Brussels, 24 October 2016

COST 124/16

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "European network for translational research in children's and adult interstitial lung disease" (ENTeR- chILD) CA16125**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action European network for translational research in children's and adult interstitial lung disease approved by the Committee of Senior Officials through written procedure on 24 October 2016.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA16125
EUROPEAN NETWORK FOR TRANSLATIONAL RESEARCH IN CHILDREN'S AND ADULT INTERSTITIAL LUNG DISEASE (ENTeR- chILD)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14).

The main aim and objective of the Action is to to create a global European-led network of multidisciplinary clinicians (adult and paediatric), scientists, and eventually stakeholders with the aim to allow accurate and early diagnosis of interstitial lung disease (ILD) and the application of structured, potentially personalised, management and therapies. This will be achieved through the specific objectives detailed in the Technical Annex.

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 44 million in 2016.

The MoU will enter into force once at least five (5) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14.

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OVERVIEW

Summary
Interstitial lung disease in children (chILD) is a term that describes a collection of more than 200 rare lung disorders. It is a heterogeneous group of non-neoplastic disorders resulting from damage by varying patterns of inflammation and fibrosis with the interstitium as the primary site of injury. As with other orphan diseases, chILD data is lacking on the natural course, phenotypic variability, associations with genotype, and effectiveness of treatments. The disease course is very variable, and depending on more than just the underlying cause; for example, within a given family, the phenotypic variability of chILD such as surfactant protein C mutation is huge. The rarity of individual chILDs contributes to a lack of randomised control trial data on effectiveness of treatments. Management strategies derive from other diseases or are based on physicians experience and remain controversial.

This Action will create a pan-Europe-led network of multidisciplinary clinicians (adult and paediatric), scientists, and patients and their families with the aim of accurate and early diagnosis with structured, potentially personalised, management and therapies. The Action will stimulate and coordinate multidisciplinary research in chILD from infancy to adulthood, as well as reveal the pathophysiological commonalities between different forms ILD at the molecular level. The results of these efforts will create large incremental changes in understanding and management of chILD. Since chILD is an umbrella term for a number of conditions most of which imply more than purely medical or scientific expertise, the Action will pay due attention to the larger societal implications of chILD research

Areas of Expertise Relevant for the Action	**Keywords**
● Clinical medicine: Paediatrics ● Clinical medicine: Respiratory systems ● Basic medicine: Cell biology and molecular transport mechanisms ● Basic medicine: Molecular genetics, reverse genetics and RNAi ● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy	● Pediatrics ● Interstitial lung disease ● therapy and management ● diagnostics

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Open access to a centralized data centre and bio-repository on chILD
● Improve clinical care of patients with chILD
● Definition and dissemination standards of care for chILD
● Promote and integrate basic research on chILD to underpin translational research with the ultimate aim to develop novel therapies or transfer adult ILD treatments into chILD
● Building on and unifying the expert networks of researchers in chILD

Capacity Building
● Linkage of translational researchers and clinicians to identify high priority targets to move into the clinic by mutual collaboration, including novel pharmaceutical agents.
● Promoting excellence and the required structures to perform clinical studies across Europe will be organised to support future grant applications.
● Sharing knowledge through dissemination via an Action website, e-newsletter, national and international

meeting, meet the professor and short term scientific missions (STSM), training schools and peer reviewed publications

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TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. Challenge

1.1.1. Description of the Challenge (Main Aim)

The main objective of the Action is to create a global European-led network of multidisciplinary clinicians (adult and paediatric), scientists, and eventually stakeholders with the aim to allow accurate and early diagnosis of interstitial lung disease (ILD) and the application of structured, potentially personalised, management and therapies. The Action will stimulate and coordinate multidisciplinary research in chILD from infancy to adulthood on a pan-European level and beyond, as well as reveal the pathophysiological commonalities between different forms of ILD at the molecular level. The results of these efforts will create large incremental changes in understanding and management of chILD.

1.1.2. Relevance and timeliness

Children's interstitial lung disease (chILD) comprises over 200 different rare lung conditions. The combined incidence of these disparate conditions is about 3.6 per 100,000 children[1]. The rarity of the conditions, usually with non-specific presenting signs, is often associated with late and / or misdiagnosis. Outcomes are frequently poor. Despite several attempts over the last two decades, progress in this field has been very slow, mainly due to a lack of a large network, which can connect all interested but scattered partners. In 2000, a multicentre survey on the diagnostic approach to chILD was a first European attempt to collect data from 187 European and non-European centres[2]. In 2004, the results of another questionnaire by the ERS Task force on chronic interstitial lung disease in immunocompetent children were published[3]. As an initiative to promote and standardise care across the EU, an application for FP7 funding (FP7 305653) was successful in 2012 to introduce a database and biobank for chILD[4]. This project has been successful in:
(1) Establishing a database and biobank;
(2) Producing standards for investigation and diagnosis[5];
(3) Establishing international peer review of cases;
(4) Initiating observational trials of outcomes and interventional trials of therapy.
chILD-EU has worked with parent groups to produce parent information and this has been translated into English, German, French and Italian. Whilst there have been great strides made for chILD this time, there remain great challenges to improving outcomes. In particular:
(a) International peer review is highlighting significant differences in diagnosis across the EU for the same chILD - aligning and reducing clinical / radiological / pathological diagnostic variability will be essential to pan-European (and international) studies;
(b) The very low incidence of cases within Europe have limited recruitment to observational studies;
(c) The chILD-EU interventional trial (the first ever in chILD) has been dogged by regulatory issues relating to use of an off-label drug, slowing down the recruitment of incident cases to the study;
(d) Some parent groups (for example in the UK, Spain, Germany and France) have been proactive in profiling chILD in their countries, but still need further support to integrate their support across the EU and beyond and have ambitions to provide more information and support to parents;
(e) There has not been the opportunity to equitably spread experience and expertise across all EU states (worthily also the involvement of the Middle East, Africa and Asia);
(f) Aligning core datasets with colleagues in North America and Australasia is an urgent need to support global interaction.
To maintain momentum and build on recent successes, the time is right for a network bringing clinicians interested in ILD at all ages and basic scientists together. This Action will provide a highly innovative environment by developing a pan-European network of experts from multidisciplinary

