Executive Summary:
Childhood interstitial lung diseases (chILD) are rare diseases and comprise a large group of childhood specific entities as well as the spectrum known from adult ILD. There are many unmet needs in this orphaned area. Ten major ones were addressed here.

1. Low diagnostic awareness for chILD and isolated treatment across Europe
European clinicians caring for isolated orphan cases of chILD were united into a critical mass of expertise
that no individual country can provide. The European management platform for children’s interstitial lung disease is open to all caregivers interested, both, professionals and lay people. For policy makers our results point to a significant population in need for more support.

2. Missing of a pan-European database and bio-bank compatible with others worldwide
We have successfully implemented a web-based data capture and biobank system running on SecuTrial®. After notification via www.childeu.net the participant is registered, trained and supported to enter pseudonymized patient data and submit biomaterials to the central site. Patient data entry started in 2014. By November 2016, 575 cases from more than 100 sites in Germany, UK, Turkey and many other countries were included.

3. Lack of verification of diagnoses by multidisciplinary expert panels
After being appropriately entered, those cases ready for international multidisciplinary team peer-review were reviewed by clinician experts, pediatric radiology experts, and if necessary specialized pathology and genetic experts. By November 2016, 363 cases are finally reviewed and followed prospectively.

4. We generated a “Best practice Checklist” for the diagnostics in suspected chILD and we compiled “Standard Operating Procedures (SOPs)” based on the results of collected current clinical practice in Europe.

5. Prospective observational data on incident and prevalent chILD cases
We actively pulled together currently isolated cases of chILD into a critical mass of patients that will enable prospective evaluation of the clinical, radiological and prognostic course.

6. Central biomaterial repository for long term storage of samples
We opened a web based biobank which can be followed on line and used for well characterized patients to elucidate the mechanisms of these rare diseases.

7. Involvement of affected families and patients
We assessed family experience with chILD and identified up to now unrecognized and unmet needs, like feeding issues. Patient care was directly assessed and improved by development of a freely available patient information booklet. This was produced in German, French, Danish, Turkish, Italian and English. A structured patient education program was assessed.

8. Quality of life and health economics
Disease specific patient reported outcomes were developed and validated. Patients’ health economics and patient reported outcomes were assessed in chILD for the first time, helping to improve the quality of life for children and their parents.

9. Clinical outcomes and lack of knowledge on currently used treatments
Following several rounds of discussion and document evaluation among the participants, key parameters for outcome follow-up were defined. The complex variable acute exacerbation was defined, criteria for evaluation were suggested. Designs to evaluate chest imaging and histology were proposed.
10. Lack of randomized and controlled interventions with off-label treatments
After a world-wide Delphi process to reflect on the needs and wishes of the community, we decided to focus on the investigations of two compounds, i.e. hydroxychloroquine and systemic steroids. 3 randomized, placebo controlled trials were designed and initiated in Germany.

In summary, the project successfully implemented a pan European management platform for children’s interstitial lung disease as a solid base for future clinical and research networks.

Project Context and Objectives:
Children with childhood interstitial lung diseases (chILD) are a large and neglected group of patients because these are rare diseases, frequently not diagnosed because the presentation is non-specific, and comprise a large group of childhood specific entities as well as the spectrum known from adult ILD. Even if the possibility of chILD is considered, there is no standard diagnostic pathway, prognosis is unknown, and treatment is anecdotal, despite the discovery of a few molecular causes (for example, mutations in surfactant metabolism genes).

Progress is very slow because of (a) lack of diagnostic awareness; (b) rarity of chILD (< 1:50-100,000 children); (c) large number of individual conditions (>200) that occur under the chILD umbrella; (d) unfamiliarity with the diseases and lack of established diagnostic pathways; (e) lack of resources for complex collaborations to assemble cohorts in which scattered, but well defined entities are followed; and (f) lack of standardized and quantifiable outcomes to enable controlled observations for any evidence based guidelines. This project has addressed these problems.

Leading European clinical scientists and paediatric pulmonologists with expertise in chILD have collaborated in order to (a) increase diagnostic awareness and tie together all chILD across Europe; (b) ensure these patients are characterized in a uniform manner, with expert verification of diagnoses by international panels of clinicians, radiologists, geneticists and pathologists; (c) establish a pan-European database and bio-bank compatible with others worldwide; (d) assess currently used treatments; (e) refine relevant clinical outcomes; (f) initiate first randomized and controlled interventions of off-label treatments, and (h) prepare and implement guidelines and treatment protocols for chILD in Europe.

Based on this concept we aimed to achieve the following six scientific and technical objectives.

Objective 1: Generation of a common European database and biobank.
Build a functionally appropriate pan-European web-based database and biobank which is compatible and can import data from similar programs world-wide.

