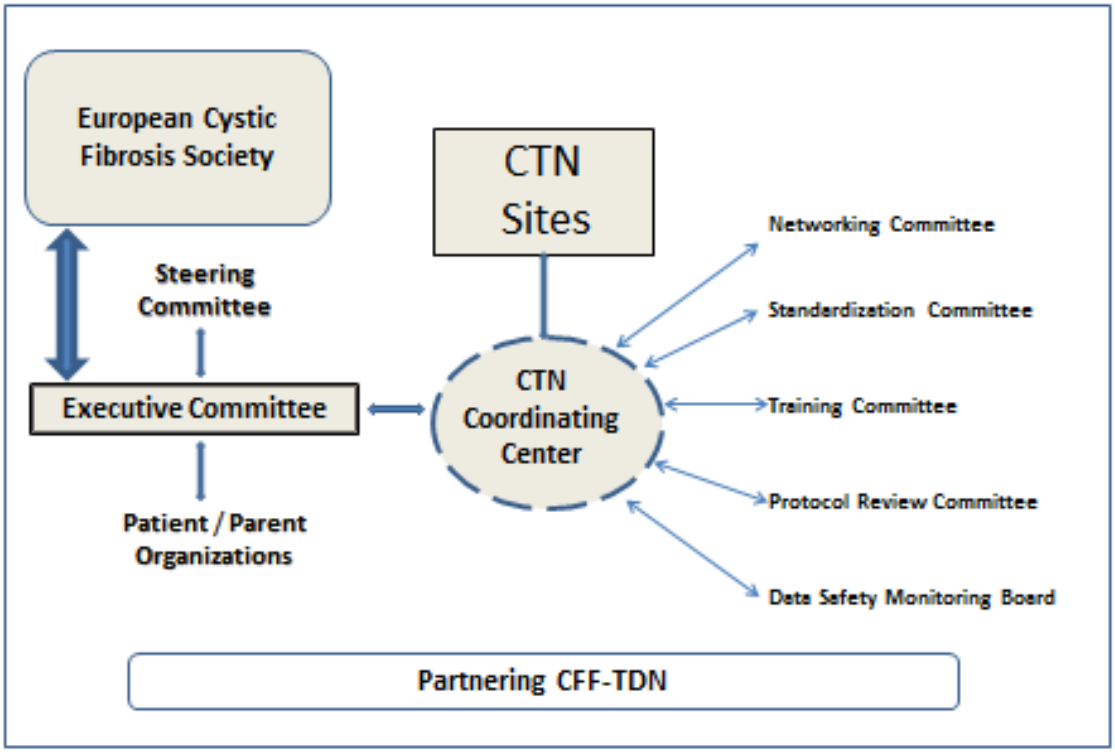
CTN Organigram



CTN Executive Committee

ECFS CTN Director

Tim Lee, Leeds, UK

ECFS CTN Co-Director

Silke van Koningsbruggen, Köln, Germany

Executive Committee members

Damian Downey, Belfast, UK
Lieven Dupont, Leuven, Belgium
Michael Fayon, Bordeaux, France
Giovanni Taccetti, Florence, Italy
Paola de Carli, Paris, France (patient organization representative)