medical specialties (e.g. paediatric & adult Pulmonology, ICU) motivated to carry out collaborative research with scientists from diverse backgrounds (e.g. genetics, imaging, cell biology, pathology, psychology, socio-economics) with the support from non EU countries, such as the middle East, Asia, America and Australia.
The FP7 project, chILD EU was able to recruit patients and assemble a dataset from a selected group of countries, but was not able to produce evidence based recommendations on treatment or prognosis of chILD. Therefore, this Action will make use of the existing retrospective and prospective chILD-EU dataset, and widen the network of clinicians to include more patients. It will contribute to standardised collection of clinical data by developing follow-up forms 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 chILD.
There is no specific treatment regimen for chILD and management, therefore it aims at improving symptoms and treating infections, to prevent complications and hence decreasing lung damage. The chILD-EU project started the first ever interventional trial. Because of the regulatory issues relating to use of an off-label medicine (these are now overcome) the project was left with little time to recruit cases to the studies. The increase in the number of specialist centres managing patients and collecting observational data will increase with the foundation of this Action. Within the core chILD-EU countries, ethical approval for studies is established. It is important to roll out inclusion of patients to additional EU, extending ethical approvals already in place and using local clinical leads to help translate patient information and consent forms. In this way, this Action will build on the foundations of the chILD-EU project and expanding them to increase patient numbers for interventional trials. chILD-EU collected large cohort cross sectional and two-year longitudinal data on chILD. The long term course is still unknown; in the literature, disease severity changes over time depending on the underlying condition and overall mortality rates are reported between 5 and 30%[6,7]. In some entities these are much higher, e.g. SpB (deficiency (a surfactant disorder). There are few treatment options and the level of recommendation in guidelines is low, mainly depending on expert opinion[5]. This Action will identify needs for urgent patient support, will provide clinical and translational research directions, and will coordinate the activity required to identify potential novel therapies for clinical trials.

1.2. Specific Objectives

1.2.1. Research Coordination Objectives

Building on and unifying the expert networks of researchers in chILD
This Action will use the contacts available for the chILD-EU project (FP7 305653), to set up a network across Europe. The aim is to roll out the results and progress of chILD-EU to the rest of Europe, using current protocols and agreements to:
(a) Align peer review opinion across the EU;
(b) Continue recruitment to observational studies of chILD;
(c) Recruit children to interventional studies of hydroxychloroquine and corticosteroids recently commenced. For this Action, experts from other countries will be invited and encouraged to join the COST Action and participate in Working Groups to stimulate translational and clinical research to pull chILD out of its orphanage, as well as adult physicians caring for ILD patients to learn lessons from adult life. With firm establishment, this European led network will be open to all experts to share knowledge and exchange experiences in patient care and biomaterials.

Open access to a centralized data centre and bio-repository on chILD.
The newly developed database from the FP7 project chILD-EU will be the core background support, and the source for SOPs to guarantee a harmonised and extended data and biomaterial collection.
The Action therefore will:

- Establish easy and open access to the current repository, which has state of the art data safety precautions.

- Use Short-Term Scientific Missions (STSM) or training schools to enable participation in existing and planned studies on morbidity, physiology and treatments of chILD, in order to generate large and prospectively collected data and sample sets for translational research. Important is the support from adult clinicians in the ILD field; their clinical trial expertise and scientific insights will benefit this Action.
- Generate data on the epidemiology of chILD. This includes data on incidence, clinical presentation, severity and phenotypes throughout the life course, long-term prognosis and how the latter is influenced by environmental exposures and different management strategies.
- Definition and dissemination standards of care for chILD.
- The already published “Best Practice Checklist", for the diagnostic investigation of suspected chILD, and subsequent follow up investigation of confirmed chILD, will be distributed to all involved countries in this Action and to patient organisations for dissemination to a wider public.
  Information on important topics of chILD for clinical practice and research will be adapted to different healthcare settings, to provide quality care and to improve quality of life.
- Awareness of the disease amongst physicians, patients and families, research partners and the general public will be encouraged. The Action will extend patient-patient contact and patient-family contact from national to international through the use of online tools (online community and social media).

Improve clinical care of patients with chILD

- Utilize data from patient organisations and existing observational cohorts to develop strategies to improve clinical care in chILD. First experience of UK families of children diagnosed with ILD, to inform clinical practice and service development was published in 20158.
- The COST Action will devise and harmonize protocols for the transition of these patients to adult care; at the moment, this is rudimentary and fragmented. The involvement of adult ILD specialists is crucial in this process.
  The COST Action will continue and follow up quality improvement strategies, by specific questionnaires, to assess management practices associated with good outcomes.

Promote and integrate basic research on chILD, by facilitating discussion between scientists and clinicians with the ultimate aim of developing novel therapies, including learning from adult experience in novel medications, e.g. perfenidone that has not been trialled in children.

