European Cooperation in the field of Scientific and Technical Research
- COST -

Brussels, 14 November 2014

COST 085/14

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1407: Translational research in primary ciliary dyskinesia - bench, bedside, and population perspectives (BEAT-PCD)

Delegations will find attached the Memorandum of Understanding for COST Action BM1407 as approved by the COST Committee of Senior Officials (CSO) at its 191th meeting on 12-13 November 2014.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action BM1407
TRANSLATIONAL RESEARCH IN PRIMARY CILIARY DYSKINESIA - BENCH, BEDSIDE, AND POPULATION PERSPECTIVES (BEAT-PCD)

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4114/13 "COST Action Management" and document 4112/13 "Rules for Participation in and Implementation of COST Activities", or in any new document amending or replacing them, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to create a network of multidisciplinary researchers. The network will promote research from basic science to clinical care, with the ultimate goal to develop treatments that lead to improvements in long-term outcome of patients with PCD.

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 80 million in 2014 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Section *2. Changes to a COST Action* in the document COST 4114/13.

A. ABSTRACT AND KEYWORDS

Primary ciliary dyskinesia (PCD) is a rare genetic disease affecting approximately 1:10,000. Cilia that line the respiratory tract are dysfunctional and cannot clear mucus properly leading to progressive upper and lower airway disease, including bronchiectasis, hearing impairment and chronic sinusitis. Cilia are common structures throughout the body, so PCD may affect other organs, for example leading to situs inversus, congenital heart defects or infertility. Mutations in 30 different genes have been identified to date, accounting for approximately 60% of PCD. The clinical picture is very heterogeneous, and as for other rare diseases data on the natural course, phenotypic variability, associations with genotype, and effectiveness of treatments of PCD are scarce. Strategies to manage PCD are derived from other diseases, and are controversial. Scientists, clinicians, allied health professionals and patient representatives unite in this Action, providing a platform for communication and exchange. The Action will facilitate PCD-related research to identify mechanisms, study disease patterns and progression, define outcome measures, improve clinical management and identify high priority therapies. This Action is a platform for preclinical studies that will lead to clinical trials.

Keywords: primary ciliary dyskinesia, outcome measures, in vivo models, clinical trials, molecular therapy

B. BACKGROUND

B.1 General background

Primary ciliary dyskinesia (PCD) is a recessively inherited rare lung disease [1]. Motile cilia responsible for mucociliary clearance are dysfunctional, causing progressive chronic suppurative lung disease, serous otitis media (glue ear) and chronic rhinosinusitis[2]. Recent data suggest PCD has a progressive, severe long-term course of lower airway disease in many [2;3]. Male infertility is common since sperm flagella have a similar ultrastructure to cilia; the incidence of female infertility and of ectopic pregnancy are less clear but can be explained by immotile fallopian tube cilia. Motile embryonic nodal cilia establish left-right asymmetry and nearly half of PCD patients exhibit *situs inversus*[4], and 12% heterotaxic syndromes associated with complex congenital cardiac defects[4;5]. More complex disease occasionally occurs in association with non-motile ciliopathic syndromes[6] for example, the X-linked *RPGR* mutations where some males are affected with both

PCD and retinal degenerative disease[7;8]. Classically PCD symptoms are present from infancy, but diagnosis is often delayed until late adulthood, or even totally missed[9]. PCD is characterised by genetic heterogeneity (more than 30 defects) with unique clinical, diagnostic as well as molecular features. However, data is lacking on phenotypic variability, genetic and environmental determinants of severity, or long-term prognosis.

Rare diseases are a major focus of EU health policy; the International Rare Diseases Research Consortium Initiative aims to develop 200 new treatments by 2020. Reported prevalence of PCD varies across Europe reflecting true variability as well as differences in access to diagnostic facilities [9]. Prevalence is estimated 1:2,000 - 1:40,000, with true prevalence probably 1:10,000 or higher[9;10]. This reflects a significant disease burden, causing progressive disease in 74,000 Europeans. 25% of adult PCD patients in USA exhibit severe lung disease requiring long term oxygen or lung transplantation[2] highlighting the need for treatments to limit disease progression. Improving the trajectory of respiratory impairment would have positive implications for health care expenditure and associated benefits to individuals, carers and society. As for other rare diseases the evidence base for PCD is sparse and there has been little clinical or translational research, with treatment strategies inappropriately extrapolated from other diseases[1;11] e.g. treatments for lung disease are derived from cystic fibrosis (CF) guidelines despite different pathophysiology. Similarly management of glue ear and hearing loss in PCD is controversial[10].

Previous research collaborations on PCD: In recent years several international initiatives have stimulated PCD research; however, the risks of continued parallel streams are duplication and loss of opportunities to build collaborations. Significant advances in understanding the genetic mutations, downstream ultrastructural defects and cellular dysfunctions in PCD can now promote targeted, collaborative research. Therapeutic innovations for other diseases can be investigated for translation to PCD e.g. small molecule therapies in CF. Research into other ciliopathies can inform directions for PCD. Two recent network European Respiratory Society (ERS) task forces and two FP7 grants were particularly fruitful. This COST Action will unite participants from all these projects under one umbrella and build on their successes:

1. A clinical ERS taskforce (ERS TF 2007-9) united paediatric pulmonologists for basic epidemiological studies [9;12] and developed a consensus diagnosis & management statement[1]. Key findings included lack of evidence based treatment[1] and disparity in diagnosis and treatment across Europe [9;12].

2. Subsequent advances in diagnostics underpinned the development of a new ERS task force (ERS TF 2014-16), to develop evidence based guidelines for the diagnosis of PCD.

3. SYSCILIA (2010-15), FP7 grant, is a basic science project devoted to ciliary disorders using a systems biology approach to dissect cilia function on the molecular and macromolecular level. Main focus is on non-motile primary cilia rather than motile cilia of PCD.

4. BESTCILIA (2012-15), FP7 project, united paediatricians to set up a European PCD registry, to identify and analyse existing patient datasets, improve diagnostics and perform a first clinical trial.