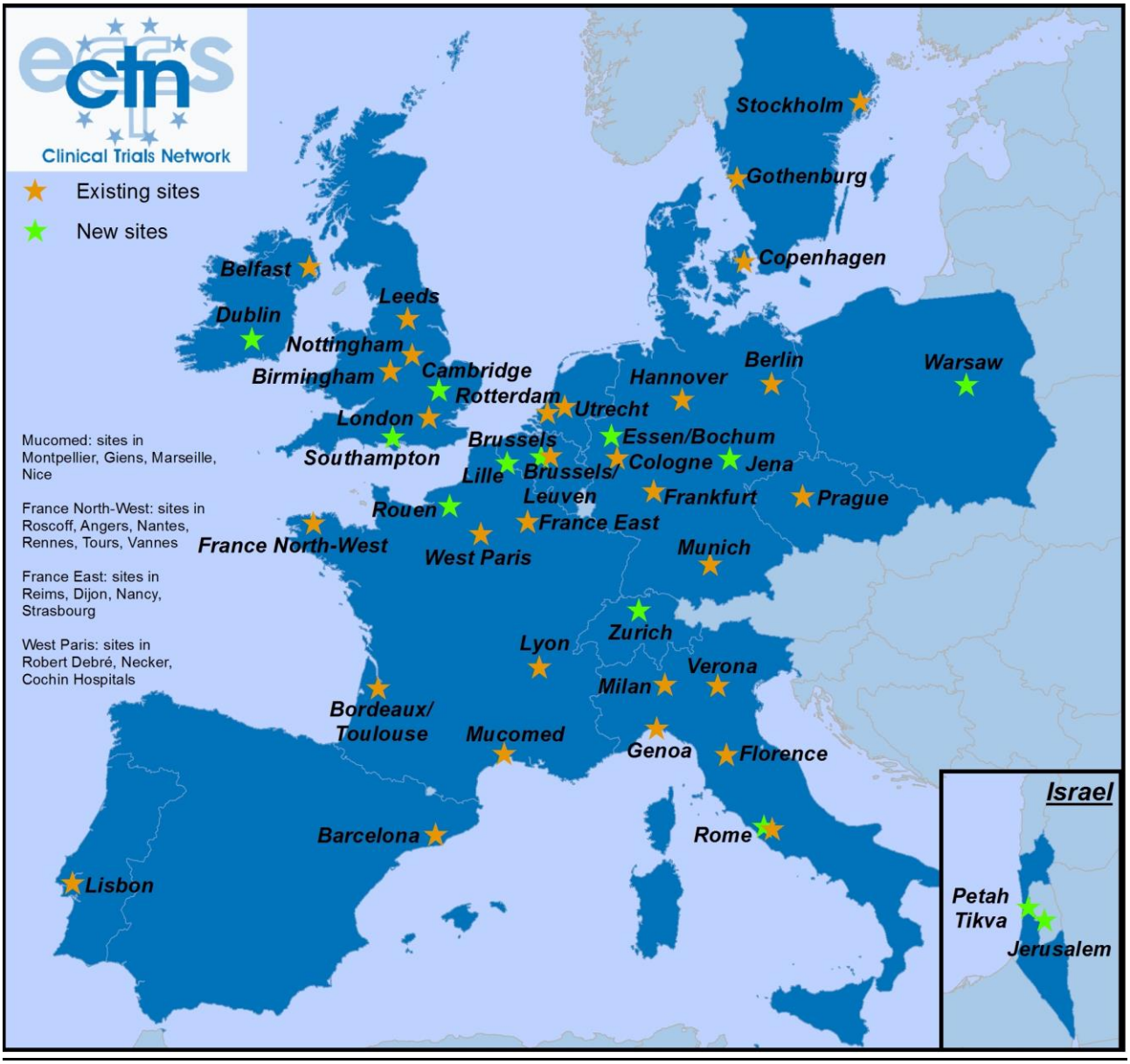
ECFS Representative

Christine Dubois, Karup, Denmark

Liaison with CFF-TDN

Silke van Koningsbruggen, Köln, Germany

CTN Sites


Clinical Trials Network
Existing sites
New sites
Mucomed: sites in Montpellier, Giens, Marseille, Nice
France North-West: sites in Roscoff, Angers, Nantes, Rennes, Tours, Vannes
France East: sites in Reims, Dijon, Nancy, Strasbourg
West Paris: sites in Robert Debré, Necker, Cochin Hospitals
Stockholm
Gothenburg
Copenhagen
Belfast
Leeds
Dublin
Nottingham
Birmingham
Cambridge
Rotterdam
Utrecht
Hannover
Berlin
Warsaw
London
Brussels
Essen/Bochum
Southampton
Lille
Brussels/ Leuven
Cologne
Jena
Frankfurt
Prague
Rouen
France East
France North-West
West Paris
Munich
Zurich
Lyon
Verona
Milan
Bordeaux/ Toulouse
Mucomed
Genoa
Florence
Barcelona
Rome
Lisbon
Israel
Petah Tikva
Jerusalem