- Identify researchers focusing on chILD (animal or cell models, genetics etc.), and on related adult ILD diseases/ scientific disciplines (e.g. off label treatment, gene therapy) and organise joint symposia with basic and translational researchers and clinicians, to exchange ideas and guide research, working with patient groups and parents. This will allow the network to develop strategies for new treatment and to build relations with EU and Industry so that commercial and non-commercial research capacity for chILD can be formed.

1.2.2. Capacity-building Objectives

The Action will support systematic fertilization of horizontal and vertical crosstalk in the area of chILD.

- Linkage of translational researchers and clinicians to identify high priority targets to move into the clinic by mutual collaboration, including novel pharmaceutical agents., such as PCT-124; a small molecule drug designed to overcome the adverse effects of a nonsense mutation by inducing selective ribosomal read-through of mRNA containing a premature stop codon and allowing translation of a full-length protein. As an example, geneticists will identify new mutations in rare diseases; stimulate scientists to develop models to test clinical relevance or to search new drugs. chILD, as a rare disease should undergo all the steps that years ago were undertaken for cystic fibrosis (CF). CF did not get much attention from the pharmaceutical industry, and as a result the outlook for patients was bleak. That has all changed now, as many pharmaceutical and biotech companies have entered the race to develop better treatments, and even cures for CF.

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- Promoting excellence and the required structures to perform clinical studies across Europe will be organised to support future grant applications.
- Sharing knowledge through dissemination via an Action website, e-newsletter, national and international meeting, meet the professor and Short-Term Scientific Missions (STSM), training schools and peer reviewed publications.

The Action will enable the recruitment, and support and encourage young researchers to consider a research interest in chILD by offering the participation in the network activities. The young researchers will help create the key curriculum for chILD training (clinical, genetics, radiology, and pathology) and the Action will support training through the training schools that will be organised during the Action.

1.3. Progress beyond the state-of-the-art and Innovation Potential

1.3.1. Description of the state-of-the-art

Interstitial lung disease in children (chILD) is a term that describes a diverse collection of more than 200 diffuse parenchymal lung disorders. These are categorized into disorders, which are (i) specific for infants and children, and (ii) disorders affecting patients at all ages[6]. There is significant overlap between adult and paediatric ILD, making the current separation of adult and paediatric ILD physicians untenable. The first chILD group comprises disorders of lung and alveolar development, disorders of unknown aetiology and disorders of surfactant dysfunction[7]. Almost nothing is known how patients with these diseases develop into adulthood. For the second group of disorders (affecting patients at all ages) it is also not clear if the long-term course is the same or different from disease presenting in adulthood; there are important developmental components in paediatric, but not adult, ILD, including treatment (for example, corticosteroid therapy in children may lead to alveolar hypoplasia). Sarcoidosis is one example that highlights the protean expressions of what may or may not be the same disease[9]; in infancy, sarcoidosis has a completely different presentation affecting in particular the extra pulmonary system, whereas in adults, pulmonary disease is most common. Patients with chILD can be characterized by the presence of at least 3 of the 4 following criteria in the absence of other known disorders: (1) respiratory symptoms (cough, rapid breathing, or exercise intolerance), (2) signs (resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure), (3) hypoxemia, and (4) diffuse abnormalities on chest X-ray or computed tomography (CT) scan. If biopsied, patterns of inflammation and fibrosis can be found, which are more or less characteristic for chILD. Fortunately progress on the genetics[10,11] on several chILD entities has led to the precise molecular identification of many disorders which were formerly lumped together into single disease categories; for example the surfactant dysfunction disorders, leading to interstitial lung diseases can be differentiated into those caused by mutations in SFTPB (Pulmonary surfactant-associated protein B); SFTPC (Pulmonary surfactant-associated protein c); ABCA3 (ATP binding cassette subfamily A member 3), SFTPA2 (Pulmonary surfactant-associated protein A2), and TTF1 (thyroid transcription factor-1). In addition other entities associated with diverse presentation, e.g. pulmonary emphysematous changes are caused by mutations in genes like filamin A or recurrent idiopathic hemosiderosis by mutations in COPA[12] and other genes. MARS[13] or GATA2[14] mutations are responsible for certain forms of pulmonary alveolar proteinosis. Many more specific genetic causes are on the horizon and need to be linked to already known phenotypes of chILD. Many patients with chILD grow up and will need to be followed in adulthood. Others may not be identified as adults with as yet undiagnosed molecular diseases due to the limited knowledge of chILD conditions in adult pulmonology; so for example, inherited SP-C mutations may not present until adult life with suspected IPF, a condition unknown in paediatrics. Conversely, effects of aging and inflammation/immunity dysregulation shown in adult ILD will play a role in the development and understanding of chILD. In addition, the results from adult clinical trials in ILD can be lesson-learning experience to the paediatric clinicians; while the PANTHER-IPF study[15] showed disappointing results; other promising drugs such as rituximab may

be an option. Therefore, joint clinical and research efforts are necessary to improve the understanding and detection of chILD at all ages, and to build a safe bridge from chILD to adult ILD. Nutritional and severe feeding problems are central in chILD and in particular, parents and parent support groups were pivotal in identifying these problems[16]. Nevertheless little is known about the needs of families for support. Increased work of breathing increases oxygen consumption and energy requirements. At the same time, hypoxemia and hypercapnia reduce the intake of nutrients, and malnutrition impairs respiratory muscle function, ventilatory drive, response to hypoxia, and also leads to impaired pulmonary defence mechanisms. The long-term course is not known for many of the specific entities. Overall mortality rates are significant and due to few treatment options. Due to lack of international networks sufficiently large numbers of children have never been collected to perform randomised controlled trials of treatment, an issue that has been addressed in the FP7 project. In particular neonates and infants may experience a rapid decline leading to death or lung transplantation, with no treatment options. In those with a more or less stable course during childhood, quality of life, exercise capacity and work capacity are often impaired. The best outcome measures to monitor disease progression have not been explored; it is known that spirometry does not correlate well with lung damage; however useful alternatives, e.g. lung clearance index, are not assessed appropriately or not available.