Additionally, experts researching the syndromic forms of cilia related diseases which are occasionally associated with PCD have convened two international meetings under the auspices of Ciliopathy Alliance. A number of national networks exist in COST (eg. Italy, UK, France, Israel) and non-COST countries (North America)

This COST Action takes these efforts forward whilst avoiding the risk of duplication. BESTCILIA developed resources, a meta-cohort of existing datasets and a European registry, but with little time to exploit them. COST gives a window of opportunity to analyse the datasets assembled in BESTCILIA to answer pertinent epidemiological and clinical questions. It will provide an opportunity for researchers from SYSCILIA, BESTCILIA, ERS TF and national networks to integrate their efforts providing a comprehensive platform for cross-discipline collaboration, whilst encouraging new recruitment of additional experts into the field.

Why COST Action? COST Action is the appropriate mechanism to develop research for treatments for PCD because it facilitates networking of clinicians, basic and clinical researchers from a variety of disciplines and patient organisations in a non-competitive collaboration. The complexity of this heterogenous disease (over 30 genes), with associated variability of diagnostic, clinical and therapeutic possibilities requires exchange between research groups and collaborations. The Action compliments and builds on, but does not duplicate work within other collaborations. Through exchange of ideas, techniques, materials and people the Action will identify and address gaps in knowledge, resources and expertise. COST Action will develop an innovative training program for Early Stage Researchers (ESR) which, with the Action's network of experts, consensus guidelines, standardised protocols and infrastructure, will underpin funding opportunities for a global translational research program of PCD led by European researchers. As a first step, >50 leading experts in PCD (including adult and paediatric pulmonologists, ENT physicians, epidemiologists, social scientists, basic scientists) from >14 European countries met in September 2013 to design a conceptual framework for future joint research on PCD across the life course. SYSCILIA, ERS TFs and BESTCILIA partners worked with others to develop the proposal, ensuring the COST Management Committee has the experience and motivation to drive further innovations. The

advantages of this coordinated approach include an accelerated translational research programme for PCD with avoidance of unnecessary replication, and the optimal use of limited resources. It will thereby enhance scientific and translational output.

B.2 Current state of knowledge

PCD is a multisystem disease. While data on lower airway disease is growing, information from other body systems such as ENT manifestations, fertility and cardiac complications is derived mainly from case reports, and even basic information on incidence is lacking. Most manuscripts focusing on PCD have been written by paediatric pulmonologists. Recent advances in knowledge have been obtained through separate collaborations of clinicians on the one hand, and scientists on the other hand. To maintain momentum and build on recent successes, the time is right for a network bringing clinicians and scientists together. **This Action will provide a highly innovative environment by developing a network of experts from multidisciplinary clinical specialties (e.g. paediatric & adult pulmonology, ENT, physiotherapy, fertility) motivated for collaborative research with scientists from diverse backgrounds (e.g. genetics, imaging, cell biology, microbiology, bioinformatics).**

Basic science: Cilia are critical to many biological processes determining normal human development and physiology. Dysfunction of *immotile* cilia cause ciliopathic syndromes[14] whilst genetic defects of *motile* cilia, and structurally related sperm flagella, cause PCD[10]. It is understood how ciliary defects lead to various features of PCD (airways disease, infertility, situs inversus), but questions remain: e.g. links between abnormal left-right patterning and congenital heart disease (CHD)[15] are not fully understood, nor is the spectrum of sperm dysmotility and incidence of male infertility. **This Action will provide networking for scientists and clinicians to coordinate research to understand PCD clinical phenotypes.**

Motile respiratory cilia are hair-like microtubular structures extending from the cell surface. They have a highly conserved ultrastructure including microtubules, dynein arm motors, nexin links, and radial spokes, essential for normal beating; defects in structure result in PCD. Cilia contain >650 proteins, and mutations in 30 genes have been identified to date to cause PCD, accounting for approximately 60% of cases[16-21]. Genes encoding components of the outer dynein arms (e.g. *DNAH5* [22], *DNAI1* [23]) or other structures, and dynein assembly and transport proteins have been associated with PCD. The genetic heterogeneity underlying PCD makes new next generation sequencing approaches attractive for gene discovery research and clinical diagnosis[20]. Recent

expansion of knowledge of PCD mutations has led to the possibility of small molecular therapies aimed at the underlying basic defect eg. Ataluren for premature stop codons. **This Action will promote research to characterise new mutations and guide diagnostics and therapies by sharing knowledge, models and patient samples.**

Model systems provide an essential molecular genetic tool set to investigate basic mechanisms and to test novel PCD treatments. In vitro models of genotype-specific human ciliated epithelium, using cells cultured submerged or at an air liquid interface [24-26], provide potentially powerful tool for preclinical PCD research. In vivo PCD models have been developed in several organisms. Ependymal cilia dysmotility causes lethal hydrocephalus in most mouse PCD models [27;28]; only *Dnah11*[29] germline mutants are fully viable. Conditional deletion of *Dnaic1* in adults overcomes the problem of hydrocephalus[30] but it cannot model PCD cilia dysfunction from early life. Mouse models exhibit upper but not lower airway pathology, the reasons for which remains unclear. Modelling cilia dysmotility in lower organisms, e.g. the unicellular Chlamydomonas has greatly facilitated our fundamental understanding of ciliary motility. Zebrafish are another powerful vertebrate genetic model to study ciliary dysmotility. **This Action will identify and characterize strengths and deficiencies of the existing PCD tools and provide the infrastructure for creating new models to fill gaps by sharing expertise, cells and models.**

Gene therapy for PCD requires delivery of the affected genetic material to the ciliated epithelial cells lining the airways. Using a lentiviral vector, Chhin et al[31]established proof-of-principle that gene therapy could correct ciliary motility in cultured airway epithelial cells of a patient with *DNAI1* mutations. Challenges to achieving PCD gene therapy are similar to CF gene therapy which has been through several trials without achieving clinical efficacy, although PCD may have some advantages. e.g. the affected cells in PCD line the surface of airway epithelium while *CFTR* is most highly expressed in cells lining less accessible submucosal glands. CF research has suffered from a lack of direct assays for phenotype correction whereas for PCD there are direct readouts, e.g. ciliary beat function. Many challenges and questions for PCD gene therapy exist. Firstly the variety of underlying genetic causes. While lentiviral vectors were effective in proof of principle studies[31;32], gene therapy for PCD will most likely require life-long repeated delivery at regular intervals as corrected cells die off and so immunogenic viral vectors may become less effective over time. Moreover, genes such as *DNAH5* (13.5kbp) are too large for viral vectors thus nanoparticle vectors may be preferable for gene therapy. Further research into safe and efficient airway gene transfer modalities is urgently required. More recently, gene editing technologies (e.g., CRISPR/Cas9, TALENs), in which the mutation of the affected gene is repaired have been developed[33]. At present their efficiency of gene repair is too low but this technology may offer exciting future possibilities

for PCD. **This Action will provide the infrastructure for researchers from different disciplines to coordinate activity towards a research programme in gene therapy for PCD, and other novel therapies.**