Objective 2: Assessment and implementation of guidelines and treatment protocols.
Establish a series of Standards Working Groups (clinical, radiological, genetic and pathological) to generate evidence-based and consensus-agreed diagnostic and management clinical guidelines. We will generate a “Best practice Checklist” for the diagnosis and subsequent follow up investigations in suspected chILD.
Our “Standard Operating Procedures (SOPs) assembly will determine current clinical practice in Europe and rate it in comparison to the available evidence.
We aim to collect all systematic observations performed in the project and try to implement the results together with evidence generated elsewhere into diagnostic and management clinical guidelines for chILD. We will over a web-based rare disease information service for patients, families and the public to provide up to date information in native language.

Objective 3: Recruitment of a carefully characterized cohort of chILD patients. Our goal is a European wide recruitment and interdisciplinary critical peer review of all chILD diagnoses submitted from across Europe. Each case will be given a diagnosis independently; if no firm diagnosis is possible, we will review the case periodically as new information becomes available. During the first year of the study, clinicians’ decisions according to local practice and outcomes will be independently monitored and assessed. In the following years, we hope that physicians will adhere to suggested specific diagnosis and treatment protocols, to aim to achieve homogenous observations in our cohort of chILD patients.

Objective 4: Determine the value of outcomes used in chILD. We will investigate with the help of consensus meetings, a Delphi procedure and expert discussions what are relevant variables and disease markers currently used in chILD. We will rank their usefulness; implement many in the electronic data base for regular determination and will discuss how may be further evaluated.

In pilot studies we aim to determine the short term variability, reproducibility and sensitivity to change of selected clinical outcomes obtained by professionals and also parents/patients/caregivers.

We will analyze complex outcome measures, starting with a short review of the literature, a definition of exacerbation in chILD and the criteria to identify an exacerbation.

A major goal will be the development of a disease-specific health-related instrument for quality of life to collect self- and parent-proxy ratings of children with interstitial lung disease (chILD) between the ages of 0 month and 18 years. These instruments will be tested for internal consistency and convergent validity. We hope to generate health-related instruments of quality of life which can be used in clinical trials in children with chILD.

We aim to continuously score chest CT scans from all chILD-entities during peer review and we also want to score histopathology slides during this process. In case we can collect sufficient images and corresponding histological slides we will pose hypotheses and elaborated on the methods how they will be tested, in order to validate the assessments made.

We will review the utility of biochemical and inflammatory serum markers for chILD.

Objective 5: Assess treatment variations used, deliver data from defined protocols and linked outcomes. In this project we will analyze treatment and outcomes of subjects collected in the observational cohort. Analysis will enable us to select pharmacologic treatments and to suggest protocols for their further evaluation.

We will develop and evaluate a patient and caregiver education program for physicians specialized in
chILD. We hope that self- and parent proxy-reports will give us feedback that we are able to improve the self-efficacy of the patients and their families, dealing with chILD.

Objective 6: Randomized interventions with off-label treatments.

We reach out to overcome the administrative hurdles to be taken also for investigator-initiated studies in Europe.

We will have extensive explorations of the unmet needs in the treatment of chILD. In consensus meeting we will discuss and prioritize possible trials. With an estimate of their feasibility, we will initiate randomized controlled trials.

In face of the limited resources and time available within this project for such plans, we will reach out for an interim analysis. We will set up the statistical analysis plan and will run it on the patients collected without un-blinding.

Project Results:
WP1 Common European database and biobank

The overall objective of this work package was the structural (electronic) implementation of a common European database and biobank. This goal was completely achieved. The well-functioning international web-based database has been well taken up by clinicians and researchers from many European and non-European countries.

The system is based on SecuTrial®, a web-based data capture system. The data safety concept was accepted by the Telematic platform, German authorities and those of the member states. In principle the medical data (MDAT), the identifying data (IDAT) and the biomaterials are stored independently and merely brought together by the treating local physician.

Fig. 1 Data safety concept of the European chILD database and biobank

After obtaining informed consent from the parents and patients if old enough, notification of a case via a web-site [http://www.klinikum.uni-muenchen.de/Child-EU/en/cases-for-register/index.html](http://www.klinikum.uni-muenchen.de/Child-EU/en/cases-for-register/index.html) and registration of the participant (physician), the participant is trained and enabled to enter pseudonymized patient data. Biomaterials are submitted to the central site.

The minimal data set was discussed among specialized physicians from UK, Germany, Turkey, Italy and France in consensus meetings and many telephone conferences, harmonized and implemented electronically.

An important feature of the system is its ability to import data which was successfully implemented and tested with the training data set. However, the exporting data base has to produce their export scripts. This issue was not solved by the team of the RespiRare database by the end of the project. Thus from RespiRare a successful import was not done.