Site list part 1

Country	Center	PI	Co-Investigators	
Belgium	Brussels (UZB)	Anne Malfroot	E. De Wachter, E. Vanderhelst	NEW
	Leuven / Brussels (UCL)	Kris De Boeck	L. Dupont, M. Proesmans, P. Lebecque, T. Leal	
Czech Republic	Prague	Pavel Drevinek	L. Fila	
Denmark	Copenhagen	Tania Pressler	M. Skov	
France	Bordeaux / Toulouse	Michael Fayon	J. Macey, M. Murris-Espin, F. Brémont	
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	France North-West*	Gilles Rault	A. Magnan	
	Lille	Anne Prevotat	N. Wizla-Derambure	NEW
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	Rouen	Christophe Marguet	S. Dominique	NEW
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	Hannover	Burkhard Tümmler	F. Ringshausen	
	Jena	Jochen Mainz	R. Michl	NEW
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	Münich	Susanne Nährig	M. Griese, R. Huber, M. Kappler	
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Israel	Jerusalem	Eitan Kerem	M. Wilschanski	NEW
	Petah Tikva	Hannah Blau	H. Mussaffi	NEW
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	Genoa	Laura Minicucci	A. De Allesandri, R. Casciaro	
	Milan	Carla Colombo	G. Pizzamiglio	
	Rome (Sapienza University)	Serena Quattrucci	S. Bertasi	
	Rome (Bambino Gesù)	Vincenzina Lucidi	F. Alghisi	NEW
	Verona	Marco Cipolli	S. Volpi	

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Sweden	Göteborg	Anders Lindblad	M. Gilljam	
	Stockholm	Lena Hjelte	F. Karpati	
Switzerland	Zurich	Alexander Möller	C. Benden, F. Singer	NEW
The Netherlands	Rotterdam	Harm Tiddens	M. Bakker	
	Utrecht	Kors van der Ent	I. Bronsveld, J. Lammers	
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	Birmingham	Edward Nash	J. Whitehouse	
	Cambridge	Charles Haworth	A. Floto	NEW
	Leeds	Tim Lee	K. Brownlee, C. Etherington, D. Peckham	
	London	Jane Davies	D. Bilton , N. Simmonds, E. Alton, I. Balfour-Lynn	
	Nottingham	Alan Smyth	A. Knox	
	Southampton	Mary Carroll	T. Daniels	NEW

Composite sites

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

Introduction: CTN history and background

Rationale for a CF Clinical Trials Network

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.

National initiatives towards organized CF research have been underway in Europe for some time. But many studies need inclusion numbers that surpass the capacity of national patient groups, hence the need for a European wide initiative.

The rationale for setting up a European Clinical Trials Network for CF is to optimize the development and evaluation of new and approved treatments for CF through efficient clinical studies in Europe. This includes advising on optimal study design, identifying the most appropriate target population, improving sample size calculations by using real life data (including data from the ECFS CF Registry) and decreasing the sample size needed by standardization of outcome parameters. Apart from study design, motivating patients to take part in research and promoting the safety of participants in clinical trials are of great importance.

The ECFS and EuroCareCF (EU Framework 6 Program) have worked together to launch the ECFS-Clinical Trials Network (ECFS-CTN), which has now been active since 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 addditional sites have been selected, who will be fully involved by 2016. This brings the total to **43 sites in 15 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

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 Belgium, Czech Republic, Denmark, France, Germany, 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.

In general the ECFS–CTN offers several services:

- Access to a large number of patients, children and adults, with well characterized clinical phenotype and high standards of care
- Quick feedback about the study design), scientific merit, feasibility and the priority of the protocol in the network
  Feasibility check / site selection
- Preferential patient inclusion in protocols selected by the network
- High standards of performance
- Data Safety Monitoring Board (DSMB)
- “Protocol Assistance”: contact with CF specialists or basic scientists with specific expertise to assist with study design
- "Outcome Parameters Assistance": contact with experts, ECFS-CTN Standard Operating Procedures, certification of sites, central reading or reference centre

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 full time coordinator (Veerle Bulteel), assisted by 2 secretaries, is 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

Chair of the protocol review committee:

Prof. Dr.Lieven Dupont

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 obtain financial disclosure forms from all reviewers and the members of the CTN Executive Committee to make sure there is no conflict of interest.

