European Management Platform for Childhood Interstitial Lung Diseases

Study Protocol

Orphans Unite: chILD better together – European Management Platform for Childhood Interstitial Lung Diseases

ChILD-EU database and observational study

CHILD-EU TRIAL

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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European Management Platform for Childhood Interstitial Lung Diseases

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CONTENTS

PROTOCOL APPROVAL

Orphans Unite: chILD better together – European Management Platform for Childhood Interstitial Lung Diseases: chILD-EU database and observational study

Funding Reference Number : 305653

Signatures

Dr Steve Cunningham Chief Investigator	_____ Signature	_____ Date
Ms Catriona Graham Trial Statistician	_____ Signature	_____ Date
Ms Marise Bucukoglu Sponsor(s) Representative	_____ Signature	_____ Date
Principal Investigator	_____ Signature	_____ Date

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
chILD	Childhood Interstitial Lung Disease
CRF	Case Report Form
CT	Computed Tomography
ECTU	Edinburgh Clinical Trials Unit
GCP	Good Clinical Practice
HR	Heart Rate
ILD	Interstitial Lung Disease
ISF	Investigator Site File
PEDS QL	Pediatric Quality of Life Inventory
QoL	Quality of Life
R&D	Research and Development
REC	Research Ethics Committee
RR	Respiratory Rate
SOP	Standard Operating Procedure
SpO2	Blood Oxygen Saturation

SUMMARY

This protocol describes two sequential interlinking studies required for the same population.

1. Establishment of a common European Database, with biobank and Peer Review confirmation of cases and annual review of progress and diagnosis
2. An observational study of treatment and outcomes in the first 12 months of diagnosis

1 INTRODUCTION

1.1 BACKGROUND

Paediatricians frequently see children with a respiratory rate as high as 80/min, perhaps with failure to thrive and hypoxemia. Within this non-specific clinical spectrum will be children with childhood interstitial lung diseases (chILD) (Deterding 2010). ChILD may also present dramatically in a term baby with severe unremitting respiratory distress leading to early death (Langston and Dishop 2009). These are rare diseases, frequently not diagnosed because the presentation is non-specific, and comprise a large number of disparate childhood specific entities as well as the spectrum known from adult ILD (Fan and Langston 2002). 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 protein genes) (Doan, Guillerman et al. 2008).

Progress is very slow because of (a) lack of diagnostic awareness; (b) rarity of chILD (< 1:50-100,000 children, 1-2 orders of magnitude less than adult ILD); (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 (Dishop 2011).

Our overarching study (ChILD-EU Orphans Unite), funded by an FP7 grant, will bring leading European clinical scientists and paediatric pulmonologists with expertise in chILD into collaboration in order to (a) increase diagnostic awareness and tie together all chILD across Europe; (b) ensure these patients are characterised 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) perform quality controlled observations of all interventions; (g) run the first randomised and controlled interventions of off-label treatments in chILD, and (h) prepare and implement evidence-based guidelines and treatment protocols for chILD in Europe.

This protocol is in two parts

(A) to describe the European ChILD-EU database and data collection
(B) to outline objective (f) of the overarching study; a controlled observational study of interventions used to assess and treat infants and children with chILD.

The protocol is combined in two parts as whilst the plans are integrated it is anticipated that Part A will continue longer term once Part B is complete.

1.2 RATIONALE FOR STUDY

There are limited studies bringing together children with interstitial lung disease and no studies assessing the response to standardised interventions in ChILD. The paucity of cases in each centre and the lack of evidence based treatment approach require a structured observation of current practice to inform future research direction. We aim to capture interventions and outcomes in well-characterised patients with suspected and proven ChILD. Such information will provide data on outcome in relation to standard interventions and support further research directions.

Part A: ChILD-EU Database and Biobank

The objective of the ChILD-EU Database and biobank is to build a descriptive collection of children with interstitial lung disease together with core biobank materials. The minimum dataset will include demographics, disease descriptors, investigations and the conclusions of an international peer review diagnostic team (www.childeu.net). Each case will be reviewed on an annual basis to ensure diagnostic accuracy and data entered from clinical encounters

into the database. The biobank will include as a minimum a blood sample for genetic analysis, digital radiology imaging, and digital imaging of pathology samples from lung biopsy where possible.