Update and maintenance of the electronic structure is continuous.
Significant results

- A well-functioning international and common European web-based database and biobank for children’s interstitial lung diseases was implemented successfully and well taken up by many European and non-European clinicians and researchers (Griese et al, manuscript in preparation).
- Diagnostic standards are demanded during usage of the data base, the important process of making the diagnosis (peer review) and during subsequent follow up investigations of confirmed chILD (Bush et al 2013, Thorax).
- Compatibility of any newly developing register with chILD-EU database provided by open exchange of our current data base dictionary. This can be downloaded as an up-to-date report any time in the register.
- Continuous update of the electronic structure and realization of complex extensions.

WP2 Guidelines, treatment protocols and their implementation

The overall objective, the integration of the multitude of different and non-standardized strategies for the diagnostic and clinical management of chILD currently used in Europe and world-wide, was achieved and suggested as “Best practice Checklist“ for the diagnosis and subsequent follow up investigations in suspected chILD. The guidelines report the results of a Delphi Consensus process and suggest if you decide to treat, then please let us all do it the same way in the absence of any evidence.

We have successfully generated SOPs, implemented them into our routines and disseminated them on our website and in an important publication in Thorax (Bush et al 2015)

We have developed and actively use a web-based rare disease information service for patients, families and the public to provide up to date information in native language. These services are installed via the chILD-EU website with listed contacts (name, email, phone) of specialists for children’s interstitial lung disease in Germany, UK, France, Turkey, Italy.

http://www.klinikum.uni-muenchen.de/Child-EU/en/services/patient_information_service/index.html

We provide a comprehensive patient information booklet with all clinical and practical information for patients to live with chILD. The booklet is now available for free in German, English, Italian, Turkish, Danish, and French. Further translations into other European languages are underway

http://www.klinikum.uni-muenchen.de/Child-EU/en/index.html

Fig. 2 Patient information booklet translated into Danish

As a result of collaboration between patients and professionals, a web-based questionnaire which was implemented in the UK, and filled in by parents of children affected by chILD, highlighted for the first time the high prevalence of feeding disorders in chILD (77%, persisting in 35%) and the unmet needs these families have (Gilbert et al 2015)

Significant results

- Best Practice Checklist was agreed upon and published in a high rank Journal as European protocols for the diagnosis and initial treatment of interstitial lung disease in children (Bush et al 2015)
WP3 Observational cohort – objectively measure and evaluate contemporary management strategies and outcomes

We have successfully implemented the Ethical approvals for data entry and biomaterial transfer within Europe; set up the case notification on childeu.net website; opened many centres and continuously enrolled cases for peer review and further follow up.

A) Patient recruitment in the chILD-EU Register from 2014 to 2016

Based on the activity in the last three years of the centers leading this application, we expected to enrol 100-150 annually with chILD, with the majority of cases being referrals from inside each country.

1. Recruiting period Jan 2014 until Nov 2014 (11 months): 144 cases
2. Recruiting period Dec 2014 until Nov 2015 (12 months): 281 cases (in total 425)
3. Recruiting period Dec 2015 until Nov 2016 (12 months): 150 cases (in total 575)

By now, 575 cases are documented (cut-off date: 30th Nov 2016, see Figure 3). Of these 121 are incident cases.

Fig 3: Patients over time in the chILD-EU register from 2014 to 2016

The reason for the faster recruitment initially was the availability of prevalent cases; with ongoing time recruitment was due to newly diagnosed, incident patients.

The database report includes the

a) chILD-EU member states Germany, UK, France, Turkey, Italy with a total of 504 patients and
b) non chILD-EU member states like Austria, Belgium, Brazil, Croatia, Denmark, Holland, Poland, Portugal, Spain, South Africa and Switzerland with a total of 71 patients

Fig 4: Patients over time in the chILD-EU member and non-member states

B) chILD-EU – project member states

In total 504 cases of the chILD EU study centres in Germany, UK, Italy, Turkey and France were documented in the chILD EU observational database. Most cases were documented by the German study centres (246 patients), followed by United Kingdom (103 patients), France (77 patients), Turkey (55 patients) and Italy (23 patients).

The recruitment was not homogenously distributed across all study sites. Germany and UK continued recruitment well with Germany additional 60 patients and UK additional 51 patients in the last 12 months followed by Turkey with 11 additional patients. France and Italy did not recruit during the last 12 months.

Fig 5: Patients over time in the chILD-EU member states per country

C) Selected sites by country
Germany
In total 245 cases of the chILD EU study centres in Germany were documented in the chILD EU observational database. Most cases were documented by the study centre in Hannover (80 patients), followed by Munich (63 patients), Frankfurt/Main (15 patients), Essen (11 patients), Oldenburg (8 patients), Tübingen (7 patients), Heidelberg and Giessen (6 patients).

All other 27 sites in Germany were recruiting between 1 and 4 patients. 15 sites of them only have registered a single patient. In Fig. 6 these sites are cumulated in category “other sites” (49 patients).