Current knowledge about airway infection in PCD mostly relies on small observational studies[34;35] using standard microbiology techniques which do not detect 90% bacterial species[36]. Combined pyrosequencing and quantitative PCR in PCD identified bacterial species belonging to 128 genera,[37] including taxa requiring specific *ex vivo* growth conditions. Such new generation molecular approaches find positive relationships between *P. aeruginosa* relative abundance and age and a negative relationship between *P. aeruginosa* abundance and lung function[37]. Longitudinal progression of the microbiome, interactions between upper and lower airway communities and interactions between viruses, fungi and bacteria[38] requires investigation. Factors pre-disposing PCD patients to infection also remain poorly understood. These may include impaired mucociliary clearance, but factors such as the low airway NO levels that characterise PCD[39], environmental exposures such as air pollution or tobacco smoke and nutrition might also be important[40;41]. **This Action will coordinate investigation of factors predisposing patients to progressive airway infection, and interactions between bacteria, host and environment.**

Epidemiology: As for other rare diseases, most epidemiological and clinical data on PCD come from case series or small clinical datasets. A systematic literature search found 50 publications with clinical information (Goutaki, 2014; in preparation). However, data quality was often poor, results were not age-stratified and populations were highly selected from specialised clinics. Only a few studies describe longitudinal data, such as changes of lung function or growth over time[3;42]. While early reports from paediatric patients suggested a relative benign course, data from adults demonstrates severe lung disease with chronic Pseudomonas infection and respiratory failure in a large proportion of patients [2]. We do not know how long-term prognosis is influenced by a timely diagnosis and appropriate management.

BESTCILIA made huge efforts in assembling standardised representative datasets from large numbers of patients, merging retrospective datasets from >2000 PCD patients into a meta-cohort. Data have been analysed for two abstracts (Goutaki & Maurer ERS Congress 2014), demonstrating the feasibility of using this international dataset, which now needs to be exploited. BESTCILIA additionally set up a prospective European registry for longitudinal data. Duration of BESTCILIA (three years), while enough to develop these resources, does not allow us to exploit them. **This Action will make use of the existing retrospective and prospective BESTCILIA datasets, propagate the BESTCILIA European registry and widen the network of clinicians to include**

more adult patients. It will contribute to standardised collection of clinical data by developing follow-up proformas for clinics. The datasets will be made available to the scientific community to answer fundamental questions on phenotypic spectrum, severity and age-related aspects of PCD.

Clinical Care: There is no evidence based treatment for PCD and management therefore aims at improving mucus clearance (physiotherapy techniques) and treating infections, to prevent chronic lung damage[1]. Three small randomised trials of commonly used respiratory drugs have occurred in PCD with negative or inconclusive results [43-45], and management is therefore based on expert opinion. [1;6] Consensus guidelines for the management of PCD in children were developed >6 years ago by an ERS PCD TF, but the evidence base at the time was poor [1]. It is therefore not surprising that management strategies for PCD vary widely between and within countries in Europe [12]. A number of advances have occurred since 2009 that will provide evidence for new guidelines. The number of specialist centres [21;46] managing patients and collecting observational data (including BESTCILIA partners) has increased; this will help identify management strategies associated with good outcomes. Introduction of new models of care (e.g. transition to adult services, expanded use of the multidisciplinary team [46;47]) have also occurred in the past 6 years and need to be considered in new guidelines. Importantly a randomised controlled trial RCT (BESTCILIA) to investigate use of azithromycin as prophylaxis to for infective respiratory exacerbations will be completed in 2015; lessons from this RCT will inform future guidelines and also future clinical studies. Newly available treatments to overcome the genetic defects underpinning CF[48] provide evidence for clinically effective small-molecule therapy in orphan diseases. **This Action will develop updated guidelines for the management of PCD which will include evidence from allied health professionals who are now central to PCD care. The Action will coordinate the activity required to identify potential novel therapies for clinical trials.**

Clinical Trials: A prerequisite of clinical trials are robust outcome measures. Spirometry remains the first line for monitoring lung function in most clinical settings, but is insensitive to detect peripheral lung disease, a common feature of PCD. In fact, significant progression of lung disease identified by high resolution computed tomography (HRCT) can occur whilst spirometric values remain stable[49]. Although HRCT is a useful staging test, it is not appropriate for repeat measurements. Multiple breath washout, with the lung clearance index (LCI) as outcome measure for peripheral airway disease, appears more sensitive than spirometry and correlates well with HRCT[50;51]. It is possible to test LCI in young children who cannot perform a reliable spirometry;

and thus in many centres it is done at each clinic visit. The role of LCI and other physiological measures as compared to conventional lung function parameters will be evaluated for clinical PCD trials[52]. Within FP7-BESTCILIA, age-specific patient reported outcome measures (QOL-PCD) have been developed and are currently undergoing validation. **This Action will evaluate the outcome measures to monitor patients in the clinical routine and in clinical trials and will develop guidelines.**

B.3 Reasons for the Action

The Action will build on research which has occurred within very successful but individual groups (particularly ERS TF, BESTCILIA and SYSCILIA); although there are collaborations within these groups, there is little exchange between basic scientists and clinical researchers. As these collaborations come to an end, the time is right to come together in this Action. Importantly the PCD research community has gaps in expertise that need filling by researchers from other backgrounds e.g. basic scientists can undoubtedly learn from the experiences of researchers of gene therapy and will require the support of bioinformatics, and clinical researchers need input from respiratory physiologists to identify outcome measures and from researchers with expertise in clinical trials. PCD patient organisations will be stakeholders in all stages of the Action. Thus the Action will lead to scientific advance, providing a platform to improve treatment of PCD whilst maintaining a patient-centred approach. Its eventual aim is to reduce the morbidity and mortality of patients and thereby the burden of healthcare costs and societal consequences of this chronic multisystem disease. The benefits of this Action include clinicians and scientists collaborating to deliver:

1. The basic science to underpin preclinical research, including infrastructure to share and develop models and knowledge of molecular mechanisms.