Part B: ChILD-EU Observational Study

The observational study aims to provide detailed information about outcomes and responses to treatment in the first year of diagnosis. We intend to study children more intensely through this period to better understand the burden of disease, outcomes and responses to standard investigations that may lead to further study.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

Part A: ChILD-EU Database and Biobank

2.1.1 Primary Objective

To collate detailed information on clinical cases of possible ChILD on a central database and biobank.

2.1.2 Secondary Objectives

(a) To review each case by an experienced international interdisciplinary peer review team to provide diagnostic oversight and feedback

(b) To provide annual updates of diagnosis and outcome in a feedback loop via peer review

(c) To store for future research, blood samples for genetic analysis of cases and parents

(d) To support paediatricians and families caring for children with ChILD

Part B: ChILD-EU Observational Study

2.1.3 Primary Objective

To describe outcomes at 1, 2, 3, 6 and12 months in infants and children with ChILD.

Outcomes measured will be

- death,
- survival on artificial ventilatory support (invasive or non-invasive),
- survival in supplemental oxygen,
- survival breathing room air,
- quality of life (QoL)

2.1.4 Secondary Objectives

To describe variance in outcome at 1, 2, 3, 6 and 12 months in infants and children with ChILD according to

1. Diagnosis and Presentation
    a. Diagnosis (Peer Review)
    b. Diagnostic certainty (Peer Review)
    c. Computed Tomography (CT) score – by component radiologist (Peer review)
    d. Blood Oxygen Saturation (SpO_2) at rest in room air at presentation
    e. SpO_2 asleep in room air at presentation (nadir)
    f. Respiratory Rate (RR) (z score) at rest in air at presentation
    g. Heart rate (HR) (z score) in air at presentation

h. Blood pressure at rest for 5 minutes at presentation

i. Weight (z-score) at presentation

j. Leland Fan 5 point severity score (Nil, symptoms, SpO_2 <90% air asleep, SpO_2 at rest, Pulmonary Hypertension).

2. Time to treatment and improvement

   a. Time from onset of symptoms/signs of ChILD to first treatment

   b. Time from onset of symptoms/signs of ChILD to diagnosis (local clinical)

   c. Time from onset of symptoms/signs of ChILD to normoxia whilst awake (SpO_2 ≥94% breathing room air at rest)

   d. Time from onset of symptoms/signs of ChILD to respiratory rate in normal range for age (Fleming, Thompson et al. 2011)

   e. Time from onset of first treatment to reduction in RR by 10%

   f. Time from onset of first treatment to reduction in HR by 20%

   g. Time from onset of symptoms/signs of ChILD to normoxia whilst asleep (SpO_2 ≥94% breathing room air at rest)

   h. Time from onset of symptoms/signs of ChILD to weight appropriate for age/height without use of calorie supplementation

   i. Time from onset of treatment to improvement in weight by 10%

3. Treatments

   a. Steroids

      i. Use of steroids

      ii. Dose, route and frequency of steroid use

      iii. Time from first presentation to initiation of steroids

      iv. Number of concomitant ChILD treatments at time of starting steroids

   b. Hydroxychloroquine

      i. Use of Hydroxychloroquine

      ii. Dose and frequency of hydroxychloroquine

      iii. Time from first presentation to initiation of hydroxychloroquine.

      iv. Number of concomitant ChILD treatments at time of starting hydroxychloroquine

   c. Azithromycin

      i. Use of Azithromycin

      ii. Dose and frequency of Azithromycin

      iii. Time from first presentation to initiation of Azithromycin.

      iv. Number of concomitant ChILD treatments at time of starting Azithromycin

4. Concomitant Medicines

5. Follow up Review

   a. SpO_2 in room air measured 4 weeks after commencing initial treatment

   b. RR at rest measured 4 weeks after commencing initial treatment

   c. Heart rate at rest measured 4 weeks after commencing initial treatment

6. Quality of Life score - PEDS QL Generic Core Scales
    a. At 0 and 12 months.
7. Questionnaire for health care utilisation and costs
    a. utilisation of inpatient and outpatient care to calculate direct costs gathered at 0, 3, 6 and 12 months
    b. loss of productivity of parents and children to calculate indirect costs gathered at 0, 3, 6 and 12 months

2.2 ENDPOINTS

Part A: ChILD-EU Database and Biobank

There is no envisaged primary or secondary endpoint to Part A which is a database and biobank.