There was a continuous increase in the number of patients registered in Germany since start of recruitment:
1. Recruiting period Jan 2014 until Nov 2014 (11 months): 74 cases
2. Recruiting period Dec 2014 until Nov 2015 (12 months): 112 cases (in total 186)
3. Recruiting period Dec 2015 until Nov 2016 (12 months): 60 cases (in total 246)

Fig 6: Patients over time in Germany per site

United Kingdom
In total 103 cases of the chILD EU study centres in UK were documented in the chILD EU observational database. Most cases were documented by the study centres in London (21 patients), followed by Liverpool (13 patients), Manchester and Nottingham (each 11 patients), Birmingham (9 patients), Edinburgh (7 patients), Southampton (6 patients), Sheffield and Newcastle (each 5 patients), Glasgow (4 patients), Cardiff and Oxford (each 3 patients) Bristol and Leeds (each 2 patients) and Aberdeen (1 patient).

There was a continuous increase in the number of patients registered in UK since recruiting started:
1. Recruiting period Jan 2014 until Nov 2014 (11 months): 20 cases
2. Recruiting period Dec 2014 until Nov 2015 (12 months): 32 cases (in total 52)
3. Recruiting period Dec 2015 until Nov 2016 (12 months): 51 cases (in total 103)

Fig 7: Patients over time in United Kingdom per site

Turkey
In total 55 cases of the chILD EU study centres in Turkey were documented in the chILD EU observational database. Most cases were documented by the study centres in Ankara (53 patients), followed by Manisa (2 patients).

There was a continuous increase in the number of patients registered in Turkey since recruiting started:
1. Recruiting period Jan 2014 until Nov 2014 (11 months): 17 cases
2. Recruiting period Dec 2014 until Nov 2015 (12 months): 27 cases (in total 44)
3. Recruiting period Dec 2015 until Nov 2016 (12 months): 11 cases (in total 55)

Fig 8: Patients over time in Turkey per site

Non chILD-EU member states
In total 71 cases of the non-chILD-EU member study centres in Austria, Belgium, Brazil, Denmark, Holland, Poland, Spain, South Africa and Switzerland were documented in the chILD EU observational database.

Fig 9: Patients over time in Non chILD-EU member states per site
Most cases were documented by the Polish study centres (31 patients), followed by Denmark (9 patients), Switzerland (8 patients), Spain (6 patients), Belgium and Austria (4 patients), South Africa (3 patients), Brasil and “other” (each 2 patients).

There was a continuous increase in the number of patients registered by all these countries, without to be a member of the chILD-EU project, i.e. without getting any resources for this. This shows the broad acceptance of the system. We thank all supporters of the register for their voluntary efforts!
1. Recruiting period Jan 2014 until Nov 2014 (11 months): 6 cases
2. Recruiting period Dec 2014 until Nov 2015 (12 months): 38 cases (in total 44)
3. Recruiting period Dec 2015 until Nov 2016 (12 months): 27 cases (in total 71)

Fig 9: Patients over time in the Non chILD-EU member states per country

D) Peer review
Of 575 patients in the database, a peer review was done by expert teams in 363 cases (63%). This meant that independent reviewers consisting of an expert clinician, radiologist, and pathologist and if necessary a geneticist, reviewed each case in a multidisciplinary team meeting. For this all data including imaging and sometimes biopsies had to be available.

In 313 cases peer review was finalized, in about 50 cases further information was recommended or necessary to achieve an appropriate diagnosis. Among the patients with no peer review request by the center are also those subjects listed which were not continued in the data base, i.e. did not have a visit 2 and following.

Fig 10: Peer review activity on cases

There were significant differences between regarding the sites for which peer review was done.

Fig 11: Peer reviews per site

Significant results
• Patient data entry increased continuously with time
• Peer reviews continuously operates well
• External monitoring of the database was done
• The patient recruitment successfully achieved the planned aim of 400 to 600 patients during 4 years
• The number of patient differed in the participating chILD-EU member states
• Non chILD-EU member states ambitiously participated in the register project without financial compensation
• Continuous effort guarantees and improves the completeness of the data
• Summary manuscripts of the experience with the review process, diagnoses, investigation and patient progress to date are being written (Cunningham et al; Griese et al, Schwerk et al)

WP4 Outcomes and disease marker – their value and further development
During several consensus meetings, a Delphi process and expert discussions we successfully agreed upon relevant variables and disease markers currently used in chILD, ranked in their usefulness,
implemented many in the electronic database and discussed several for further evaluation.

In pilot studies we determined the short term variability, reproducibility and sensitivity to change of selected clinical outcomes obtained by professionals and also parents/patients/caregivers (Hengst et al 2016, manuscript submitted).

Together with a short review of the literature, a definition of exacerbation in chILD and the criteria to identify an exacerbation was published under the title “Management of children with interstitial lung diseases: the difficult issue of acute exacerbations” (Clement et al 2016).