2. Preclinical data and infrastructure to support the first Europe-wide translational research agenda on PCD: providing bench, bedside and population perspectives.

3. Guidelines for conduct and protocols of clinical trials e.g. regarding outcome measures.

4. Consensus guidelines for age appropriate care, including respiratory, ENT & fertility management that spans paediatric, transition and adult care, in different healthcare settings.

5. Training of ESRs through Training Schools and Short-Term Scientific Missions (STSMs) ensuring sustainability and development in the field of PCD research. In

addition STSMs will provide opportunities for experts to visit institutions to provide specialist training and standardisation across sites.

B.4 Complementarity with other research programmes

The Action brings together PCD researchers, basic scientists and clinicians providing the opportunity for continued advances and exploitation of collected datasets beyond the end of BESTCILIA, ERS TF and SYSCILIA (see B1) activities. For example, BESTCILIA partners have assembled existing clinical datasets, and developed a registry of PCD patients. BESTCILIA finishes in 2015, and the COST Action will ensure that the investment to develop the registry and conduct feasibility studies will be exploited in continuing European research networks. SYSCILIA will also finish in 2015 and the large-scale protein-protein interaction data sets, genetic analyses, as well as cell model systems generated by SYSCILIA can be exploited to reach the Action's goals. Based on the basic biology findings produced by SYSCILIA novel diagnostic as well as therapeutic strategies will be generated. The ERS TF is focussing on PCD diagnostics and will be complimentary to the aims of this Action to improve treatment and management. Additionally the Action will link with scientists in the international Ciliopathy Alliance http://www.ciliopathyalliance.org to learn from their experience of non-motile ciliopathies; not only will this provide opportunities to consider the associations between PCD and the syndromic ciliopathies caused by defects of non-motile cilia, but also to learn from their research of molecular therapies. Further details of collaborations are detailed in section E3.1. This COST Action will participate in the organization of key meetings (e.g. ERS Congress, Gordon Research Conferences: Cilia, Mucus and MC interactions, ERS PCD Diagnostic Task Force) allowing coordination of joint research workshops and meetings.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of the Action is to create a global Europe-led network of multidisciplinary primary ciliary dyskinesia (PCD) clinicians and researchers. The network will promote research from basic science to clinical care, with the ultimate goal to develop treatments that lead to measurable improvements in long-term outcome of patients with PCD.

C.2 Objectives

In general, the objective of the COST Action is to strengthen the infrastructure for research on PCD:

1. Building on and unifying the expert networks of researchers in PCD.

2. Providing targeted training for ESRs in Training Schools and on Short-Term Scientific Missions, in the clinical and basic science aspects of PCD.

3. Building on standardized prospective data collection, developing infrasructure for data and sample sharing.

Specifically the COST Action has 4 overarching scientific objectives:

1. Promote and integrate basic research on PCD to underpin translational research with the ultimate aim to develop novel therapies

2. Provide representative data on the epidemiology of PCD e.g. long-term prognosis and how the latter is influenced by environmental exposures and different management strategies

3. Improve clinical care for patients with PCD.

4. Improve the evidence base for treatment of PCD, by planning the conduct of clinical trials.

C.3 How networking within the Action will yield the objectives?

The Action will achieve its objectives by supporting networking of leading groups with research interests in PCD. The Action serves as a facilitative platform where researchers can talk about and coordinate sharing data and material. In addition the Action will seek collaboration with industry and with researchers not primarily engaged in PCD but with skills critical for the success of the Action e.g. clinical trials, gene therapy. Representatives from patient organisations will be included in all aspects of the Action. The means for achieving these objectives through networking include:

1. An inaugural conference sharing the state-of-the art from basic science and clinical perspectives, to identify knowledge gaps that require prioritisation to drive the Action agenda (one inaugural conference).

2. Annual conferences bringing together four Working Groups (WGs) with patient organisations, industry, targeted researchers from other disciplines and other interested individuals.

3. Workshops for WG (two each year) to provide a focus for the WG's tasks whilst allowing opportunities for innovation.

4. Short Term Scientific Missions (STSMs) to transfer expert ideas, skills and knowledge between institutions and to support mobility and career progression of early-stage researchers (at least 20).

5. Cross-disciplinary Training Schools to promote education of early career researchers and clinicians (at least 4).

6. Identification of research funding opportunities and establish contacts with national and European policy makers to promote the need for funds from governmental and non–governmental sources for collaborative research in the field of PCD.

7. Sharing of patient registries, databases, SOPs, in vivo/ ex vivo models and patient samples, underpinned by regulatory approvals and agreements between participants for sharing.

C.4 Potential impact of the Action

The COST Action is the first network of scientists, clinicians and patient representatives to push the European research agenda for development of new treatments specifically for patients with PCD. There are a number of research groups in Europe which are independently generating high quality data. The time is now right to coordinate these efforts to accelerate and streamline the research agenda. The ultimate **impact on patients** is our measure of success for this Action and to reflect this patient representatives will be invited to participate in all aspects of the Action. The expected **scientific impacts** are:

- A Europe-wide research network positioned to obtain platform grants for treatments for PCD.

- Accelerated understanding of the underlying genetics and pathophysiological mechanisms, to facilitate identification of potential target therapies for clinical trials.

- Sharing of *in vivo* and *ex vivo* models for pre-clinical studies of novel therapies.

- Further development of the BESTCILIA registry and longitudinal database. This will result in Europe-wide tools to provide knowledge of the natural history of PCD across Europe.

- Guidelines for outcome measures for monitoring patients in clinical trials and longitudinal epidemiological studies.