In the last decade, only a few international initiatives have stimulated chILD research. This COST Action will collect all groups under one umbrella taking advantage of previous achievements, will foster access to the latest established infrastructure and will promote the field of chILD substantially by building on the success of previous activities:

- The results of a clinical European task force (ERS) on chILD were published in 2004. That document gave a state of the art and was written by a nucleus of paediatric pulmonologists caring for chILD.
- The FP7 grant (chILD-EU-FP-305653) brought together in 2012, paediatric ILD specialists to produce guidelines, a common register and biobank and to initiate the first randomized controlled trials in chILD. However the level of recommendation of guidelines is low mainly depending on expert opinion[5]. Importantly, participation in the register and randomized trials for non-members of the chILD-EU consortium is not possible, as significant administrative hurdles (Ethics, national competent authorities, and site contracts), although relatively inexpensive, could not be undertaken by any other European countries, because of lack of resources.
- In International Partner Countries (North America, Australia) chILD networks are either established or being put together, and a close cooperation is highly desirable. Thus, there is an urgent and unmet need to establish a European wide evidence base for understanding the natural course and management of chILD across the life span and to develop novel effective therapies. A prerequisite for all this is a network structure, which makes access to what is established possible. Such a global Europe-led network of multidisciplinary chILD (childhood interstitial lung disease) clinicians and researchers will be built with this COST Action.

1.3.2. Progress beyond the state-of-the-art

This Action will advance the field beyond the current state of the art in the following ways:

- It will increase **diagnostic awareness** for chILD across Europe, and increase the recognition and differentiation of the specific entities. Performance indicator: more cases known, peer reviewed and followed in data bases.
- It will **link all** relevant **groups** for chILD, including the national, European and international respiratory and general paediatricians, patients and parents groups, imaging groups, pathologists, geneticists, translational and clinical scientists. Performance indicator: new parents´ groups and interdisciplinary research teams will develop.
- It will create a **network** of researchers and clinicians to improve cross fertilization of knowledge **from infancy to elderly**. Performance indicator: new research into cellular or animal model systems and biomarker studies for neglected chILD entities. New collaborations breaking down age barriers

- It will evaluate and standardize **outcomes**. Those clinical efficacy measures, which reflect how a patient feels, functions or survives, will serve as the gold standard. The Action will describe study endpoints, including clinical scoring, pulmonary exacerbations, and quality of life. At the moment the available patient symptom score is the Leland-Fan-clinical scale; which is a 5 point scoring system to index patients from asymptomatic to symptomatic with pulmonary hypertension. Performance indicator: Definition of outcomes for the development of new scores for disease progression measurements.
- It will **prospectively follow up** an increased number of chILD patients and adult patient with chILD characteristics to determine the natural history of the subgroups of chILD including the prospective recording of clinical, serological, physiological and imaging biomarkers. Performance indicator: expansion of the cohort of prospectively studied subjects in the database and biobank.
- It will address **feeding difficulties**, one of the major problems in the management in chILD. Performance indicator: number of available weight, height and BMI in confront to normal values.
- It will identify areas of good practice and areas of need associated with **transition** from paediatric to adult care. Performance indicator: number of patients involved in an active transition care in different countries of the Action.
- It will help to include subjects from **all countries of the COST Action** to make them aware of and to allow participation in existing randomised controlled interventions of chILD. Performance indicator: number of subjects included from different countries, particularly countries new to the collaborative.
- It will train Early Career Investigators (ECIs) through **training schools**, meetings and Short-Term Scientific Missions (STSMs) ensuring sustainability and development in the field of chILD research. In addition, STSMs will provide opportunities for experts to visit institutions to provide specialist training and standardisation across sites. Performance indicator: number of clinicians, researchers, active parents included from different countries, and visiting different centres.

1.3.3. Innovation in tackling the challenge

The Action will improve the health of children with chILD across Europe, providing integrated health care for these rare diseases, and the sharing and developing diagnostic skills and best practices across member states, as well as finding treatment options. An important innovation of this Action is to collaboration with adult experts on ILD, allowing the exchange of knowledge on data collection and treatment trials but also the possibility to include in the data collections a cross age-group to see on prognosis and difficulty in adulthood. Even more important is the cross fertilisation of trial expertise to discover drugs able to improve health status and reduce later life complication.
As in other rare disease the pan-European approach is very important and allows new perspectives in the field of chILD. The Action will give rise to cross country research opportunities and a exchange in expertise and new input for future research grant and collaborations.

1.4. Added value of networking

1.4.1. In relation to the Challenge

A wide network of researchers and clinicians from COST Member Countries and International Partner and Near Neighbour Countries will provide access to cohorts of patients, which are large enough for focused clinical trials, to different patient support groups and dedicated clinicians and researchers on chILD worldwide. chILD is rare; the individual components of chILD are ultra-rare. No single European country could successfully assess and study the chILD population. Moreover the collaboration between adult physicians and paediatricians specialising in chILD will increase the opportunity of potential treatment options and allow an overview of possibilities to share experience in RCTs and allow a cross age group evaluation of different therapies. COST Action is the appropriate mechanism to develop research for treatments for chILD, because it facilitates networking of clinicians, and basic and translational researchers from a variety of disciplines and

patient organisations in a non-competitive collaboration. It 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.
Without such a COST Action it is very likely that a pan-European network on this large and important disease area will never or much later be established.