Fig. 12: From Clement et al, Eur Respir J 2016; 48: 1559–1563

We developed a disease-specific HrQoL instrument to collect self- and parent-proxy ratings of children with interstitial lung disease (chILD) between the ages of 0 month and 18 years. As in many other QoL instruments, we also found a slightly left-skewed raw score distribution in the direction of less perceived impairment of the child and slight ceiling effects.

With some exceptions, we found an excellent internal consistency (Cronbach’s α > .90) of the total scale and subscales. Hence, HrQoL can be measured robustly with the PedsQL Core module and also our developed additional chILD subscale. The convergent validity of the chILD subscale could be demonstrated by substantial positive correlations with the generic HrQoL instruments of PedsQL Core module. Comparison between clinical groups with different disease-specific characteristics suggests external clinical validity, with disease severity impacting significantly on the children’s HRQoL. As an example, the results of the patient reported outcomes assessed for pulmonary exacerbation are given in the following table 1:

Tab 1: Contrasts of Pulmonary exacerbations (until baseline) for confirmation of criterion validity of the chILD specific QoL Scale, PedsQL Psychological health summary score, Physical health summary score, Total score

We conclude that the PedsQL infants scales and Core module and also our developed additional disease specific chILD subscale is a psychometrically robust multidimensional measure for the assessment of HrQoL of children with interstitial lung disease. In future, the use of health-related-quality-of-life as an additional outcome variable in clinical studies, as recommended for example by the Food and Drug Administration (FDA) for clinical trials, will probably extend our knowledge on the effects of interventions for children and adolescents with interstitial lung disease (Goldbeck et al, manuscript in preparation)

During peer-review of submitted cases, we have continuously assessed and scored chest CT scans from all chILD-entities. We have optimized a system for CT scans and we have used for histopathology the ATS scoring system. For validation of the assessments made we posed three hypotheses and elaborated on the methods how they will be tested. These hypotheses are: H1 - CT scanning can be used to diagnose histological patterns seen on lung biopsy thus obviating the need for invasive testing. H2 - CT scanning can be used to make definite diagnoses, obviating the need for further testing. H3 - Multidisciplinary team diagnosis and categorization of pediatric diffuse parenchymal lung disease (chILD) is poorly reproducible
between teams.

The levels and utility of specialized biochemical and inflammatory serum markers in chILD was reviewed to great detail and a summarizing publication was generated (Biomarkers in interstitial lung diseases. Nathan N et al. Pediatr Respir Rev 2015; 16:219-224).

- Significant results
  - Short term variability, reproducibility and sensitivity of selected clinical outcomes (Hengst et al 2016, submitted)
  - Complex patient reported outcomes, i.e. acute exacerbation definition (Clement et al 2016)

WP5 Treatments – determine variability and efficacy, deliver data to define specific pharmacologic treatments

After we successfully developed a protocol for the assessment of current ChILD treatment regimens in Europe, multicentric data collected on treatments used, protocols were suggested to record treatment effects and side-effects in disease specific-subcategories.

In all patients systemic steroids were the commonest used medication, followed by Azithromycin and Hydroxychloroquin (Fig. 13)

Figure 13: Analysis of different medications used in the whole cohort (n=366)

In order to understand in what diseases these drugs were used, we displayed the disease categories currently utilized in the register (Table 2).

Table 2: Definition of included disease categories

The analysis showed that hydroxychloroquine was next to prednisolone and among the most widely used compounds, in particular in the surfactant dysfunction group patients (A4)(Figure 14).

Figure 14: Amount of Hydroxychloroquine intake in different subcategories

Follow up

All patients with at least one follow up visit (n=227) have been included for outcome analysis. Figure 15 shows the distribution of disease subcategories compared to baseline visit.

Figure 15: Distribution of different disease categories at baseline visit (n=366, blue) and at the last follow up visit (n=227, red)

Comparing the clinical condition of the cohort at last follow up with baseline characteristics we realized a trend of clinical improvement as the amount of patients on ventilator or oxygen support decreased (Fig 15)
whereas patients who did not need any respiratory support increased. Weather this was related to treatment or related to the natural disease course cannot be answered by this analysis.

In conclusion we have shown that

• glucocorticostroids, azithromycin and hydroxychloroquine are the most common used drugs in the treatment of chILD.
• these drugs are predominantly used in defined subcategories, namely A4 and B1. As most patients registered to child-EU have a final diagnosis coming from group A4 and B1, these categories seem to be the best disease specific categories for future studies.
• currently a controlled trial on the effectiveness of hydroxychloroquine in the treatment of chILD is running (Stop- and START-HCQ). Therefore, there is no need for another HCQ-study at the moment.
• although an expert-recommendation (after an expert-Delphi-Process) for the treatment of chILD with steroids and azithromycin has already been published by the chILD-EU-Group, we realized an enormous heterogeneity in treatment modalities with glucocorticosteroids making an analysis of treatment effects impossible at this stage.

A relevant question for a randomized controlled study could be whether a steroid pulse plus a continuous treatment with prednisone between 2 pulses is superior to treatment pulses alone.

