

Early View

Study protocol

The disease-specific clinical trial network for Primary Ciliary Dyskinesia (PCD-CTN)

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The disease-specific clinical trial network for Primary Ciliary Dyskinesia (PCD-CTN)

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Abstract

Primary Ciliary Dyskinesia (PCD) is a rare genetic disorder characterized by impaired mucociliary clearance leading to irreversible lung damage. In contrast to other rare lung diseases like cystic fibrosis (CF), there are only few clinical trials and limited evidence-based treatments. Management is mainly based on expert opinions and treatment is challenging due to a wide range of clinical manifestations and disease severity. To improve clinical and translational research and facilitate development of new treatments, the clinical trial network for PCD (PCD-CTN) was founded in 2020 under the framework of the European Reference Network (ERN)–LUNG PCD Core. Applications from European PCD sites interested in participation in the PCD-CTN were requested. Inclusion criteria consisted of patient numbers, ERN-LUNG PCD Core membership, use of associated standards of care, experience in PCD and/or CF clinical research, resources to run clinical trials, good clinical practice (GCP)-certifications and institutional support. So far, applications of 22 trial sites in 18 European countries were approved including >1400 adult and >1600 pediatric individuals with PCD so far. The PCD-CTN is headed by a coordinating centre and consists of a steering and executive committee, a data safety monitoring board and committees for protocol review, training and standardization. A strong association with patient organizations and industrial companies are further cornerstones. All participating trial sites agreed on a code of conduct. As CTNs from other diseases demonstrated successfully, this newly formed PCD-CTN operates to establish evidence-based treatments for this orphan disease and to bring new personalized treatment approaches to the patients.

Introduction

Primary Ciliary Dyskinesia (PCD, MIM 242650) is a rare, genetic, multisystem disorder mainly characterized by impaired mucociliary clearance which might result in irreversible destructive airway disease. Available data on the epidemiology of PCD is limited, but the estimated prevalence is 1:10.000 individuals (1) with at least 74,000 Europeans estimated to be affected. The reported prevalence of PCD varies widely between countries because only a fraction of individuals is correctly diagnosed and registered, and access to diagnostic facilities differs regionally. In addition, there is a variable occurrence in distinct populations (1), while the recorded prevalence in national registries remains markedly lower in adults than in children (2). PCD is both genetically and clinically heterogeneous. To date, there are more than 50 genes reported to be associated with PCD (1). There is limited information on the natural history and the long-term course of the disease, but it is clear that the disease is a serious threat to lung function already at preschool age and that the course of lung function after diagnosis shows a high degree of variation (3). Furthermore, it has been shown that the majority of individuals with PCD presents with chronic respiratory infections, bronchiectasis (already evolving in childhood), progressive decline in lung function and chronic rhinosinusitis (1, 4). Some individuals even progress to respiratory failure with the need for lung transplantation (5). There seems to be a genotype/phenotype correlation in PCD, with subjects carrying mutations e.g. in the genes *CCDC40* (6) or *CCNO* (7) displaying worse lung function outcomes and individuals with mutations in e.g. *DNAH9*, *RSPH1* and *RSPH9* showing milder respiratory phenotypes, as reported in small cohorts (1, 8-10).

There is no cure for this chronic disorder and treatment modalities are mainly symptomatic and supportive, aiming to reduce secondary effects of dysfunctional

motile cilia such as mucostasis, bacterial infections and destructive inflammation. Evidence-based treatment is very limited, and management strategies are based on expert opinions and experiences (11-13). Most of the strategies are extrapolated from other respiratory diseases like cystic fibrosis (CF) or non-CF-bronchiectasis. Daily airway clearance regimens are of utmost importance to prevent mucostasis, along with consequent antibiotic treatment of recurrent infections. The treatment of non-respiratory manifestations, such as fertility problems, congenital heart defects or brain malformations, are organ-specific. The management strategies are individualized, since no standardized treatment methods exist and experts from different disciplines need to be involved.