1.4.2. In relation to existing efforts at European and/or international level

The FP7 chILD-EU project (2012-2016) united paediatricians from 5 countries to set up a European chILD registry, to identify and analyse existing patient datasets, review current diagnostic and treatment standards, and to initiate the first clinical trials in chILD. This project has lifted chILD activities for the first time in Europe to a sufficiently high level to be internationally competitive. However, this initiative was limited to only five partners and had no resources to include the other European countries.
This COST Action takes these efforts forward whilst avoiding duplication. COST gives a window of opportunity to analyse the datasets assembled in chILD-EU and to answer pertinent epidemiological and clinical questions. It will provide an opportunity for researchers from previous smaller collaborations to integrate their efforts providing a comprehensive platform for cross discipline collaboration, whilst encouraging new recruitment of additional experts into the field. Thus this COST Action will sustain those efforts, as financially intensive developments (register, biobank, trial set up, authority permissions, etc.) have already been established, and will allow the urgently needed expansion of the program to all European countries.
The FP7 chILD-EU group, the previous European Respiratory Society chILD Task force members and internationally, the US-chILD group as well as the Australasian rare respiratory disease initiative are in close contact, willing to develop collaborations to improve diagnostics, management and research and to share resources. The COST Action will unite participants from these projects under one umbrella, build on them and will add a value from networking, which would otherwise be lost completely.
Significant advances in understanding the aetiologies, different genetic mutations, and cellular dysfunctions as well as diagnostic and management approaches in chILD are expected. Insights from therapeutic innovations from adult ILD can be approached in this collaborative research effort.
This COST Action represents a unique opportunity for taking a large, neglected disease-area out of the orphanage by pan-European networking.

2. IMPACT

2.1. Expected Impact

2.1.1. Short-term and long-term scientific, technological, and/or socioeconomic impacts

The COST Action is the first network of scientists, clinicians and patient representatives to push the European research agenda for development of large patient cohorts of chILD to develop new treatments specifically for patients with chILD or chILD subgroups. The FP7 EU project started to collect and generate high quality data on diagnoses and initiated the first ever clinical trial in this group of rare diseases. The time is now right to coordinate these efforts and to increase the study population 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 **impacts** are:

Scientific (S&T) short-term impacts:
- A Europe-wide research network positioned to obtain platform grants for research for improved

diagnostic modalities and treatments for chILD.

- Accelerated understanding of the underlying genetics and pathophysiological mechanisms, through coordinated approaches and reduction of duplication. This will facilitate identification of potential target therapies for clinical trials.
- Further development of the chILD-EU registry and longitudinal database. This will result in Europe wide tools to provide knowledge of the natural history of chILD across Europe by meta-analysis of the database, and a registry of patients for clinical trials.
- Translate big data from the FP7chILD-EU project and basic research results into clinical applications.
- Testing of the existing outcome measures identified during the chILD-EU project and the development of new outcome measures for monitoring patients in clinical trials and longitudinal epidemiological studies. Defined outcome measures in the chILD-EU projects are respiratory rate/O2-saturation/O2-demand; retractions; coughing; dyspnoea; pO2 (capillary); weight for height.
- In terms of patient health, improve diagnostics by implementing the recent published guidelines for chILD during peer-review and discussions of cases.

Scientific (S&T) long-term impacts:

- A highly motivated and well-trained cohort of Early Career Investigators (ECIs) with excellent understanding of basic science and clinical aspects of chILD research. Having trained together from an early stage it is anticipated that the scientists and clinicians will have excellent appreciation of the strengths and limitations of each other's' research, and be positioned to continue moving translational research in chILD forward.
- Provide the evidence base for the development of policy strategies for prevention, early diagnosis, therapy and health economics as well as addressing health inequalities.
- In terms of patient health, implement results from the clinic trial on hydroxychloroquine and steroid treatment for specific groups of chILD.
- In line with the objectives of the EU proposals, the Action will stimulate stakeholders to advance the development of new therapeutic options with concrete benefits for patients living with rare diseases. At the moment drugs used in adult ILD do not have an Paediatric Investigation Plan for many meds being used in adult ILD, and the Action will address this.

Socioeconomic impacts:

Along with other rare diseases, chILD produces a significant healthcare and economic burden because of delayed diagnosis, poor management and the absence of disease-specific treatment options. The consequences of missing treatment options and the suboptimal management of nutritional and feeding problems in patients with chILD include poor disease control, days off work/ unemployment for the parents, and expensive ineffective treatments.

The anticipated **societal/ public healthcare impacts** of the Action are:

- Identification of current good practice of treatment options which can be rapidly rolled out across Europe (evidence based consensus report and collected data from the chILD EU registry).
- Reduction of health costs by increasing awareness of the disease and promoting the diagnostic guidelines to reduce age at diagnosis and therefore starting early and preventive treatment to maintain lung function and the reduced the decline over the years to come.
- Improvement of quality of life for patients and their family.

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.