A further interesting question is, whether azithromycin is a valuable treatment option especially in patients coming from subcategories A4 and B1. A similar protocol as the STOP- and START-HCQ protocol could be used and it is likely, that enough patients will be included, after the HCQ-Study has been finalized. Otherwise this would lead to necessary competition, as both indications are very similar.

We developed and evaluated a patient and caregiver education program for physicians specialized in chILD. The primary outcome was self-efficacy. As an example the results of the intention to treat sample set are given. Both, for self- and parent proxy-reports significant improvement of self-efficacy scores at the follow-up assessment compared with baseline scores were obtained.

Figure 16: Pre- post comparison of the primary outcome self-efficacy

For the secondary outcomes satisfaction with counselling, health related quality of life, physician’s satisfaction with patient education, and patients’ satisfaction with the information material similar results were obtained.

This pilot study provides preliminary evidence that the structured patient education program improved self-efficacy and parents and patients’ satisfaction with counselling. The program is feasible in clinical practice.

 welt Significant results

• SOP’s to record treatment effects and side-effects in disease specific-subcategories
• We developed instruments for patient education and successfully tested in a pilot study a structured patient education program (Goldbeck et al 2016, manuscript in preparation)

WP6 Randomized interventions with off-label treatments
Following extensive consensus meetings we have successfully setup the trial protocol for 1) a randomized placebo controlled intervention with hydroxychloroquine in infants and children with chILD and 2) for the investigation of medium term tapered oral systemic steroid treatment, randomized against placebo.

We have completed the ethics and competent authority process in Germany. We have finalized agreements between Sponsor (LMU-Munich) and study administrative sites in Marburg, Mainz and Munich. Agreements were finalized between Sponsor (LMU-Munich) and several German study sites.

We have continued administrative work in other countries.

Ethics and competent authority applications / approvals:
In UK, Italy and Turkey was the 1) hydroxychloroquine (HCQ) trial applied to the ethics committee and the competent authorities. We received the approval of the ethics committee in UK, Turkey and Italy and of the competent authority in UK. The 2) systemic steroid trial was not applied due to small size of patients in relation to the high costs of patients insurance per country and trial (see Tab 3).

Tab 3: Ethics committee and competent authorities’ approvals for the clinical trials HCQ and Stop EAA

Patient insurance Germany, UK, Turkey, Italy
All patients in clinical trials have to be insured. Patients’ insurance was provided by HDI Gerling the partner commonly selected by the sponsor, the Klinikum der Universität München. In Germany the insurance was contracted with Ecclesia Insurance broker for the HCQ and EAA clinical trials. The insurance policies for UK, Italy and Turkey were provided by the Munich Rück and contracted with the Atrials insurance broker.

Tab 4: Scheduled insurance completion

The actual costs for the insurances were significantly higher than initially estimated: 20,000,00 € were planned for all 5 Countries and both trials (see GA305653 – Annex I – DoW: page 97). Actual payments for above named insurance policies are 31074.25 €. We postponed the implementation of EAA trial in three countries also additional due to our limited financial resources.

Contracts for interventional trials
Due to complex legislation in the clinical trials many contracts are necessary before opening a site:
- Central contracts: between sponsor (LMU-Munich) and other partners/beneficiaries (see Tab 5)
- National site contracts: between sponsor (LMU-Munich) and German sites (see Tab 6)
- National coordinator contracts: between sponsor (LMU-Munich) and each national coordinator (beneficiary) in Padova (Italy), Edinburgh (UK), Ankara (Turkey) and Paris (France) (see Tab 6)
All this posed a non-anticipated excessive burden for which no appropriate resources were available. Nevertheless the tasks had to be done and were done by the central trial management in Munich.

Tab 5: Contracts prepared and status of processing for HCQ- and EAA trial
Monitoring for interventional trials in Germany

All recruiting sites were regularly monitored (see Del 6.4). Monitoring reports are available in German language initially and since January 2016 in English.

Based on the enormous administrative hurdles to be taken in Germany and then in a similar fashion in all other countries who intend to participate in the studies, we had to realize that our initial goal to complete those studies within the chILD-EU project had to be revised. This was done in an amendment in December 2015 and extensively discussed with our Project Officer in great detail. We revised the description of work and reached out for an interim analysis. To that end we intended to set up and program the statistical analysis plan. We further assessed feasibility and realization of the study based on the cases included until the end of chILD-EU study extension without braking the randomization code. This statistical instrument can later be used again when the studies were continued and completed.

In Germany 5 sites are initiated: Munich, Hannover, Essen, Bochum, Frankfurt, Leipzig and Giessen. Initiation is expected soon for Berlin, Heidelberg and Lübeck/Kiel.

We were very happy to generate good pilot data in all 3 randomized controlled protocols. We learned many details very useful to optimize study performance.

For all 3 studies we have prepared complete statistical analysis plans. These are deposited in the confidential part of the report. They very nicely show the potential of these pilot studies and point to their continuation.