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

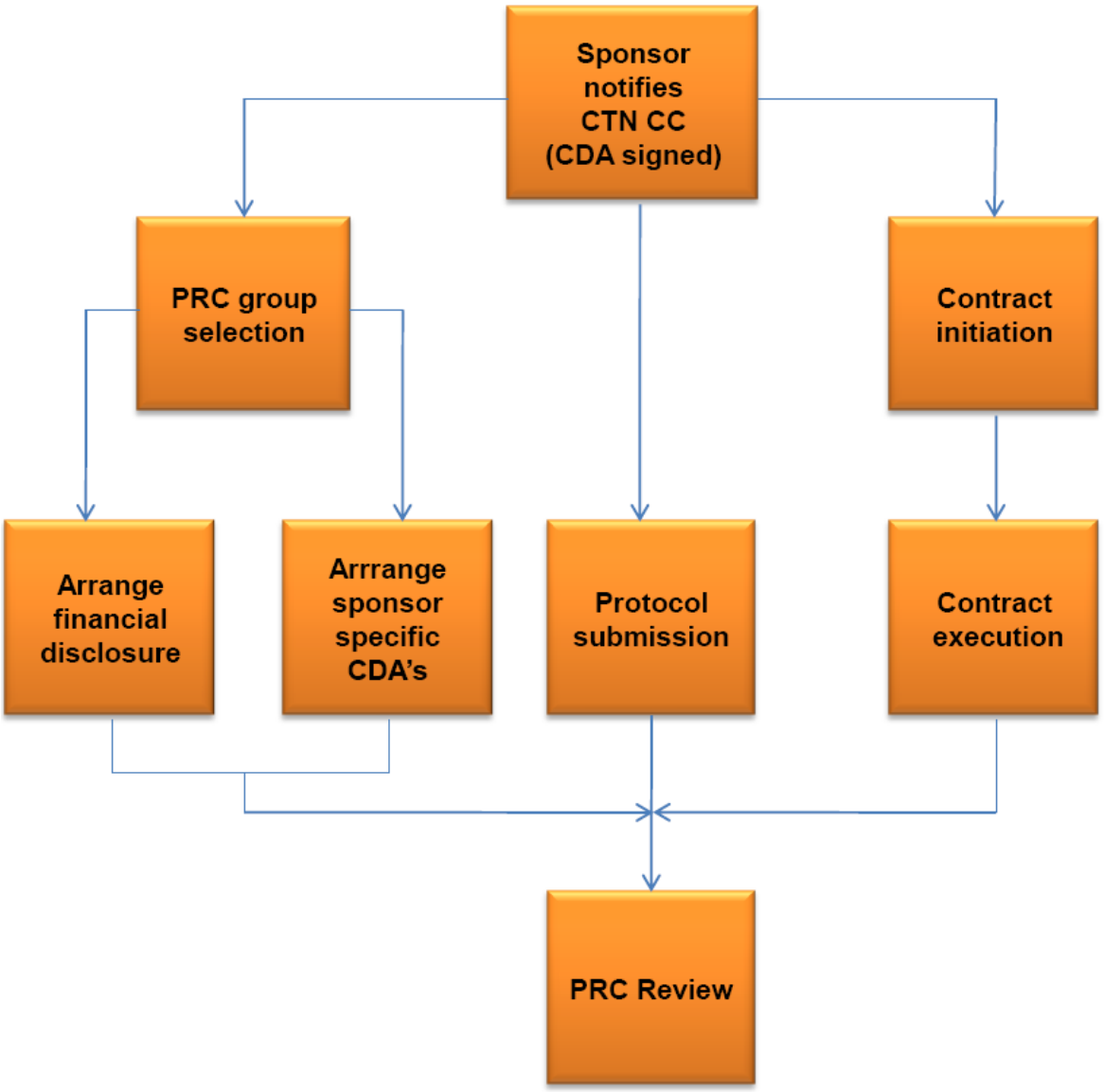
   a. The Company has arranged confidentiality agreements with all reviewers AND
   b. The Study Evaluation Agreement has been signed by both parties AND
   c. The protocol has been provided to the CTN coordinator

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.