2.2. Measures to Maximise Impact

2.2.1. Plan for involving the most relevant stakeholders

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The availability of a well-characterised cohort of patients supported by a network of accessible **clinicians and other professionals caring for chILD** will provide a commercially attractive hub with which to communicate and better understand the needs of this patient group. The Action's work will be actively published in manuscripts and online with the clear intention of attracting commercial interest in our cohort from established and developing health related industries.

These efforts will be complemented by the EMEA directive on the development of medicines for children, providing important incentives for **the pharmaceutical industry** to research neglected or rare conditions, such as chILD. Ultimately, this Action is intended to lead to the development and commercial exploitation of novel therapies in the field. Participants in the Action have contacts with key strategic partners in industry thereby ensuring rapid implementation of promising results for further development.

The principal end users to benefit from this Action are patients with chILD and their families. **Representatives of chILD patient organisations** are involved in Action and will be invited to attend and speak at the annual conferences. chILD patient organisations are stakeholders of the Action. Thus, the Action will lead to scientific advance, providing a platform to improve treatment of chILD whilst maintaining a patient-centred approach.

Another important group of stakeholders are the basic and translational scientists working on chILD and clinical scientists concerned with diagnosis and treatment of chILD patients (paediatricians, adult chest physicians, psychologists); they are involved in the Action.

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 chILD. The wider rare diseases network can build on the experiences from this Action, with direct impact on the care of patients.

2.2.2. Dissemination and/or Exploitation Plan

Since the target audience and opportunities on social media will change over the course of the Action, the Management Committee will include a Dissemination Coordinator who will target key individuals, organisations and groups. Dissemination and exploitation of results are a central task of this Action and will be a standing item on the agenda of Management Committee meetings. The Dissemination Coordinator will monitor and evaluate the Action's dissemination plan, advising the Steering Committee if the approach needs changing. The Action will make full use of the knowledge and networks of the Action participants, especially the rapidly evolving field of social media, and not just conventional scientific channels.
The anticipated target audiences for the dissemination will be:

- The extended network of multidisciplinary participants of the Action.
- Patients, their families 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 chILD: chest physicians, paediatricians, surgeons, physiotherapists, specialist nurses, psychologists, nutritionists, social workers, etc.
- Biomedical and pharmaceutical companies.
- National and European level regulators and policy makers including national guideline-producing bodies.
- General public.

The COST Action will use diverse **dissemination methods** to reach stakeholders:

An **Action website** will provide general information on the major aims of the Actions and the scientific missions of the WGs. The website will provide the public face for the Action, advertising activities such as conferences, workshops and training schools that are open to researchers from outside the network to promote further dissemination. 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.

- For **internal information sharing and project coordination** the Action will use an on-line password protected project management tool (e.g. Basecamp). This will support topic-based discussions, document sharing, and to-do lists. Shared documents will include experimental protocols, documents from training schools, and manuals and working documents of the Management Committee and WG meetings.
- **Patient information** will only be handled in formats that are approved by ethical boards, following data protection regulations. For this purpose the software running the chILD database, i.e. Secutrial, is fully configured and available to all authorized participants in the Action.
- **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. Indeed, it is already ensured that the patient survey is open access. The Management Committee 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.
- **Dissemination to non-specialist clinicians** caring for patients with chILD will be done by publication of review articles in peer-reviewed journals targeting a more general audience (e.g. European Journal of Paediatrics, Archives of Disease in Childhood and other general paediatric and adult medicine journals).
- **Oral presentations and poster presentations** will be made at the annual European Respiratory Society (ERS) Congress and other meetings where large numbers of target stakeholders will be present.
- The Action will seek opportunities to have continua to have **congress sessions** at the ERS and overseas e.g. American thoracic society (ATS).
- **Early Career Investigators (ECIs)** will be actively encouraged to present COST outcomes at clinical and scientific meetings.
- Dissemination activities through **chILD 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 any guidelines or recommendations for management.
- The Action will use existing contacts with patient organisations to disseminate information using their established websites, Facebook, twitter and other social media and networks. Participants of the Action will be asked to volunteer to translate short reports suitable for a lay audience for inclusion on their websites, and short communication for social networking.

2.3. Potential for Innovation versus Risk Level

2.3.1. Potential for scientific, technological and/or socioeconomic innovation breakthroughs

The Action targets a large group of rare to ultra-rare conditions scattered over Europe and the rest of the world. Without its implementation the chances of progress are very unlikely if not absent, as it will be almost impossible to network on a pan-European level without any funds and impetus. Indeed, there was no significant pan-European initiative until the FP7. As the Action aims to include a large group of clinicians, scientists and patients organisations the potential to increase knowledge, stimulate research and improve management is huge. chILD is rare, and the average European children´s hospital will see no more than 5 cases/year, hence networking is vital if new research and

clinical trials to improve management are to be conducted. Standardising diagnosis and management will aid small as well as bigger hospitals to treat patients correctly and allow discussions and evaluation of difficult cases by many different specialists.