Part B: ChILD-EU Observational Study

2.2.1 Primary Endpoint

12-month review or time to death.

2.2.2 Secondary Endpoints

Described in section 2.1.4

3 STUDY DESIGN

Part A: ChILD-EU Database and Biobank

A web-based data capture system and a Biobank of cases of ChILD, based on SecuTrial®, has been built as an extension of an existing database located in Munich. Appendix 1 has a more detailed description of the database.

Biomaterials will be located in Munich and will at least include, where possible, as a minimum blood (plasma, serum, or EDTA), CT chest images and tissue biopsy samples from patients with proven chILD. All biomaterials will be obtained during diagnostic or therapeutic procedures and only otherwise dispensable material will be collected.

All cases will undergo International Peer Review to confirm or suggest alternative expert opinion diagnosis. Cases where an alternative diagnosis is considered most likely by the International Peer Review team will not enter the Observational Trial, but data collected up to that point will be retained for future case review and standardisation.

Part B: ChILD-EU Observational Study

12-month multi-centre observational study.

Consent will be sought to begin observations from time of presentation at hospital during which the diagnosis is made. Participants will commence in the study from the point of signed informed consent and will continue in the trial for 12 months.

It is anticipated that data will be collected at seven time points, summarised in the following table.

Every effort should be made to see a participant as close as possible to the scheduled time point. If the visit occurs outside of the recommended visit window then a justification may be sought.

At 12 months, the observational study will be completed but clinicians and parents will be invited to continue providing minimal dataset information on an annual basis.

	Study entry(A)	Peer review(A)	4 (+/- 1) week	8 (+/- 1) week	12 (+/- 2) week	26 (+/- 4) week	52 (+/- 4) week(A)
Registration dataset	X						
Peer Review dataset		X					
Outcome			X	X	X	X	X
HR			X	X	X	X	X
RR			X	X	X	X	X
SpO2			X	X	X	X	X
Treatment			X	X	X	X	X
Spirometry(B)			X	X	X	X	X
QoL		X					X
Utilisation of health care		X			X	X(A)	X
CXR(C)						X	X
Review of case and diagnosis		X					X

Study entry = 'I have a chILD' notification
Registration dataset = respiratory symptoms, respiratory signs, hypoxaemia, radiological abnormality, duration of symptoms, site details, email address
Peer Review dataset = Complete dataset (includes chest x-ray and spirometry, if possible)
CXR = Chest X-Ray
(A) = the database study has observations made at entry to the study, peer review, a questionnaire at 6 months, and annual review
(B) = when possible
(C) = when available as part of standard care

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Part A: ChILD-EU Database and Biobank

The number of participants is limited by patient presentation only. The study is open to presentation from all European countries, but has focussed support in France, Germany, Italy, Turkey and the United Kingdom. In the UK and Ireland prevalence was estimated as 3.6 per million children, but is likely under-estimated due to misdiagnosis and the absence of a common register.

The number of sites will be determined in each contributing country.

Part B: ChILD-EU Observational Study

We anticipate that there will be approximately 130 patients per year across Europe who may be eligible. As the population has a high degree of diagnostic uncertainty, few treatment options and the study does not require significant additional investigations, we anticipate a high recruitment level from this number. We would hope to continue recruitment for 30 months.

4.2 INCLUSION CRITERIA

Part A: ChILD-EU Database and Biobank

This includes infants and children presenting to hospital with Clinician-suspected interstitial lung disease or at least three of the following four criteria present:

(1) respiratory symptoms for at least 14 days
   a. cough,
   b. rapid and/or difficult breathing,
   c. exercise intolerance

(2) respiratory signs
   a. tachypnea,
   b. adventitious sounds,
   c. retractions,
   d. digital clubbing,
   e. failure to thrive, or
   f. respiratory failure

(3) hypoxemia

(4) diffuse abnormalities on a chest radiograph or CT scan.