Into the exogen allergic alveolitis trial (Stop-EAA), 4 patients were included (Fig. 17). The primary end-point was vital capacity (VC): The blinding of the subjects is still kept. These initial data demonstrate the feasibility of the study protocol even in small and rather ill children in a multicenter setting. In all patients a causative antigen was identified and in all removal of the underlying antigen was demonstrated. All subjects showed a clear improvement over time irrespective of the study drug given, a result well in concordance with the study hypothesis. Side effects of treatment may occur, thus controlled treatment similar to the study design can be recommended. The continuation of the study was urgently recommended by the data safety monitoring board.

Fig. 17 FVC as primary outcome in the exogen allergic alveolitis trial (Stop-EAA),

7 patients have been included in the START hydroxychloroquine trial. The primary end-point was change in O2-saturation. Patients could either start the medication or stop it in a randomized fashion, blinding of the subjects is still kept.

Fig. 18: O2-saturation as primary outcome in the hydroxychloroquine START trial (START-HCQ).

5 patients have been included in the STOP hydroxychloroquine trial:
There was a wide variation in baseline physiologic measures, several subjects having normal values of O2-saturation and lung function; blood gas analysis need to be considered in future protocols. The compliance, in particular in the STOP trial needs to be reinforce in future patients. Training of sites to adhere to complete study protocol procedures needs to be enhanced very much. There were no unusual safety signals from the study. The data safety monitoring board urgently suggested the continuation of the study.

Significant results

- Ethics and competent authority process in Germany finalized. Approval of the EAA and HCQ trial received and 3 randomized trials started.
- Ethics and competent authority process in UK finalized, in Italy and Turkey finalized with Ethics, but not competent authority approval (due to lack of time during the active chILD-EU program). In France no efforts were undertaken to participate in the study.
- 7 recruiting sites in Germany.
- Stop-EAA (exogen allergic alveolitis) trial with 4 patients completed.
- START and STOP hydroxychloroquine trials running with 12 patients included.
- Completed statistical analysis plan
- Test run of statistical analysis

Potential Impact:

Innovation and Impact

At conclusion of the ChILD-EU project we can state that we have fulfilled all the expected impacts of our work programme.

(1) We have united European clinicians caring for isolated orphan cases of chILD into a critical mass of expertise that no individual European country can provide.

(2) We have actively pulled together currently isolated cases into a critical mass of patients that enable us to evaluate and elucidate the clinical, radiological and prognostic course of these rare diseases.

(3) We have collected biobank of specimens from well characterised patients to elucidate the mechanisms of these rare diseases, linking with the basic science facilities beyond this project.

(4) We have enabled individual clinicians to be more effective through a supportive peer review of diagnosis with recommendations for best practice, and subsequent outcome review by anonymized data provided by the common European database.

(5) We have improved the quality and consistency of diagnostic accuracy; benefiting patients and clinicians. This includes the provision of pan-European access to accredited genetic testing in the clinical frame work, which is used to an increasing extent.

(6) We have defined biomarkers and complex clinical constructs like exacerbations, as outcome measures.
for usage in clinical and research studies.

(7) We have not installed therapeutic trials of medicines in the frame of N=1, placebo-controlled interventions, as the administrative hurdles were too high, but we have initiated three double blind randomized controlled trials in drugs currently used in chILD.

(8) We have prepared the analysis of various treatment/intervention regimens for chILD which are currently being used off-label and haphazardly in order to evaluate their effectiveness and adverse events.

(9) We have built a uniquely well-characterised patient group which will encourage the development and testing of novel diagnostic and therapeutic approaches, in a group of conditions with few current therapeutic options.

(10) We have used this pan European chILD communication network to better support patients and their families by providing knowledge and evidence-based clinical guideline frameworks for clinician practice.

(11) We have continued and deepened our partnership work with European chILD parent network to ensure practice reflecting and incorporating outcomes of importance to the quality of life for children and their parents.

(12) We have led to a better care of patients afflicted by rare chILD diseases for which no dedicated treatment is currently available.

(13) We have made available to a broad community a common European Database and Biobank, to collect and evaluate data across the broad spectrum of chILD.

The outputs we have generated include the new availability to the community of

(1) Patient derived outcomes, i.e. measurements of quality of life. These outcomes are novel and now available for the first time to be utilised across studies of rare respiratory disease in children

(2) A critical mass of clinicians caring for children with chILD and a network supporting a rapid access for newly emerging Clinical Research Network for industry testing of diagnostics or therapeutic options

(3) Well characterised cohorts of children with ChILD helping EU health related industries to understand the needs of these patient groups and orientate their development strategies accordingly.

(4) A communication portal to a critical mass of patients for which new potential therapies can be tested, which are collected in the chILD-EU database and biobank enabling EU health related industries to plan studies and future developments.