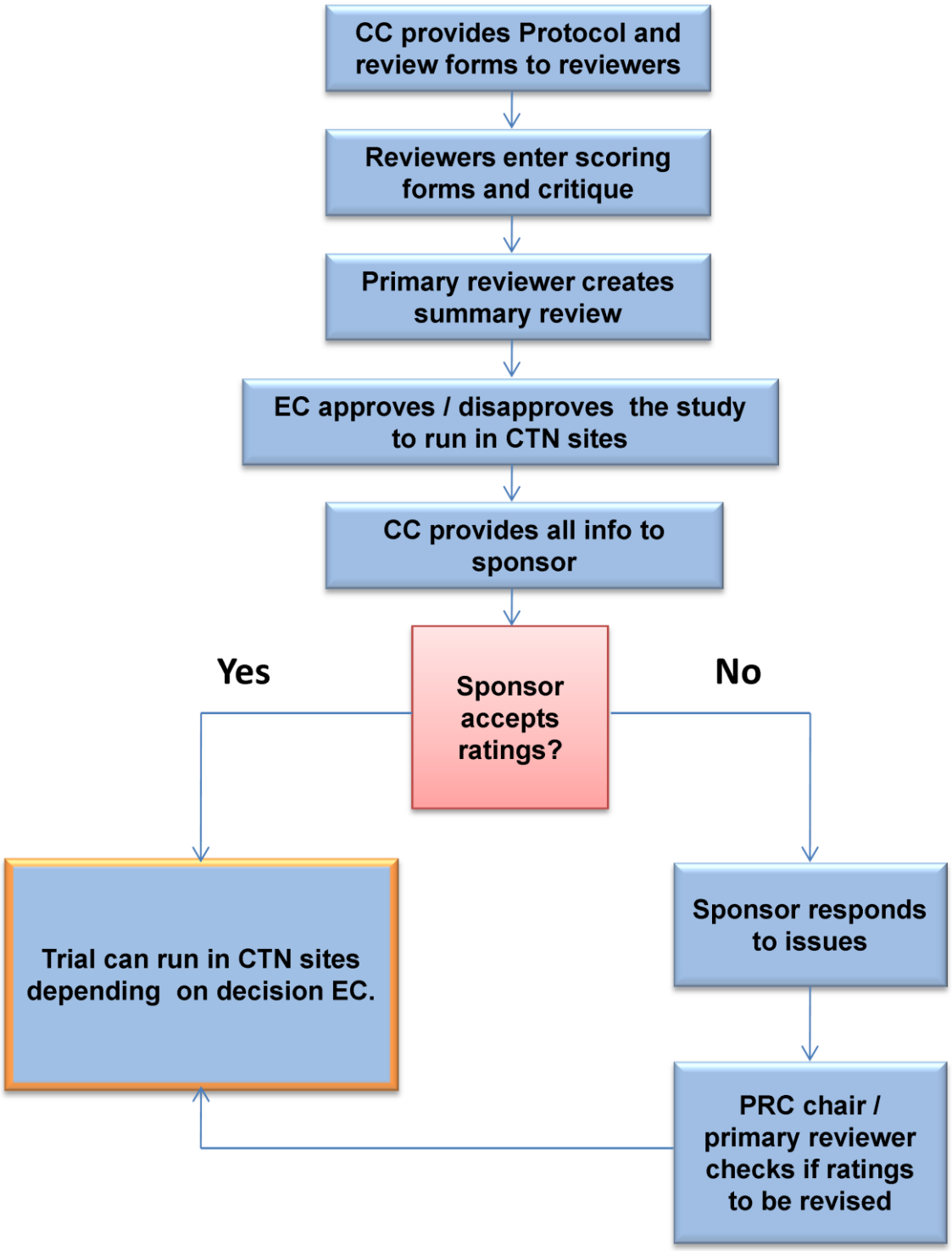
8. The sponsor can choose to resubmit a revised protocol (1 time).

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

CC = CTN coordinating centre EC = CTN Executive Committee PRC = CTN Protocol Review Committee



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 and can take place in parallel with the protocol review. 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).

Follow up of trials conducted in CTN sites

If the protocol review has been successful and the clinical trial is selected by the ECFS-CTN, it will run in the CTN centres selected by joint agreement between the centre directors and the pharmaceutical company.

The ECFS-CTN coordinating centre follows up on study startup and enrolment every 3 months.

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.