Part B: ChILD-EU Observational Study

Consent to take part in the ChILD-EU Database and Biobank study as outlined above.

4.3 EXCLUSION CRITERIA

Part A: ChILD-EU Database and Biobank

A participant would be excluded from the database if ineligible to participate in the ChILD-EU Minimal Dataset observation and follow up study.

Exclusion criteria are common causes of diffuse lung disease, including but not exclusively:

Cystic Fibrosis

Respiratory Distress Syndrome

Bronchopulmonary Dysplasia

Acute Infection (viral or bacterial)

Inherited or acquired immune deficiency

Part B: ChILD-EU Observational Study

As above

5 PARTICIPANT SELECTION AND ENROLMENT (Part A & B Combined)

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified either by clinicians who are paediatricians caring for children with respiratory disease or by parents of children with suspected or proven interstitial lung disease. Children aged between 0 - 16 years will be eligible. Patients aged 17-18 who were diagnosed

with ILD during their childhood are also eligible to be included on the database and biobank study.

The 'I have a ChILD' webpage will enable clinicians to notify the central team of a potential case. The flow chart in Figure 1 summarises the process. The child.net web page will have a link for parents of a child with ChILD with instructions about how to contact the research team.

The assigned study ID will be made up of country initials, site number and a patient number created sequentially.

5.2 CONSENTING PARTICIPANTS

Clinicians providing care for the child will obtain informed written consent. It is anticipated that the majority of patients will be in-patients in hospital and parents and children will be provided with adequate time to consider participation (according to local circumstances, but over 24 hours where feasible). For those who are not in-patients, consent will be sought after parents and children have had adequate time to consider the study and ask questions. Where possible information leaflets will be sent out by email or post prior to a clinic meeting for those being consented as out-patients. Children over 16 years will provide consent with assent sought from the parents. There will be separate information sheets and consent forms for Part A and B of the study.

5.3 SCREENING FOR ELIGIBILITY

The 'I have a ChILD' webpage will ask screening questions of clinicians along the principles of the American Thoracic Society ChILD guidelines. Those cases with symptoms consistent with ChILD will be consented. Cases where screening questions are not consistent will have the case discussed with a member of the ChILD-EU team to establish eligibility.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Those ineligible and non-recruited will continue to receive care as per current standard by their local clinical team (i.e. no change).

5.5 WITHDRAWAL OF STUDY PARTICIPANTS

Study participants may withdraw from the study at any time.

Participants wishing to withdraw may do so in the following ways:

(a) No further contact by the study team, but agree that their local clinician can continue to provide information obtained from routine clinical review (i.e. no study specific documentation will be used)

(b) No further contact by the study team and no further data from the child, but all data/samples provided to that point can be retained and used.

(c) No further contact by the study team and all data and samples must be returned to the local clinical team, with complete removal of patient data from the database/biobank.