Recently, the first randomized, placebo-controlled trial on pharmacotherapy in PCD was published (14). This was a multicenter study of maintenance treatment with azithromycin for six months in 90 individuals with PCD aged seven to 50 years showing a reduced frequency of respiratory exacerbations and positive airway cultures compared to placebo. At the same time, it is well known that a wide range of other medicines is used empirically in individuals with PCD but without supportive evidence from randomized controlled trials (11-13). Consequently, there is an urgent need to generate knowledge from clinical trials for the effective management of individuals with PCD using a collaborative, multicenter approach.

Especially in the field of rare diseases such as PCD, i.e., with small patient populations, collaboration between specialized centers is extremely important to obtain sufficient sample sizes for the assessment of outcome parameters with adequate statistical power. Thus, a clinical trial network (CTN) provides a centralized infrastructure for the successful implementation of clinical trials. The purpose of this publication is to present an overview of important and coherent activities within the

European Reference Network (ERN)-LUNG PCD Core network (<https://ern-lung.eu>) with a special focus on the newly established PCD-CTN (<https://ern-lung.eu/portfolio-items/clinical-trial-network-for-primary-ciliary-dyskinesia-established/>), including its interaction with the ERN-LUNG International PCD Registry (15; ClinicalTrials.gov NCT02419365).

Clinical trial networks

The first CTNs were established in the field of cancer research in the late 1950's, followed by several disease specific CTNs in the 1960's. Over the years, CTNs have successfully established new treatment approaches for specific groups of patients. In the field of respiratory diseases, the Cystic Fibrosis Foundation (CFF) in the USA founded the first specific CTN in 1998 and, thus, pioneered CF treatment, having played an important role in the development and use of specific cystic fibrosis transmembrane conductance regulator (CFTR) modulators, which in the meantime have been approved for use in up to 90% of the CF population (<https://www.cff.org/About-Us/About-the-Cystic-Fibrosis-Foundation/Our-History/>).

The European Cystic Fibrosis Society - Clinical Trials Network (ECFS-CTN) was founded in 2009 and stimulated the development of other disease specific CTNs in Europe (21). This network currently provides access to 57 large and experienced CF centers, located in 17 different countries in Europe, caring for 21,500 children/adolescents and adults with CF. Since 2009 more than 80 protocols have been reviewed, with up to ten studies running at the same time. Furthermore, the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) was established in 2012 to facilitate multidisciplinary collaborative research in non-CF bronchiectasis. The initiative's goals are, among others, to create a European

bronchiectasis registry facilitating research and quality improvement initiatives across healthcare systems, to build a network of researchers and clinical experts in bronchiectasis to guide future research and clinical priorities, and to facilitate applications to industry and European Union funding sources to build bronchiectasis research capacity in Europe (22). EMBARC has been supported by a large community of more than 150 centers in more than 40 countries. It is therefore one of the most successful Clinical Research Collaborations (CRCs) within the European Respiratory Society (ERS) (23), involved in the publication of >10 original papers in less than four years and the development of several consensus documents as well as supporting several clinical trials. A second funding period (2017-2020) of EMBARC as an ERS CRC has been approved, EMBARC2. Core of the ongoing study Bronchiectasis Research Integrating Datasets, Genomics and Endotyping (BRIDGE) is to develop an international bio-resource (blood, DNA, sputum and other biological materials) based on the registry for use in translational research, but it also aims to generate recommendations for the design and conduct of bronchiectasis trials including study end-points and research priorities in each area (23).

ERN-LUNG PCD CORE Network

ERN-LUNG is a network of European Healthcare Providers (HCPs) dedicated to ensuring and promoting excellence in care and research for the benefit of patients affected by rare respiratory diseases. ERN-LUNG's vision is to be a European knowledge hub for rare respiratory diseases with the aim of decreasing morbidity and mortality from such diseases in people of all ages. ERN-LUNG consists of nine core networks representing the diversity of diseases and conditions affecting the lungs (<https://ern-lung.eu/governance>). The network's current set up has evolved since its

creation in 2017 and will continue to do so with better and more inclusive geographical coverage.

The ERN-LUNG PCD Core network currently consists of 28 participating centers and 8 affiliated partners in 23 countries (<https://ern-lung.eu/reference-centers-2/>). The ERN-LUNG PCD Core network aims to optimize current efforts to improve PCD patient care and quality of life. The exchange of biological materials for diagnostic purposes is the current main means in PCD to improve and formalize cross border patient care. This is especially important, as diagnosing PCD is complex and not all centers can provide all recommended methods needed to detect the whole range of PCD variants.