Dissemination and Exploitation
We have successfully reached our key deliverable the integration of clinicians across Europe with parent groups also across Europe to produce patient relevant evidence based clinical guidelines. These
guidelines were published in a high–impact peer reviewed Journal and together with the best-practice check list and SOP’s disseminated via our website, which was very frequently utilized.

Under the top 20 downloads in 2016 were all provided SOPs (Fig. 20) and the patient information booklets in German, English, Turkish and Danish (Fig. 21).

Clinicians working in isolation when dealing with rare diseases were joined via the European management platform for sharing of knowledge and standardized guidance. This reassured and unburdened physicians especially when best practice approaches which have been shown in the past to be successful and safe, are used in clinics across Europe.

An important innovation was the inclusion of patient reported outcomes, which helped to assess the impact of the diseases on the quality of life of the patients and their families.

The established database and biobank provides a durable platform for the discovery mechanisms of disease, and hence of new therapies, and their rapid translation into clinical practice. We provide the platform for translational development yielding a structure for future trials of medicines in well characterized groups throughout Europe and beyond.

In order to ensure the rapid dissemination of the results to textbooks, national and international guidelines, members of the consortium are currently active in writing in both guidelines and books and monographs in the field.

Commercial aspect
Now the availability of a well characterised cohort of patients supported by a network of accessible clinicians provides a commercially attractive hub with which to communicate and better understand the needs of this patient group.

Our cohort is of interest for established and developing health related industries. These novel structures will increase the competitiveness and innovative capacity of European health-related industries to address issues in rare diseases on a global health scale and to help the development and commercial exploitation of novel therapies in the field.

Dissemination

(1) Dissemination within the Consortium and the chILD-EU community
We have used monthly newsletters which were distributed to all clinicians and experts in the chILD-EU register and to all known clinicians, including overseas in America and Australia. Additionally all newsletters are published on the chILD-EU website: [http://www.klinikum.uni-muenchen.de/Child-EU/en/news/newsletter/index.html](http://www.klinikum.uni-muenchen.de/Child-EU/en/news/newsletter/index.html)

(2) Dissemination to patient associations
We have included patient organizations and lay people from affected families by having representatives on register and clinical study review boards, in the data-monitoring and ethical boards. We have closely worked together with patient’s organization in research on the needs and problems of affected patients and their families. We have produced a joint scientific publication on this topic. Our website and the patients sites were closely linked. Patients booklets were produced in 6 languages, each in close cooperation with national patient organizations if available and had patient organizations disseminate these key milestone information within their individual countries.

(3) Dissemination to researchers outside the Consortium
The mainstay of dissemination was via peer-reviewed publications of the consortium. About 30 have been published and several are in preparation. Major public meetings were targeted, e.g. the meetings of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2013, 2014, 2015 and 2016. At these meetings symposia, “hand-on” courses or special lectures on chILD were held. Additionally we organized
a) the national Turkey chILD - EU congress “Interstitial lung diseases in children – sharing knowledge and experience across Europe-“ hold in Ankara in January 2016 and
b) the national UK chILD – EU meeting “Interstitial lung diseases in children – sharing knowledge and experience across Europe-“ hold in Edinburgh in June 2016 and
c) a 2-days “hands on” chILD - EU Symposium in Munich during November 2016 to address a wider audience
Numerous web-based expert trainings within and outside the consortium and to the wider European community of professionals in chILD were organized.
World wide web – broadcast (webinar) by ATS Assembly on Pediatrics (Peds) Journal Club about “Persistent tachypnoe of infancy” was hold on the 07th Oct 2016.

(4) Dissemination to the healthcare sector and society
The first ever patient education program was designed and completed including 98 affected patients and their parents affected with chILD. This program is available for free and implementation in other sites and institutions.

A comprehensive patient information booklet was developed and made available free of charge on the chILD - EU website (www.childeu.net) in German, English, Turkish, Italian, Danish and French language. Printed versions are available to hand out to patients involved in the education program and for individual request. Additionally a patient information service was provided on the chILD-EU website http://www.klinikum.uni-muenchen.de/Child-EU/en/services/patient_information_service/index.html

(5) Dissemination to civil society
The coordinator of the project presented the chILD-EU Register in the radio broadcast “Das Gesundheitsgespräch” on Bayern 2 (http://cdn-storage.br.de/MUJluUOVBwQlbtChb60Hu7ODifWH- by/-JS/9-8f9-4y/160227_1205_Gesundheitsgespraech_Seeltene-Erkrankungen---Waisenkinder-der-
Additions to the Wikipedia article “interstitial lung disease” were made to visualize children’s interstitial lung disease (https://en.wikipedia.org/wiki/Interstitial_lung_disease#cite_note-3).

List of Websites:
URL: www.childeu.net

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Related documents

[final1-2017-01-29-ce-final-report-4-1-grafiken.pdf]

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Permalink: https://cordis.europa.eu/project/id/305653/reporting

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