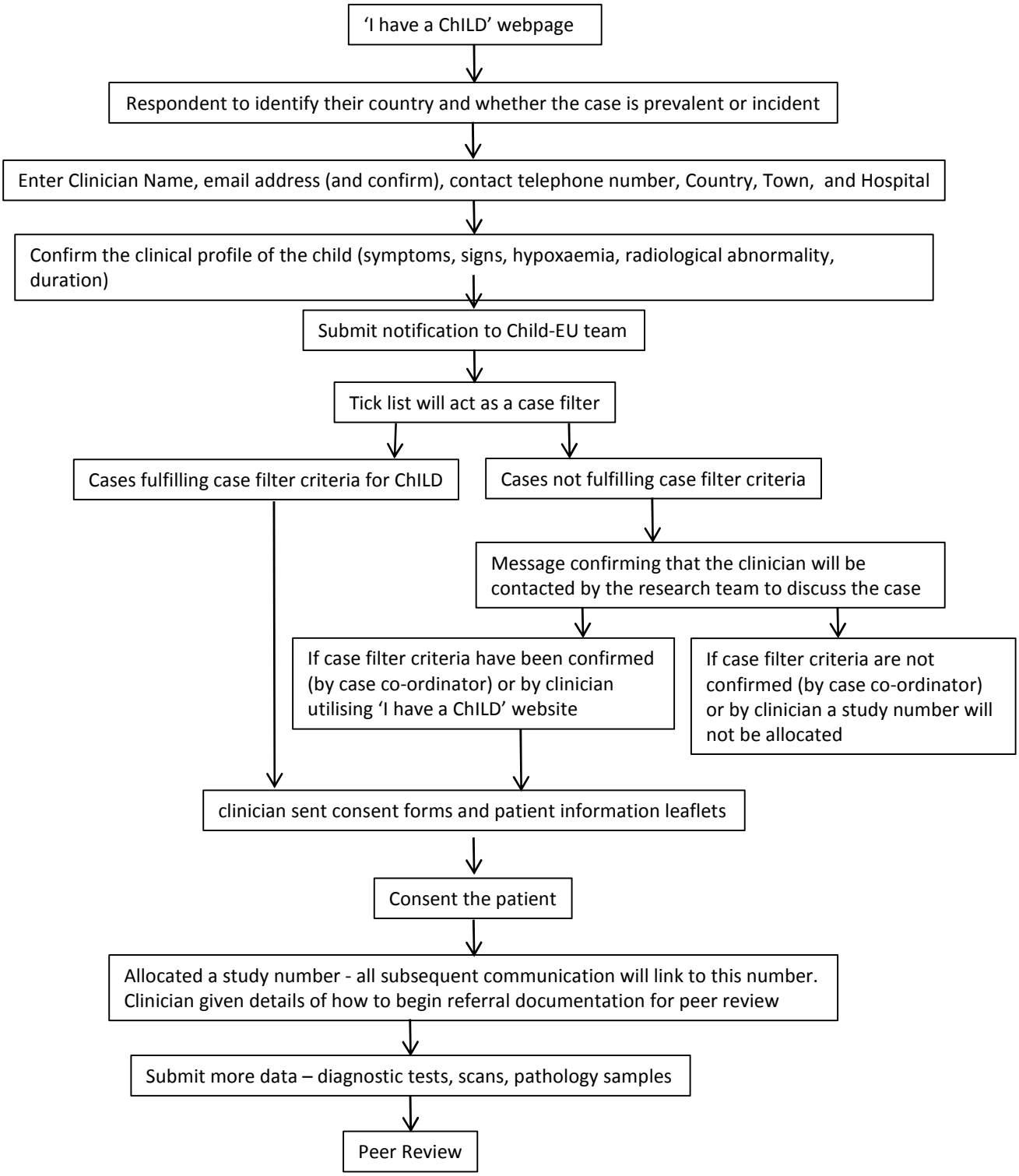
'I have a ChILD' webpage
Respondent to identify their country and whether the case is prevalent or incident
Enter Clinician Name, email address (and confirm), contact telephone number, Country, Town, and Hospital
Confirm the clinical profile of the child (symptoms, signs, hypoxaemia, radiological abnormality, duration)
Submit notification to Child-EU team
Tick list will act as a case filter
Cases fulfilling case filter criteria for ChILD
Cases not fulfilling case filter criteria
Message confirming that the clinician will be contacted by the research team to discuss the case
If case filter criteria have been confirmed (by case co-ordinator) or by clinician utilising 'I have a ChILD' website
If case filter criteria are not confirmed (by case co-ordinator) or by clinician a study number will not be allocated
clinician sent consent forms and patient information leaflets
Consent the patient
Allocated a study number - all subsequent communication will link to this number. Clinician given details of how to begin referral documentation for peer review
Submit more data – diagnostic tests, scans, pathology samples
Peer Review

Figure 1

6 STUDY ASSESSMENTS

The study assessments are detailed in the study design, section 3

7 DATA COLLECTION

Data will be collected and submitted by the clinical team providing care, in liaison with local research nurse support where available. The Principal Investigator is responsible for the quality of the data recorded in the case report form (CRF) at each Investigator Site.