ERN-LUNG PCD Core members continuously update diagnostic and clinical PCD guidelines. There is a close cooperation e.g. with the CRC BEAT-PCD funded by the ERS, which is a recently established network of researchers and healthcare professionals aiming for improvement of patient diagnosis and care (24).

ERN-LUNG PCD Core is headed by a coordinator and supported by a coordinating team. All members participate in the ERN-LUNG International PCD Registry (<https://www.pcdregistry.eu/> (15)) to facilitate evaluation of clinical outcomes and to enable large clinical studies. Further, within ERN-LUNG, a Population Registry (<https://www.popreg.ern-lung.eu>) has been implemented. With this initiative, patients interested in participating in clinical trials, disease specific registries and research projects can register in the system and are contacted by experts from the specific ERN-LUNG Core that covers the patients' disease area such as PCD. This Population Registry is open to all interested patients and not restricted to specific countries. Registered patients in the Population Registry have the possibility to

become registered in the ERN-LUNG International PCD Registry, with measures in place that prevent double entries.

ERN-LUNG International PCD Registry

The ERN-LUNG International PCD Registry was initially launched in 2014 within the BESTCILIA project (15). It has lately been expanded through the REGISTRY WAREHOUSE project of ERN-LUNG (2). The registry aims to facilitate the recruitment of patients for clinical and research studies. Data on family history, symptomatology, socio economic status, clinical manifestations, disease course, treatments, outcomes and natural history, as well as diagnostic data are collected. Patient data are continuously contributed by participating centers (2). For participation in the ERN-LUNG International PCD Registry the centres need to meet necessary legal and ethical requirements, which are depending on national conditions. The registry management team assists with all necessary processes. Participation in the registry is mandatory to become an ERN-LUNG PCD Core member or associated partner. The ERN-LUNG International PCD Registry is registered in the European Rare Disease Registries Infrastructure (https://eu-rd-platform.jrc.ec.europa.eu/erdri_en).

Establishment of the PCD-CTN

The disease-specific CTN for PCD was founded in 2020 under the framework of ERN-LUNG. It initially consisted of 18 clinical trial sites in 12 countries in Europe and included >1100 adult and >1100 pediatric individuals with PCD. However, four more sites from three countries were recently accepted to the CTN, resulting in a CTN with 22 clinical trial sites and access to >1600 adults and >1400 children with PCD that

are potentially available for participation in trials (Figure 1). More centres are expected to apply for membership. All centres fulfilled the participation criteria including patient numbers ($n > 30$: adults, children or both), experience in PCD and/or CF clinical research, membership of ERN-LUNG PCD Core with implementation of associated standards of care, human and material resources to run clinical trials and certification of good clinical practice (GCP). An annual update in the form of a feasibility survey is needed, since several fundamental and important characteristics (such as the number of patients, age distribution, genetic characteristics, new methods or services within diagnostics, monitoring and treatment) are under constant development (Table 1). All centres provided confirmation of local institutional support, agreed on a code of conduct and are all equal partners in the PCD-CTN (Table 1). The PCD-CTN is managed daily by a director of the coordinating centre and is additionally staffed by a part-time academic secretary and several committees: a steering and executive committee, a committee in charge of data safety monitoring and committees for protocol review, training, and standardizations of diagnostic procedures and important outcome measures (Figure 2).

Aims

The overall aims of PCD-CTN are to intensify clinical research primarily by encouraging and contributing to the initiation of RCTs in PCD patients and to bring new medicines to the patients as quickly as possible. New medicines with a direct effect on the underlying defect naturally have a very high priority, while the development of an evidence base for medicines that are already widely used for patients with PCD also deserves a great deal of attention. Thus, we aim to increase clinical and translational research and to facilitate the development of evidence-based management including novel treatments for PCD. To achieve these aims,

improved access to patient populations is ensured by the network of participating clinical trial sites including the ERN-LUNG International PCD Registry. Through the structures of the established PCD-CTN, clinical trials can be successfully pursued, planned and executed in a sufficient number of patients. The network also promotes a strong collaboration with patient organizations and pharmaceutical companies.