- A highly motivated and well trained cohort of early career researchers with excellent understanding of basic science and clinical aspects of PCD research. Having trained together from an early stage it is anticipated that scientists and clinicians will have excellent appreciation of the strengths and limitations of each other's research, and be positioned to continue moving research in PCD forward.

The Action will impact at an operational level, boosting European competitiveness and innovative capacity to address global health issues for PCD patients. The anticipated **operational impacts** are:

- A stable, highly multi-disciplinary network of PCD researchers across Europe. The network will have a scientific base with an expert knowledge on basic and translational interdisciplinary research in PCD. It is likely to attract skilled researchers from associated backgrounds.

- Enhanced funding opportunities for collaborative research and translation, as a consequence of evidence of collaborative working, publishing jointly and sharing resources.

Along with other rare diseases, PCD produces a significant healthcare and economic burden because of delayed diagnosis, poor management and no disease-specific treatment options. This is particularly evident for countries with low expenditure on health[12]. The consequences of

suboptimal management of chest and hearing in patients with PCD include poor educational achievement, days off work/ unemployment, expensive ineffective treatments and ultimately accelerated decline in lung function leading to expensive respiratory support and/ or lung transplantation in 25% of patients[2]. The anticipated **societal/ public health impacts** of the Action are:

- Identification of current good practice which can be rapidly rolled out across Europe (evidence based consensus report)
- Consideration of models of diagnosis and care for both high- and low-income European countries.
- The data required for a health economic evaluation.
- Research infrastructure for new treatments and improved management to improve disease severity, quality of life, educational attainment and contribution to the economic community in the workplace.
- Reduced numbers of patients requiring long-term respiratory support and lung transplantation.

C.5 Target groups/end users

The principal end users to benefit from this Action are **patients** with PCD and their carers. Representatives of PCD **patient organisations** across Europe have been involved in the preparation of the proposal and will be invited to speak at the inaugural conferences and subsequent meetings and to participate in dissemination. Another important group of stakeholders are the **scientists and clinicians**. Basic and translational scientists working on PCD (epidemiology, models, physiology, genetics, infection & immunology, cell biology, imaging, bioinformatics) and clinical scientists concerned with diagnosis and treatment of PCD patients (paediatricians, adult chest physicians, ENT, fertility, physiotherapists, nurse specialists) all of whom were involved in the preparation of the proposal. Participants in the Action have contacts with key strategic partners in **industry** thereby ensuring rapid implementation of promising results for further development. **National and EU policy makers** will be interested in the guidelines and research developments in new therapies

which will feed into healthcare provision for patients with PCD. The wider **rare diseases** network can build on experiences from this Action, with direct impact on the care of patients.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The Action's scientific programme has been developed to achieve the objectives and deliver the benefits outlined in section C. Specific tasks to meet these objectives will be coordinated through four highly integrated Working Groups (WG), whose work will be channelled by a programme of conferences, workshops, Training Schools and STSMs. Collaborations between WGs will provide a truly innovative environment for this scientific programme. The Action will remain flexible to enable the implementation of new ideas and perspectives not foreseen during the planning stage, and to enable inclusion of scientists who did not participate in the planning stages. The WGs will concentrate on the following tasks:

WG1 Basic science unites scientists to identify the infrastructure and data required to develop novel treatments for PCD. They will: a) develop data for an open website of known human mutations; b) identify and validate existing models of PCD, including cell culture & animal models; c) identify new models to test genotype specific therapies; c) build the infrastructure with which cells, tissues & tools for studies *in vitro* (cell based systems) and *in vivo* (murine and non-vertebrate models) can be exchanged; d) collaborate on preclinical treatment studies, and develop protocols and SOPs; e) advance the understanding of pathogens in PCD; f) identify imaging techniques that may be translated into clinical practice e.g. for diagnostics or patient monitoring.

WG2 Epidemiology will a) use the meeting platform to identify datasets and additional data providers, and design joint analyses; b) include existing datasets into the meta-cohort developed in the framework of BESTICILIA; c) actively recruit adult physicians and study relevant topics (severe lung disease, ENT, fertility treatments); d) develop standardized forms for prospective multicentre data collection; e) perform data meta-analyses to describe changes in PCD phenotype and severity over the life course, understand patterns of disease progression, identify environmental influences and interaction with genetics, develop prognostic prediction tools and describe the effectiveness of different management strategies using observational data.

WG3 Clinical care will: a) undertake an international survey of paediatric & adult physicians and allied health professionals (e.g physiotherapists) to assess current practices including respiratory, ENT and fertility; b) identify areas of clinical practice associated with good outcome (with WG2);

c) identify needs associated with transition from paediatric to adult care by survey/ focus groups with patients and physician and compare young adults who have gone through a formal transition program with peers who have not; d) identify priority areas for research on therapeutic drugs (e.g. mucolytic agents, decongestants, mucociliary clearance), including novel treatments.

WG4: Clinical trials will a) identify relevant outcome measures for clinical trials in children and adults (physiological/lung function measures that are sensitive and responsive to disease progression and therapeutic interventions); radiologically assess lung disease progression, and compare validated PROs (from BESTCILIA) to physiological measurements); b) draw on the expertise gained from the randomised clinical trial in PCD in BESTCILIA; c) plan, set up and coordinate observational and interventional multicentre trials in PCD, and investigate the effectiveness of known therapies and of novel agents in humans.

WGs will work together, bringing their respective expertise on shared tasks. For example, WG2 will identify treatments in common use (e.g. mucolytics, nasal spray) from longitudinal datasets, WG3 will provide the patient and clinician perspectives on these treatments and WG4 will design the clinical trials to test the therapies of interest.

D.2 Scientific work plan methods and means

COST Action WG1-4 will share expertise and collaborate on the research tasks needed to meet the corresponding objectives (sections C and D). WGs will be coordinated by a WG lead who will be a member of the Scientific Steering Group, ensuring that WGs are updated on each other's work, thus facilitating inter-WG collaborative opportunities. WGs will meet throughout the COST Action with additional meetings by teleconference as required. Joint meetings between WGs will be encouraged where appropriate. Meetings will be open to participants who join the Action. ESRs will participate in all aspects of WG tasks.