3. IMPLEMENTATION

3.1. Description of the Work Plan

3.1.1. Description of Working Groups

The Action contains six Working Groups (WGs) promoting multidisciplinary research:
WG1: Network of scientists: a network of researchers (genetics, systems- and molecular biology, animal models, psychologists, clinicians and health-economists) together with chILD-EU members will be gathered to discuss unmet needs and determine future research priorities. The WG will allow a two-way dialogue between basic and clinical scientists (1) to identify the basic science gaps most important to the clinical community, (2) for the clinical and lay community to understand what is scientifically possible, (3) to coordinate optimal use of human samples. This work group will thereby inform future directions of basic and patient oriented research aimed towards the development of treatment.
WG2: Monitoring disease progression by physiological measurements, imaging and patient reported outcomes (PROs). This WG will provide a platform to identify relevant outcome measures for clinical trials in children: a) identify physiological / lung function measures that are sensitive and specific for monitoring exacerbations, disease progression and therapeutic interventions; b) investigate CT scores as measures of lung disease progression in comparison to lung function; c) psychologists will develop patient reported outcomes (PRO) in close cooperation with parents groups.
WG3:chILD phenotype across the life course. This WG will a) use a meeting platform to connect chILD researchers, identify existing datasets and design joint analyses, including integration with chILD-EU and relevant adult databases; b) merge existing datasets into a meta-cohort; c) actively recruit adult physicians into relevant common topics (e.g. genetic causes of UIP or NSIP patterns of lung injury, and other relevant outcome variables); d) develop standardized clinical record forms for prospective multicentre data collection; e) perform a meta-analysis for individual-patient data to describe changes in chILD phenotype and severity over the life course, understand patterns of disease progression, identify environmental influences on disease progression (e.g. breastfeeding, smoking, virus infections[14]), develop a prognostic prediction tool and compare outcomes of different treatments (observational trials).
WG4: Feeding problems and their possible approaches in different age groups and subgroups of chILD. This WG will: a) identify and included paediatric gastroenterologists and dieticians; b) compile data on feeding difficulties in chILD -related disease (e.g. height, weight, BMI, calorie intake and type of feeding (oral, tube, PEG), presence of gastro-oesophageal reflux, psycho-social situation); c) identify relevant research needs and therapeutic approaches (e.g. Vitamins, supplements, special formula, different routes of feeding); d) compare approaches; e) discuss evaluation options and psych-social support measures.
WG5: Transition from paediatric to adult care. This WG will: a) identify areas of good practice and areas of need associated with transition from paediatric to adult care; b) assess current practices of transition and related problems in an international survey of paediatric and adult physicians; c) investigate patients' perceptions of care and compare young adults who had gone through a formal transition program with peers who had not; d) undertake a health economics assessment of programs of transition of care.
WG6: Planning and coordination of clinical studies: a) collaborate with WGs 1, 3-6, to identify promising therapeutic interventions, and with WG2 to determine outcome measures; b) draw on the expertise gained with the randomised clinical trials in chILD in chILD-EU and the much wider adult ILD clinical trial experience; c) plan, set up and coordinate observational and interventional

multicentre trials in chILD, investigating the effectiveness of known therapies and of novel agents in humans.

The expected outcomes from the WGs include:
WG1: (a) Review manuscript describing current pre-clinical models and the basic science gaps identified by the clinical community as most important. (b) Inventory of active research groups working on translational chILD disease neonatal models; associated infrastructure to share cells, tissues, tools, reagents. (c) Guidelines and training models for appropriate CT imaging in patients to allow meaningful interpretation. (d) List of potential biomarkers of disease progression and recommended methods of assessment.
WG2: (a) Tools and instructions for monitoring disease progression by patient reported outcomes (PROs). (b) Publication rating relevant outcome measures including exacerbations in clinical trials of chILD. (c) Publication on CT scores of molecularly defined chILD (ABCA3, SFTPC) cohorts describing lung disease progression. (d) Publication of chILD health economics comparing costs across Europe.
WG3: (a) Documented training and routine usage of the chILD clinical database by at least three physicians specialized in chILD per participating country. (b) Establishment of at least one chILD reference team (clinician, paediatric pathologist, paediatric radiologist) per participating COST country. (c) Work sheets for a standardised collection of clinical information during follow-up visits. (d) Rules and procedure for use of the datasets and associated biomaterials by the scientific community. (e) Publications on chILD phenotypes across long term course on (1) Clinical presentation, prognosis of different chILDs, lung function progression and onset of respiratory insufficiency, (2) Correlation between CT pattern and scores, and histology at time of biopsy relating these findings to prognosis, (3) Treatments used and associated outcomes of defined forms of chILD. (f) Manuscript on disease progression related to exacerbations. (g) Large standardised patient datasets, which can be used to answer questions on the epidemiology of chILD, and to generate hypotheses that can then be studied prospectively.
WG4: (a) Gastroenterologist, dietician and paediatrician collaboration; (b) Manuscript on feeding problems and their management; (c) Identification of relevant research needs, management and psychological problems related to nutrition.
WG5: (a) Publication describing European practices regarding the transition of patients with chILD from paediatric to adult care; including the identification of good practice and areas of need, based on the results of an international survey of paediatric and adult physicians. (b) Description of the patients' and parents´ perceptions of care and formal transition in different heath settings. (c) Development of formal pathways for transition care.
WG6: (a) Estimation of large pan-European cohorts for chILD-specific interventional and observational trials. (b) Outline(s) for future clinical trials and their feasibility, prerequisites for successful completion.