Function and agreements (“Code of conduct”)

PCD-CTN Code of Conduct is a document that all site members have agreed to, which contains the guidelines for cooperation between the members, but also between the members and pharmaceutical companies. The following aspects on procedures to follow are discussed: i) when sites are contacted by pharmaceutical companies with inquiries for interest or feasibility of pharma initiated interventional drug trials, ii) in case of investigator initiated interventional drug trials (IIT) involving at least one CTN site and iii) registry-based studies initiated by pharma or investigator involving the ERN-LUNG International PCD Registry (15).

Aspects concerning confidentiality, conflicts of interest, GCP compliance, quality management, publication policy, financial agreements, relationships with sponsors, communication, responsibilities of membership, as well as failure to comply with these codes of conducts are all covered by this document.

Patient involvement

Since the beginning of the PCD networks, a major concern was to include patient/parent representatives. The ECFS-CTN also reports that active involvement of patient organizations was crucial for its success (21). Therefore, it was undoubtedly important to involve patient/parent representatives in the network. We feel that it is mandatory to keep patient organizations informed about ongoing trials and activities of the network, which is assured by inclusion of all patient

representative in the steering committee and three in the protocol review committee, and by regular meetings with patient representatives and through a PCD-CTN newsletter.

Partnership with pharmaceutical/industrial organizations

Although the national patient organizations support the network intellectually, little financial support will be brought in, because these organizations raise money mainly for educational tasks on a national level.

The PCD-CTN would not be financially dependent on pharmaceutical or commercial companies, but the CTN will facilitate their work and as such the CTN will need some funding and support to organize the network. We therefore decided to write the aforementioned Code of Conduct to provide guidance for our partnership with the pharmaceutical organizations. The close collaboration between PCD sites enables the CTN to provide pharmaceutical companies with an updated number of patients in the network as well as updated number of sites that meet specific study inclusion criteria. Since the PCD-CTN holds experienced PCD physicians and researchers the CTN can also assist pharmaceutical companies in building of study designs.

The PCD-CTN will also offer a variety of services to pharmaceutical companies (description and requested updated information of the different clinical sites as presented in Table 1, commentaries about study design, possibility of inclusion rate, capabilities to deliver outcome measures adhering to quality assured standardized operating procedures (SOPs)) for which a fee will be charged. The pharmaceutical companies will be assured that high standards will be maintained in all centres. The CTN is not a Contract Research Organisation (CRO) and the conduct, responsibility and sponsorship of the study remain in the hands of the pharmaceutical companies.

Structure of the PCD-CTN

For the composition of the PCD-CTN and associated structures, the reader is referred to Figure 2 and the following paragraphs.

Coordinating centre

The CTN director and the coordinating center have been appointed by the ERN-LUNG PCD Core network and will act as contact for the network, interacting with pharmaceutical/industrial organizations, patient-parents organizations, collaborators as well as potential partners. The director is in continuous contact with all sites of the CTN and is responsible for the everyday activities of the network. He or she also supervises the decisions of the distinct committees and coordinates workflows such as the protocols' review process. The CTN is co-chaired by two deputy coordinators from other member sites in two different countries within the EU, and an academic secretary at the coordinating centre.

Executive committee

The executive committee (EC) consists of the PCD-CTN director and both deputies, as well as the coordinator of the ERN-LUNG PCD Core and one additional PCD Core member. They represent three PCD trial sites from three different European countries. The EC is responsible for the development and adaption of the global strategies of the CTN and it meets 1-2 times monthly. The members of the EC are elected for three years with a possibility of re-election for another three years. Membership is limited to six years in total.

Steering committee

The steering committee (SC) is composed of one principal investigator from each PCD-CTN member site, all members of the EC, the chair of the additional committees, and all appointed patient-parents representatives. The SC meets four times a year, which for 2020/2021 was on a virtual basis due to the COVID pandemic

restrictions. The election of members to the other committees was carried out during the SC meeting, April 2021. At each SC meeting, updates are presented on all network activities, including news from the individual sub-committees. Any new policies or future action plans are drawn up beforehand. These are then discussed, if necessary, amended and agreed. A representative from partnering network is also invited to these meetings. In addition, a work and financial plan will be discussed and agreed for the upcoming year. Depending on the situation, the meetings will be held face-to-face, digital or as hybrid meetings.