WG1: Basic Science: will allow a two way dialogue between basic and clinical scientists (1) to identify the basic science gaps (2) with the clinical community to prioritise scientific research and (3) to coordinate optimal use of samples. This work group will thereby inform future directions of basic research aimed towards the development of therapy. WG activities will include:

1. Gathering the data for and planning of an open "one stop" database, where PCD relevant data can be shared and accessed e.g. known pathogenic human mutations, data from animal models (Chlamydomonas, Zebra fish and mouse), associated phenotypic data where available and non-pathogenic SNP data.

2. Evaluation of pre-clinical models that are required for different approaches, e.g. for stop codon read through drugs such as Ataluren, gene therapy approaches and palliative therapies. Assess how existing models address the current and proposed needs, identifying gaps.

3. Developing infrastructure for sharing of cells, tissues, reagents and tools.

4. Coordination of research to understand of the microbiology of upper and lower airway that may contribute to development of bronchiectasis e.g. microbiome contributing to persistent infection or biofilm formation, factors pre-disposing PCD patients to infection (e.g. low NO levels).

5. Evaluation of imaging tools for PCD diagnostics or research E.g. *in vivo* mucociliary clearance by radiolabel tracking; standardizing high speed video analysis of beat pattern for diagnostic and models systems; developments of high resolution CT image analysis to assess early changes and disease progression; 3D histological-resolution (i.e. ~ 0.1-10 μm) of lung structure in model systems or as disease surrogates (e.g. non-destructive 3D imaging of upper airways in mouse) by phase contrast μCT.

Expected outcomes from WG 1 include:

- Identification of genetic data sets and understanding of how they should be shared. A best practice statement on how to share the data with the clinical and scientific communities.

- State-of-the-art manuscript describing current pre-clinical models. Mechanisms for sharing these models.

- Register of key PCD research reagents and mechanisms for reassessing this list. A mechanism for the open sharing of PCD research reagents for researchers to sign up to.

- State-of-the-art manuscript regarding the microbiology of PCD including both conventional and molecular microbiology.

- Improved use of imaging in patients and model systems to: provide functional readouts of disease state, improve early markers of disease progression and localise target

structures and molecules in specific mutation contributing to basic cell biology of disease.

WG2 Epidemiology: aims to make use of all existing datasets on PCD patients to gain essential knowledge on the clinical presentation and natural history of PCD and on factors influencing the disease course. This is essential for planning intervention studies. The WP will also facilitate standardised prospective data collection in the future. WG activities:

1. Identify existing clinical and epidemiological datasets from PCD patients. This includes using the meta-datasets collected in BESTCILIA (observational datasets and European registry), as well as identifying additional data from national and regional registries and clinical studies. Efforts will be made to include relevant numbers of adult patients.

2. Standardise and pool these datasets in meta-cohorts, which contain information on large numbers of patients with well-defined data. Establish the approvals and agreements needed for international sharing of the data. Identify how the datasets can be optimally used by the scientific community.

3. Assemble clinicians and scientists interested in the natural history of PCD, taking care to invite specialists hitherto underrepresented in PCD research, such as adult chest physicians, ENT doctors, cardiologists and fertility specialists for prospective multicentre data collection.

4. Perform data meta-analyses e.g. changes of phenotype and severity over the life course and understand patterns of disease progression; effects of environmental influences (such as active or passive smoking or air pollution) and nutrition (.e.g. antioxidants) on PCD and gene-environment interactions; the effectiveness of different management strategies on defined outcomes, using observational data.

Expected outcomes from WG2 include

- Large standardised patient datasets (meta-cohorts), which can be used to answer questions on the epidemiology of PCD, and to generate hypotheses which can then be studied prospectively.

- A standardised procedure and regulations for use of these datasets by the scientific community;

- Forms for standardised collection of clinical information in follow-up appointments.

- A series of scientific publications, based on large and representative study populations, which describe: clinical presentation and long-term prognosis of PCD, such as body growth, lung function growth and decline, development of chronic lung disease and respiratory insufficiency; ENT pathologies and course of hearing loss over time; incidence and severity of fertility problems in males and females; time course of bacterial colonisation; evidence for the existence of distinct phenotypes of PCD with relevance for treatment and long-term outcomes.

- Development of prognostic tools, allowing prediction of short- and long-term outcomes in affected patients. Care will be taken to employ up-to date methods for developing such tools, and to design them for easy use in clinical practice.

WG3 Clinical care

This WG aims to identify areas of good practice to develop guidelines and protocols which can be used to improve patient management. The findings of the WG will be used to inform about which treatments to test in clinical trials. The WG will include a multidisciplinary grouping of adult and paediatric chest physicians, ENT, fertility clinicians, specialist nurses and physiotherapists. WG activities will include:

1. A systematic review of published data regarding treatment and management of adults and children with PCD (chest, ENT, fertility etc.). The review (s) will include pharmaceutical treatments (e.g. mucolytics), non-pharmaceutical treatments (e.g. airway clearance techniques, hearing aids) and surgical interventions (e.g. fertility interventions and ventilation tubes/ grommets). It will also assess the evidence base regarding models of delivery of care in different health care settings, and at different stages of life (e.g. transition to adult care, management of respiratory failure, end of life);

2. Undertake an international survey of paediatric and adult physicians to assess current practices including management of respiratory, ENT and fertility, and models of

delivery of care. Where possible, the data will be linked to WP2 analyses to identify practices associated with good clinical outcomes;

3. Identify outcome measures for monitoring patients in clinical settings with WG 2&4 (chest/ upper airway microbiology, audiology, lung function measurements, health related quality of life). WG2 will evaluate retrospective data on different outcome measures; WG4 will focus on outcome measures for clinical trials, whilst WG3 will identify measurements that are appropriate for monitoring patients throughout life in the clinic;

4. Identify priority areas for research on therapeutic drugs (e.g. mucolytic agents, decongestants, mucociliary clearance), and non-pharmaceutical management e.g. airway clearance and exercise.

Expected outcomes from the WG3 include:

- Identification of treatments and management that appear to be associated with good clinical outcome, leading to a consensus/ evidence based statement for management of adults and children with PCD.

- Identification of aspects of delivery of care (e.g. care models, transition) associated with good clinical outcome, leading to a consensus/ evidence based statement for delivery of care.