Global reviews (Europe – US)

Only for studies that will run both in Europe and US, the company can ask CFF-TDN and ECFS-CTN to perform a global combined protocol review. The CTN coordinating centre can provide you with more information on this process.

ECFS-CTN follows similar procedures for protocol review as the CFF Therapeutics Development Network (TDN) in US.

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.

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

Other Services

- Assistance in the setting of CF-specific outcome parameters such as lung clearance index, nasal potential difference, sweat test…: 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
- Putting you in contact with expertise in specific domains
    - Basic scientists
    - Specific expertise areas in clinical research
    - Patient needs
    - …

Fees for services (valid for 2015)

Fees Protocol review (not optional)

Detailed feedback about study design and priority rating for the study:
5,000 to 10,000 €.

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 700 € per site.

Fees for other services

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

ECFS-CTN other Committees

Standardization

Chair of the Standardization Committee:

Prof. Isabelle Sermet

The aim of the ECFS-CTN Standardization Committee is to harmonize clinical outcome parameters used in CF clinical research by implementing Standard Operating Procedures for the main endpoints used in clinical therapeutical trials. This will ensure a better visibility for clinical research in Europe and improve evaluation and follow-up on patients throughout Europe.

The ECFS-CTN Standard Operating Procedures on several outcome parameters are available upon request to the ECFS-CTN coordinating center. Implementation of ECFS-CTN Standard Operating Procedure is validated by a processs of site certification. This process is ongoing for NPD, LCI, Chest CT and ICM.

The ECFS-CTN offers Nasal Potential Difference and Lung Clearance Index central reading and certification via our core facilities in Paris and London respectively.

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.

Different standardization working groups have been formed:

- Inflammatory markers
- Lung Imaging
- Microbiological explorations
- NPD
- ICM
- Sweat Testing
- Nutritional Evaluation
- Respiratory Functions

As part of the work of the ECFS-CTN Standardisation Committee, data on clinimetric properties (reliability, validity and responsiveness) were collected for CFTR biomarkers (nasal potential difference (NPD), sweat chloride measurement and intestinal current measurement (ICM)) and for inflammatory markers and Lung Clearance Index.

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 bronchoalveolar 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.

CFTR biomarkers: time for promotion to surrogate end-point?
K. De Boeck, L. Kent, J. Davies, N. Derichs, M. Amaral, S.M. Rowe, P. Middleton, H. de Jonge, I. Bronsveld, M. Wilschanski, P. Melotti, I. Danner-Boucher, S. Boerner, I. Fajac, K. Southern, R.A. de Nooijer, A. Bot, Y. de Rijke, E. de Wachter, T. Leal, F. Vermeulen, M.J. Hug, G. Rault, T. Nguyen-Khoa, C. Barreto, M. Proesmans and I. Sermet-Gaudelus on behalf of the European Cystic Fibrosis Society Clinical Trial Network Standardisation Committee
Eur Respir J 2013; 41: 203–216

The ECFS-CTN wants to reach a consensus on Lung Clearance Index (LCI) and chest computed tomography (CT) procedures and will try to provide an evidence-based proposal for LCI and chest CT to be used as surrogate endpoints for clinical trials.

Training

Chair of the Training Committee:

Prof. Judy Bradley

The training committee is responsible for:

1) Monitoring the training status of investigators at each CTN site (e.g. GCP training, informed consent training).
2) Providing an annual training course for ECFS-CTN investigators and study coordinators. This training course is linked to the ECFS annual conference.
3) Liaising closely with the CFF-TDN and ERS School to ensure that appropriate training resources and courses are shared.

Networking

The purpose of the ECFS-CTN Networking Committee is to build active links between CTN and key partners involved in clinical trials in CF. This way existing resources and available expertise is used, policies are streamlined and impact is increased.

In order to help the ECFS-CTN achieve this goal, the committee is in contact with the following groups.

Regulatory bodies.

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

  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

- Research networks in EU member states.
- National and European CF Patient Organizations.
- The US CF Foundation Therapeutics Development Network (US CFF TDN). There are two yearly face to face meetings and monthly teleconferences with the US CFF TDN.
- The learned societies such as the European Respiratory Society (ERS).

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 trust and support
- The CF Patient Organizations and the Patients: for 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

Quick guide for companies

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Tips for a smooth process:

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