Other committees

Protocol Review Committee

The protocol review committee (PRC) includes one chair among five physicians (four pulmonologists and one ENT (ear/nose/throat) physician, all with expertise in conducting clinical trials), three patient/parent representatives from three different countries the European Union and an epidemiologist. As required, additional experts are available ad hoc, e.g. pharmacologists, microbiologists or radiologists. The protocol review process includes evaluation of the study design, safety and ethical aspects, feasibility and the scientific value of the proposed study. This also includes the patient-parent perspective on the trial. Before protocol review, a contract is made between PCD-CTN and the pharmaceutical/industrial company or collaborator. The PRC writes a summary report and gives feedback about the study design with advice on potential adjustments. On the basis of this information, the EC votes whether the trial will be conducted within the network and prioritizes its level of performance in relation to other reviewed studies. The PCD-CTN director supervises the whole process and is responsible for communication between the PRC and potential collaborating partners. Depending on specific characteristics of the site, such as the

total number of patients, the number of patients with specific genetic profiles, care of adult or pediatric patients and the location, the PCD-CTN can inform individual pharmaceutical companies about the potential for participation among member sites and will be able to propose distinct trial sites as suitable for particular studies, so that interested companies can select between potential participation of sites. Until now, the PCD-CTN has been contacted by diverse companies with potential trial protocols to review.

Standardization Committee

The standardization committee is composed of one chair and five other clinical experts in PCD research, pulmonologists from six trial sites in six different European countries. This committee will establish Standard Operating Procedures (SOPs) defining and harmonizing of the diagnostic methods to assure correct and high standard PCD diagnosis at sites as well as SOPs for monitoring tools for main study outcome parameters. By using harmonized SOPs at the various trial sites for clinical trials, study outcome parameters will be less variable and more comparable which will thereby strengthen and facilitate the interpretation of the outcome data. The standardization committee will work on specific topics forming distinct sub-groups and will prepare consensus documents to create high quality SOPs.

Training Committee

This committee is responsible for keeping all participating PCD-CTN members up to date in relation to clinical research tasks. Through annual training schools, preferably alongside major scientific meetings such as ERS conference, PCD-CTN site's staff (research coordinators, study nurses and investigators) will have the opportunity to improve their knowledge and skills in the conduct of PCD related clinical research

including RCTs. Additionally, online GCP-training for the members is projected. Training schools with theoretical and practical topics are organized once a year. This committee includes four experienced physicians from four trial sites in four different European countries.

Data Safety Monitoring Board

A data safety monitoring board (DSMB) of independent experts from outside the PCD-CTN will be appointed and instructed by a subcommittee of two experts from two trial sites in two different European countries. The DSMB will work independently from the network, and will be available upon request of pharma companies.

The DSMB, an independent group of experts that advises PCD-CTN, will include

- a) two experts in PCD from two different European countries
- b) at least one statistician/epidemiologist (also member of the PRC).

The primary responsibilities of DSMB are to

- 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and
- 2) make recommendations to PCD-CTN concerning the continuation, modification, or termination of the trial.

The DSMB should review each protocol for any major concern prior to implementation. During the trial, the DSMB should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial.

Evaluation of the PCD-CTN – performance metrics

PCD-CTN will ensure ongoing reporting of performance metrics, defined as figures and data representative of the organization's actions, abilities, and overall quality to

be presented at its home page. In an annual report, among other data, will be included: the number of centres, the number of patients covered by the network, the number of projects, feasibility checks and protocol reviews for pharma companies, scientific publications, trial results, number of patients recruited to trials and the number of active and completed trials.

The strengths of the PCD-CTN

PCD-CTN has emerged from the ERN-LUNG PCD Core network and is thus strongly rooted in a well-functioning, European-wide organization with great ambitions to promote the provision of health care for patients with rare diseases. The main strength of the network is its access to >3000, clinically well-characterized adults and children with PCD, the majority of them bearing a genetic diagnosis and having a high standard of care already defined by the accreditation of the sites through membership of ERN-LUNG.