- Identification of outcome measure for monitoring adults and children longitudinally (chest, hearing etc.), leading to a consensus/ evidence based statement (with WP4).

WG4 Clinical Trials: aims to improve current knowledge on treatment options and outcome parameters to optimally plan future clinical trials. This will be done by analysing data from a) the very few existing or ongoing clinical trials (BESTCILIA); b) mostly single-centre observational studies; c) large epidemiological datasets together with WG2 and d) newly identified treatment strategies and outcome parameters together with WG3. Participants will be a multidisciplinary group of clinicians, physiologists and biostatisticians.
WG activities will include:

1. A systematic review of published studies regarding all kinds of interventional trials in adults and children with PCD (such as observational studies or RCTs). The review will include all studies that help to assess the effect of an intervention on disease course or the ability of different outcome parameters to monitor the effect of those interventions.

2. Together with WG3 identify therapeutic possibilities and outcome measures for clinical trials.

3. Together with WG2 identify subgroups of PCD patients ("phenotypes"), which may be suited differently to therapeutic options. These subgroups will be based on e.g. genetics, clinical presentation, disease course and functional measures. Based on the pathophysiological background of PCD and comparable to other diseases with heterogeneous clinical pictures it is assumed that different therapies work differently in those subgroups.

4. Characterize new outcome parameters that are suited as endpoints for future clinical trials and identify the usefulness of those parameters. Possible new outcome parameters include clinical markers (e.g. cough frequency or daily amount of nasal secretions), new lung function outcomes (e.g. electrical impedance tomography, EIT), new imaging techniques (e.g. 19F 3D ultra-short echo time MR imaging), patient reported outcomes (e.g. QOL-PCD being validated in BESTCILIA) or microbiological outcomes (e.g. longitudinal changes in the diversity of the microbiome).

5. Identify challenges or difficulties in existing studies. This includes e.g. the use of insensitive outcome parameters or inappropriate sample size or statistical methods.

6. Apply all of the results above to the planning of future clinical trials.

The expected outcomes from the WG include:

- Identification of therapeutic options and outcome measure best suited to serve as endpoints for clinical trials (with WP3).

- Identification of PCD phenotypes that need to be considered differently in clinical trials. This is only possible using very large epidemiological datasets together with WP2.

- Identification of PCD-specific challenges in existing clinical trials.

- Outline(s) for future clinical trials. This evidence-based outline will then help to raise new funds to implement those trials.

E. ORGANISATION

E.1 Coordination and organisation

The Action will be carried out according to "Rules and Procedures for Implementing COST Actions". The COST Action will be coordinated by a Management Committee (**MC**). The MC will elect the Action Chair, Vice-Chair and task coordinators at their first meeting which will be held at the start of the Action. The Task Coordinators will include a coordinator for the Scientific Steering Group (**SG**), a Dissemination Coordinator (**DC**), a STSM and Training School Coordinator (**TSC**). The **MC** will formally lead the COST Action, defining and managing the Action strategy. It will coordinate scientific and financial activities within the Action and will maintain contact with COST Coordinators and Office. The MC will meet annually to review the strategy of the Action in light of developments and progress. It will set new objectives according to developments of WGs. The MC will identify relevant research programs for scientific exchange and potential collaboration. The MC will develop reports related to the Action and will coordinate the preparation of a proposal for future EU programmes. It will also disseminate publication policies.
The **SG** will be a small, responsive group of individuals committed to meeting the Action objectives. The SG will include the Action Chair, DC, STSM/TSC, the four WG Leaders and an ESR. Additional members will be added if needed with agreement of the MC. The SG will support the MC by making decisions to be ratified by the MC as appropriate: with DC establish and update the website and project management tool, with STSM/TSC organizing and coordinating the conference agendas, workshops & STSMs. The SG will establish the infrastructure and regulatory approvals for sharing of patient data sets, human samples and in vivo models. The SG will meet twice a year with further 2 monthly communications by web-based interfaces and conference calls.
A **DC** will coordinate the set-up and maintenance of the Action´s website and project management tool with up-dated information on recent activities and downloadable resources and protocols (see H2). DC will raise awareness regarding opportunities to contribute to national and international conferences and meetings outside the Action to widen the influence of the Action. The DC will be

supported by two members of the MC and an ESR.
The **TSC** will work with two members of the MC and two ESRs, including at least one person from a low income/resource-poor country to set up the program of course based Training Schools and to coordinate and promote other training opportunities. Training Schools will be open to all ESRs from the network but also to interested persons from outside the network. The TSC will seek opportunities for Action members to access existing training activities among partner centres. Thus trainees from all partner centres will benefit from the world-class expertise in individual centre.
As the number of participating countries and institutions of the Action expand over time, the structure and size of the organisational structures may be adapted by the MC, always in accordance with "Rules and Procedures for Implementing COST Actions".

E.2 Working Groups

The Action has four WG, each with a leader appointed by the MC, to ensure effective and close cooperation of WG participants. As each WG grows and develops, co-leaders may be elected and small core WG committees may be formed. Two annual workshops will be organized for each WG, to enable clinicians and researchers to present progress, identify bottlenecks and consider future perspectives. Where appropriate two WGs may meet together, or a WG may hold a workshop with another network with similar interests e.g. ERS PCD Taskforce or SYSCILIA. The WG lead will communicate back to the MC priorities for research topics. WGs are closely interrelated, and all WGs will meet at the annual conference to enable exchange on scientific progress between groups. Additionally, WG leaders will work together 2 monthly within the SG to synchronize scientific activities. The active involvement of ESRs will be a central task of each WG.