Data will be collected from:

(a) Hospital medical records, including laboratory and radiology (electronic and paper)

(b) Radiology (anonymised CT chest images), uploaded directly to ChILD-EU database or images provided on a disc.

(c) Pathology (slides, blocks or imaging)

(d) Blood samples for genetic analysis (volume taken appropriate for age: 0.5 ml <1 month, 1 ml 1-24 months, 3 ml >2 years). EDTA samples will be obtained at the same time. Parents will contribute 10ml blood samples.

(e) CRF

(f) Quality of Life questionnaires (PEDS QL)

(g) Utilisation of health care questionnaire

It is anticipated that the initial referral data will be entered on to a CRF and that this information will form the referral for Peer Review.

Subsequent visits at 1, 2, 3, 6 and 12 months will also be based on CRF completion. Data managers will facilitate entry of data to the database.

Country specific trial co-ordinators and data managers will encourage data completion by having regular site contact. ECTU will be responsible for data cleaning and Quality Control checks for all UK data.

Data from all participating countries will be stored on the ChILD-EU SecuTrial Database. This platform is in use for current EU clinical database management. Briefly described: SecuTrial® is an internet based system with connection to a rational ORACLE® data base. The software serves as remote data entry system for pseudonymized medical data. It includes functions for data entry in electronic forms, for data view, analysis and export. The clinical data are organised in groups of forms, which builds the complete data set. Medical data can be collected with these forms over a time line of different visits. The succession of entries per patient is represented in a history (=audit trail).

A description of the database is available in Appendix 1.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

It is anticipated that there will be 130 new incident cases of ChILD each year across Europe that may be recruited to the observational trial (approximately 40 in the UK). In addition there will be approximately 300 prevalent cases that clinicians may recruit to the database minimal dataset. All possible cases will be recruited and no sample size calculation is possible for this observational study.

8.2 PROPOSED ANALYSES

Part A: ChILD-EU Database and Biobank

There will be descriptive statistics of cases and outcomes only.

Part B: ChILD-EU Observational Study

Analysis [1st 12 months]

Initial analysis will be descriptive presenting changes over time in characteristics measured broken down by key variables of interest such as type of treatment, diagnosis etc. To determine what factors are related to outcome we will model outcome with collected data taking into account likely covariates. If appropriate we will consider missing data using the guidelines from www.missingdata.org.uk.

Analysis [2nd 12 months]

Repeat of the same type of analysis as for 1st period. Possibly with addition of comparisons of response rates between two periods

The study will have a statistical analysis plan containing full details of the statistical aspects of this study produced by the trial statistician prior to seeing the data.

9 ADVERSE EVENTS

This is a database and observational study only. This section is not required.

10 PREGNANCY

This is a study of children under 16 years of age. Whilst pregnancy may occur this study has no intervention therefore we do not require instruction under this section.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The ChILD-EU Trial Management Group will have oversight of the Database and Biobank, and the Observational Study.

The observational trial will be coordinated by a Trial Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), and a Trial Manager.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

11.2 PEER REVIEW TEAM

The Peer Review co-ordinator for the UK will be based at the Royal Brompton Hospital, London and will facilitate the review of cases from the clinical, radiological and pathological perspective from all round Europe.

11.3 TRIAL STEERING COMMITTEE

The ChILD-EU Steering Committee will facilitate frequent, expert planning and review of the whole ChILD-EU programme. The Steering Committee will meet once a year, and have monthly conference calls. Pressing issues which are related to circumscribed topics will be addressed by additional phone conferences, including the involved task leaders. The terms of reference of the ChILD-EU Steering Committee, the draft template for reporting and the names and contact details are detailed on the ChILD-EU website (www.childeu.net).
Professor Peter Propping, Institute of Human Genetics, University of Bonn will Chair the Ethical Review Board of the consortium.

11.4 DATA MONITORING COMMITTEE

The ChILD-EU Data and Safety Monitoring Board will have oversight for the whole ChILD-EU programme but its services will not be needed for the database and observational study.

11.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the consortium and Research Ethics Committee (REC) review. In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the consortium direct access to all study records and source documentation.