Furthermore, the close association with the ERN-LUNG International PCD Registry will ensure an ongoing registration of new patients in various studies in addition to the obvious possibility of further understanding of the longitudinal natural history of the disease, genotype-phenotype associations and possibly additional recruitment opportunities from centres not covered by the network. In addition, there is also a close interconnection between networks caring for individuals with non-CF bronchiectasis such as EMBARC or ERN-LUNG nCF-BE (non-CF bronchiectasis) as some investigators participate in the networks of both diseases. Individuals with non-CF bronchiectasis also have the possibility to register themselves in the ERN-LUNG Population Registry and thus get in contact with centres participating in the different networks assisting to find a specific diagnosis. During its set-up, the PCD-CTN has

secured inspiration and support from ECFS CTN (21) and will continue in the future to learn from their experiences, obtaining where needed advice and guidance. PCD-CTN will also work closely with the US PCD foundation (US PCDF) to strengthen the development of the overall global research effort within PCD.

The establishment of a committee for ongoing systematic evaluation of methods for diagnostics and adoption of modern outcome parameters will ensure implementation of technological advances and scientific strength in future trials.

Finally, the diverse representation of patients/and family members in the PRC provides a strong opportunity for highly relevant constructive criticism and guidance to pharmaceutical companies in the development process of the protocols.

Conclusion

With 22 trial sites from 12 European countries, the PCD-CTN provides outstanding expertise and sufficient patient numbers, including both children/adolescents and adults with PCD, for the successful conduct of clinical trials. The network has already grown since its establishment in February 2020 and is expected to grow even further.

Also centres with smaller numbers of PCD individuals ($n < 30$) already have the opportunity to enter their patients into the International PCD Registry, who are managed then under the ERN-LUNG PCD Core coordinating centre or the neighboring local ERN-LUNG PCD Core and/or PCD-CTN centre. Thus, PCD individuals supervised at smaller centres do already have the opportunity to participate in clinical or research trials.

The agreed code of conduct between all trial sites defines interaction between the network sites and with pharmaceutical companies. The established committees

assure a well-functioning process in the development of a clinical trial. Information on the PCD-CTN has been provided to potential collaborators, pharmaceutical and industrial companies and is available on request. Patient/parent representatives are both actively involved and highly supportive of this initiative and will increase the awareness of specific clinical trials and facilitate access to participation in the studies. Furthermore, protocol review will lead to improvement in the feasibility of clinical trials and established SOPs will facilitate evaluation/interpretation of study outcome parameters. For PCD, as a rare disease, this CTN builds a strong basis to implement high quality clinical research in order to identify new therapies potentially restoring ciliary function, increase evidence for already used therapies and facilitate that evidence-based targeted drug treatments progress from clinical trials to patients.

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Table 1 Details on available information from all participating centres of the PCD-CTN

Information requested	At application for membership	At yearly overall feasibility survey
Patients with PCD - overview		
Pediatric, adult, or mixed centre	x	
Number of patients currently under direct care at the centre (adults/children)	x	x
Number of patients within different age groups (0-2 years/2-6 years/6-12 years/12-18 years/>18 years)		x
Number of patients with genetically confirmed diagnosis		x
Number of patients with specific bi-allelic mutations		x
Experience		
Industry-sponsored trials (PCD or CF-related; past 5	x	x

years)		
Investigator-initiated-trials (PCD or CF-related; past 5 years)	x	x
GCP certifications	x	x
Inspection of a regulatory authority	x	x
Publications (PCD, Non-CF bronchiectasis and CF-related publications (past 5 years))	x	
Site information		
Ethic committee (local, central)	x	x
Monitoring regulations	x	x
Experience with the use of EDC (Electronic Data Capture) systems	x	x
Resources for clinical research (personnel, database, available outcome parameters, available clinical research facility)	x	
Institutional support	x	
Commitment to work within PCD-CTN (hours dedicated to work for the CTN/ month)	x	
Diagnostics and follow-up		
Frequency of outpatient visits per patient	x	x
Standard Operating Procedures for diagnostic methods and monitoring tools for patient follow up and for study outcome parameters on site	x	x
Participation in a national program for improving quality in PCD care	x	
Participation and entering patients in a Registry	x	
Recruitment strategies typically used at your centre		x
Treatment practice		
Fraction of patients with distinct medication (e.g. hydrator therapy, mucolytics, chronic antibiotic therapy, bronchodilators, inhaled corticosteroids, physiotherapy)	x	
Multidisciplinary Team (PCD/CF dedicated)	x	