E.3 Liaison and interaction with other research programmes

This COST Action will develop a new network of basic scientists, epidemiologists, translational scientists and clinicians all working to improve the treatment of patients with PCD. Previous and current collaborations have not been so multidisciplinary in nature. The Action will liaise with other European and international research programs using existing networks and collaborations of scientists or of clinicians. For example, basic scientists of the COST Action are participants in FP-7 SYSCILIA and clinicians are participants in the ERS Task Force and FP-7 BESTCILIA as outlined in B4. The COST Action will seek to hold joint seminars or meetings with these other research programmes. In so doing the Action will expand, strengthen and diversify the network. The COST

Action will actively seek opportunities for collaboration with other COST Actions and European and international research programmes. For example, COST Action: Developmental Origins of Chronic Lung Disease

E.4 Gender balance and involvement of early-stage researchers

Gender balance: This COST Action will respect an appropriate gender balance in all its activities and the MC will place this as a standard item on all its agendas. Equal treatment of researchers, irrespective of gender is a key issue for this Action. A significant number (40%) of the experts who were consulted during the development of this COST Action proposal are female, including internationally recognised researchers. The proposer of this Action is female and mother of dependent children. The gender gap at leadership level is a cause of the perpetuated gender imbalance in sciences which will not occur in this Action. This Action will promote career development by creating a networking platform for ESRs and scientists, offering role models to discuss personal development and also strategies to facilitate work-life balance. The Action will respect gender balance in all activities, for example when allocating funds for STSMS, when considering oral presentations and chairs of sessions.

In addition to gender, the MC will positively strive to meet the needs of different people and create environments where everybody feels respected, valued and able to meet their potential. Examples of diversity may include, but not be restricted to academic seniority, race and ethnicity, religion, culture, age and disability.

Involvement of ESRs

The Action is committed to support and develop ESRs. Promotion of ESRs will be placed as a standard item on all MC agendas. The Action is committed to promote excellent education, training and career development. Interaction between senior academics, clinicians, students and post-doctoral fellows and invited speakers from academia and industry at Conferences, Workshops and Training School activities will provide career development opportunities. ESRs will be encouraged and supported to develop supervised management and administrative roles within the Action e.g. ESRs will work with the DC, and will have representation on the SG. ESRs will be encouraged to take on academic roles e.g. chairing sessions, oral presentations, authoring manuscripts and reports.

F. TIMETABLE

The duration of the Action is 4 years. An initial inaugural conference will provide 1st MC meeting. WGs will meet every 6 months; consecutive WG meetings will ensure cross-fertilization with an aim of all WGs meeting at the annual scientific meetings. Where appropriate these workshops will be held in collaboration with other COST Actions or networks. MC meetings will occur annually linked to the scientific meeting. SG will meet face-to-face 6 monthly with teleconference communication every 2 months. The preliminary timetable is:

	Year 1	**Year 2**	**Year 3**	**Year 4**
Scientific conferences	1st MC meeting	X	X	X
WG1 meeting	XX	XX	XX	XX
WG2 meeting	XX	XX	XX	XX
WG3 meeting	XX	XX	XX	XX
WG4 meeting	XX	XX	XX	XX
MC meeting	X	X	X	X
SC meetings	XXXXXX	XXXXXX	XXXXXX	XXXXXX
Website and project management programme set-up	X			
Website and project management updates	X	X	X	X
Summer School	X	X	X	X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, BE, BG, CH, CY, CZ, DE, DK, EL, ES, FR, IL, IT, NL, NO, PL, PT, RS, TR, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 80 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

Since the target audience might change over the course of the Action, the MC will appoint a DC who will maintain vigilance for key individuals, organisations and groups. Anticipated target audiences are:

- The network of multidisciplinary participants of the Action
- Patients and patient organisations
- The larger basic and translational research community in this or related fields outside the Action
- Clinicians and allied health professionals caring for patients with PCD: chest physicians, paediatricians, ENT surgeons, fertility specialists, physiotherapists, specialist nurses etc.
- Biomedical and pharmaceutical companies including SMEs
- National and European level regulators and policy makers including national guideline-producing bodies

- General public.

H.2 What?

The COST Action will use a variety of dissemination methods to reach stakeholders:
Action website will provide general information on the major aims of the Actions and the scientific missions of the WGs. It will provide a public face for the Action, promoting activities such as conferences, workshops and Training Schools that are open to researchers from outside the network. Furthermore, relevant international conferences and symposia outside the Action will be announced. The website will report achievements (publications of original research and reviews for peer-reviewed journals, awards, press releases, workshop proceedings etc.). It will provide information for interested researchers how to join the Action. Contact details of WG Leaders and the MC will be provided for researchers interested in participation.
For internal information sharing and project coordination the Action will use an on-line password **protected project management tool** such as Basecamp. This will support topic based discussions, document sharing, to-do lists etc. Shared documents might include experimental protocols, documents from Training Schools, and manuals and working documents of the MC and WG meetings.
Patient information will only be handled in formats that are approved by ethical boards, following data protection regulations.
The results of the Action will be made available to the scientific community via peer-reviewed publications in **scientific journals**, presentations at scientific meetings and presentation on the website. Where possible, systematic reviews, SOPs, guidelines and scientific papers on new outcomes will be published in peer reviewed scientific journals with open access to these documents and supplementary data. The MC will develop a policy to ensure that collaborative results are jointly analysed and published in accordance with principals of academic integrity reflecting ownership of data and academic contribution. All publications will acknowledge the COST Action. Where possible in line with copyright restrictions, published manuscripts will be made available on the Action website, along with supplementary materials.
Dissemination to non-specialist clinicians caring for patients with PCD will be by publication of review articles in **peer-reviewed journals targeting a more general audience** (e.g. Archives of Disease in Childhood). Participants of the Action will additionally seek opportunities to present to ‘generalists’ e.g. ENT and neonatal audiences.

Oral presentations and poster presentations will be made at the annual European Respiratory Society Congress and other meetings where large numbers of target stakeholders will be present. The Action will seek opportunities to have a session at the ERS. ESRs will be actively encouraged to present COST outcomes at clinical and scientific meetings.
Dissemination activities through **PCD patient organizations** are important to ensure engagement of patients with the research, to spread new knowledge and to guarantee the wide and rapid uptake of guidelines or recommendations for management. The Action will use existing contacts with patient organisations to disseminate using their established websites, Facebook etc. Participants of the Action will be asked to translate short reports suitable for a lay audience for inclusion on patient organisation websites.

H.3 How?

Dissemination and exploitation of results are a central task of this Action and will be a standard item on the agenda of MC meetings. The DC will monitor and evaluate the Action's dissemination plan, advising the SG if the approach needs changing. Participants in the Action, including the proposer, have experience in dissemination activities in Framework funded projects and Task Force activities. The Action will make full use of their knowledge and networks.