11.6 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor, a ChILD-EU Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Investigator sites will be risk assessed by the ACCORD Quality Assurance Manager, or designee, in order to determine if audit by the ACCORD Quality Assurance group is required.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

A favourable ethical opinion will be obtained from the appropriate REC and local Research and Development (R&D) approval will be obtained prior to commencement of the study.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator must be familiar with the protocol and the study requirements. The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. Responsibilities may be delegated to an appropriate member of study site staff. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained. The decision of a participant or a participant's parents to participate in clinical research is voluntary and should be based on a clear understanding of what is involved. The information provided to the participant or the participant's parents will be age appropriate and consistent with their level of understanding.

Participants or participants' parents must receive adequate oral and written information – age appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated

person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant or participant's parents must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant or participant's parents must be given sufficient time to consider the information provided. It should be emphasised that the participant or participant's parents may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant or participant's parents will be informed and agree to their medical records being inspected by representatives of the consortium but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant or participant's parents will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant or participant's parents will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

In England, Wales and Northern Ireland the parents will provide the informed consent for all children under 16 years of age. Participants aged 6-15 years will be provided with age-appropriate information sheets and asked for their assent.

In Scotland, if the PI considers that the participant is capable of providing informed consent then the participant will be asked to consent to the study and the parents will be asked for their assent. If, in the opinion of the PI, the participant is not capable of providing informed consent, the parents will be asked to consent and, if appropriate, the participant will be asked for assent. If, during the course of the study, the PI considers that the participant has become capable of providing informed consent then the participant will be asked to consent to continue in the study and the parents will be asked for their assent.

At all sites, if the participant is over 16 years the participant would be asked for consent to the trial.

At all sites, if the participant turns 16 during the trial the participant would be asked for consent to continue in the trial. If the participant wishes to withdraw from the study the PI will follow the procedure described in section 5.5 (Withdrawal of Study Participants).

12.2.2 GCP Training

All staff will comply with the principles of Good Clinical Practice (GCP).

12.2.3 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the consortium or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.4 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D, if required, for approval prior to participants being enrolled into an amended protocol.

13.2 PROTOCOL VIOLATIONS AND DEVIATIONS

It is not possible to deviate from the protocol because this is an observational study. In the event that an Investigator needs to perform a procedure outside the protocol recommendations it will be recorded, along with the nature and reason, within the CRF/database but is not considered a deviation. The peer review process will not start until patient consent has been obtained.

13.3 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor and consortium.

13.4 END OF STUDY

The end of the observational study is defined as the last participant's last visit. The database will continue with no definite end. A summary report of the study will be provided to the necessary bodies, as required at the end of the observational study.

13.5 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

14.2 PUBLICATION

The Study Management Team of the ChILD-EU Programme will prepare and publish reports from the studies under the consortium programme. In addition to publication in international peer-reviewed journals, annual updates will also be available on the website. The chILD web-site will be an open repository to direct physicians and health care professional to current SOPs, classification, diagnostic algorithms and ways to easily approach the chILD-EU consortium.

15 REFERENCES

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APPENDIX 1: DESCRIPTION OF DATABASE

The chILD-EU database has been designed to be compatible and to harmonise data dictionaries with chILD databases in North America. Prevalent and incident chILD cases in the UK will be imported into the chILD-EU database, including parental and clinical perspectives of illness.

SecuTrial® is programmed in Java 2 SE and implemented for the WebObjects® (WO) Application Server. The WO Components framework for server side generation of web pages and the Enterprise Object Framework, which represents the object-relational model of the tables in the database and controls the data access, are used. One central component is the form builder, based on the WO Components framework, which generates the application specific forms from data base queries. The user management is abstracted in the framework IAS User management. The underlying database is implemented in SQL with ORACLE®-specific extensions. In all parts of the internet-based RDE-data capturing- and data base system conform to the strictest security requirements (see also 4.). The complete system comprehends many important additional functions including, pseudonymisation function, messaging system, monitoring via a query system, comment and discussion system, help functions, status of patients and adverse events, statistics reports, data export tool.
Previously, all these features have been approved and authorized by the national data protection authorities of the European countries involved in this consortium, when Secutrial®, the medical research database system going to be implemented, was used in other European and international web-based studies and applications.