3.1.2. GANTT Diagram

The duration of the Action is 4 years. An initial inaugural conference will provide a 'start-up" meeting. WGs will meet every 6 months; consecutive WG meetings will ensure cross-fertilization with an aim of at least one annual scientific meeting at which all WGs meet. Management Committee meetings will occur annually linked to the scientific meeting. Scientific Committee (SC) will communicate every 2 months. The preliminary timetable is shown below:

	Year 1	Year 2	Year 3	Year 4
Scientific conferences	Kick-off	X	X	X
WG1	X - X	X - X	X - X	X - X
WG2	X - X	X - X	X - X	X - X
WG3	X - X	X - X	X - X	X - X
WG4	X - X	X - X	X - X	X - X
WG5	X - X	X - X	X - X	X - X
WG6	X - X	X - X	X - X	X - X
SG teleconf meetings	X–X–X–X–X–X	X–X–X–X–X–X	X–X–X–X–X–X	X–X–X–X–X–X
Website; Project management & programme set-up	X			
Updates website & programme		X	X	X

3.1.3. Risk and Contingency Plans

The risks of failure for the Action are small because:

- The Action will use the experience of the FP7 chILD-EU project that started to work on Standard Operating Procedures (SOPs), has established a chILD database/registry and started the first ever-randomised controlled trial in chILD. This expertise will be used to improve COST Action.
- This Action already includes 23 countries of which 18 are COST countries, 1 near neighbour country and 4 international partners, so the network is growing.
- The consortium has strong expertise in all areas of the project, from paediatrics to adult care, from patient organisations to quality of life experts). All of the groups are recognised at the international level.

The risks associated with the project are divided into general (1), recruitment (2) and data management (3) risks

1. **General risks**

Network of scientists

- To mitigate this risk the network has developed and put into action effective communication strategies for intra and inter country communication (via country networks and the Paediatric Assembly of the European Respiratory Society) and has effectively placed international parent groups within this structure. Also research seminars will be used to recruit more scientists for the Action.

Implementation of diagnostic and therapeutic guidance for chILD

- The Action has a solid basis of diagnostic and therapeutic guidance for chILD available. The Action will maintain the available standard operation procedures (SOPs) update and will rely on the COST network to expand knowledge in the field. Communication between different experts as well as different countries with the support of the patient organisations will allow the Action to proceed and resolve the difficulties.

2. **Recruitment risks**

- This Action will give the opportunity to numerous clinicians and scientists to be active in the field, however patient recruitment is time consuming and may result in low recruitment of subjects into the observational database or the investigator initiated trials. The Action however involving a large number of COST members with special expertise in ultra-rare diseases from Europe as well as overseas will be able to offer sufficient incentives from peer review and expert advice to attract and recruit sufficient patients into the project. At least the Action will be able to build on the existing chILD-EU database and initiated and ongoing studies; these are invaluable crystallization points

for the preparation of future randomised clinical interventions and appropriate applications for such more costly trials in the future.

3. **Data management risks**

- The Action will use a pre-existing common European platform for data collection and management, which may generate a large amount of prospectively collected data over time. From the beginning, the data will be optimised by targeting a low number of critical obligatory variables, but with high quality. Of importance is a deep and complete characterization of all chILD cases to achieve a peer-reviewed working diagnosis. From our current experience that can be achieved in almost all cases. This will allow a reliable accumulation of comparable cases with the associated biomaterials. The biomaterials can be used in future studies for genetic diagnosis of particular cases. Tools to extract and analyse the data captured into the register are available and this collection of algorithms will continuously be adapted to the needs of the scientists utilising the information.

  The Action Management Committee in close collaboration with the Work Group Leaders will ensure that risks will be identified at the earliest possible stage, so that efficient countermeasures will be taken well in time.

3.2. Management structures and procedures

The Action will be carried out according to “Rules and Procedures for Implementing COST Actions”. The Management Committee will coordinate the COST Action. The Management committee 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 and a Training School Coordinator (TSC). The Management Committee 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 yje COST Association. The Management Committee will meet annually to review the strategy of the Action in light of developments and progress. It will thus set new objectives according to innovative input from the WGs. The Management Committee will identify relevant research programs for scientific exchange and potential collaboration. The Management Committee will develop reports related to the Action and will coordinate the preparation of a proposal for future EU programmes. It will also discuss and disseminate publication policies. A Scientific Steering Group (SG) will be a small, responsive group of committed individuals. The SG will include the dissemination coordinator, the Training Schools Coordinator, and the six WG Leaders and an Early Career Investigator (ECI) . Additional members will be co-opted if needed with agreement of the Management Committee. The SG will support the Management Committee by making decisions, which are then ratified by the Management Committee as appropriate: establishment and updating the website and project management tool**,** organizing and coordinating the conference agendas, workshops & STSMs. The SG will establish the infrastructure and regulatory approvals for sharing of patient data sets, bio-banked 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 Dissemination Coordinator 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. The Dissemination Coordinator will raise awareness regarding opportunities to contribute to national and international conferences and meetings outside the Action to promote the Action. Moreover the Dissemination Coordinator will be supported by two members of the Management Committee and an ECI. The Training Schoo**l** Coordinator (TSC) will work with two members of the Management Committee and two ECIs, including at least one person from an Inclusiveness Target Country (ITC) to set up the program the training schools and to coordinate and promote other training opportunities.

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Training schools will be open to all ECIs 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. 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 Management Committee, always in accordance with “Rules and Procedures for Implementing COST Actions”.

3.3. Network as a whole

The Action will achieve its objectives by supporting networking of leading European, International Partner and Near Neighbour Countries groups with clinical and research interests in interstitial lung disease. In addition, the Action will seek collaboration with industry and with researchers not primarily engaged in chILD but with skills critical for the success of the Action e.g. clinical trials expertise. For example, the Action will include interested small and medium enterprises specialized in drug development into our discussions to develop strategies to bring drugs already in clinical usage into orphan drug development programs. This will lead to new concepts for both investigator and industry initiated trials. Representatives from patient organisations will be included in all aspects of the Action. In order to increase the success rate; the Action will also expand the network outside Europe, allowing access to a substantial, well phenotyped and ethnically diverse chILD population as well as the opportunity to learn from centres of excellence outside Europe.