Abbreviations: PCD: primary ciliary dyskinesia; CF: cystic fibrosis; CTN: clinical trial network; GCP: good clinical practice; EDC: Electronic Data Capture

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Figure 1: Map showing the participating centres of the PCD-CTN (blue pins). The PCD-CTN consists of 22 trial sites from 12 European countries including >3000 children and adults with PCD. The map was created with R (16) and RStudio (17), the packages "maps" (18), "ggplot2" (19) and "dplyr" (20) were used.

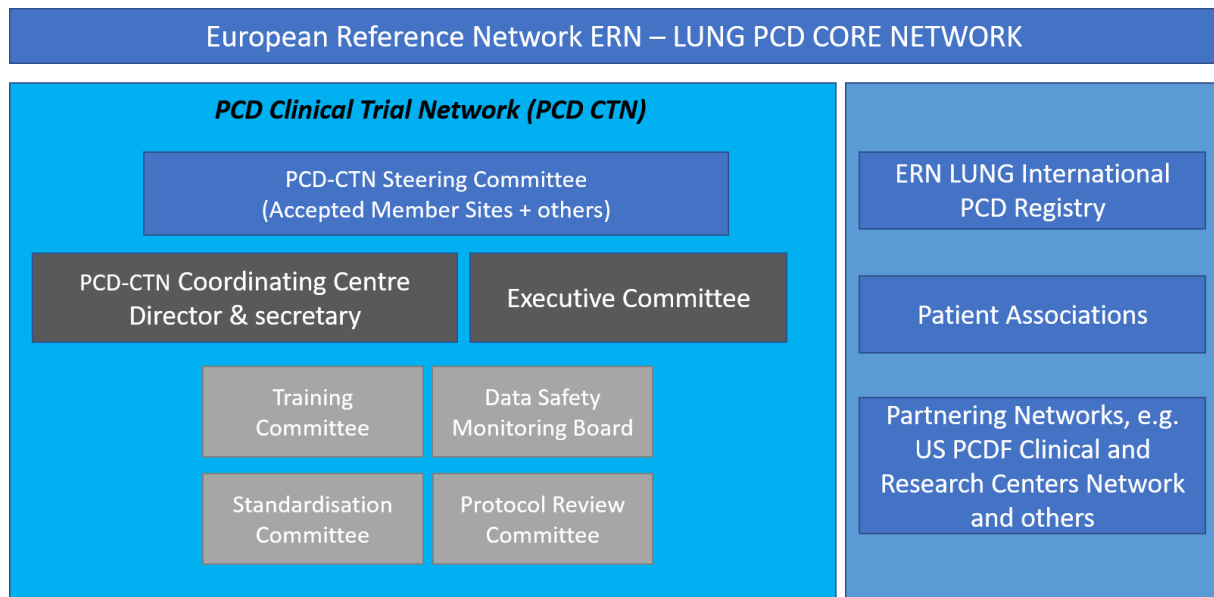


Figure 2: Organisational diagram representing the structure of the clinical trial network for primary ciliary dyskinesia (PCD): PCD-CTN. The PCD-CTN was founded under the framework of the European Respiratory Network (ERN)-LUNG PCD Core in 2020. Core structures are the steering committee (SC), the executive committee (EC) and the coordinating centre. The coordinating centre provides a director and an academic secretary. The EC includes the PCD-CTN director and both deputies, the ERN-LUNG PCD Core coordinator and one additional ERN-LUNG PCD Core member representing three different European trial sites. The SC is composed of one principal investigator from each PCD-CTN member site, all members of the EC, the chair of the additional committees, and all appointed patient-parents representatives. The PCD-CTN includes several sub committees: a committee in charge of data safety monitoring and committees for protocol review, training, and standardizations of diagnostic procedures and important outcome measures. Important cornerstones of the PCD-CTN are a strong association with the ERN-LUNG International PCD Registry, the patient organizations and partnering networks, like the US PCDF (US PCD Foundation).