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COllaborative Neonatal Network for the first European CPAM Trial (CONNECT): a study protocol for a randomised controlled trial

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ABSTRACT

Introduction Consensus is lacking on the optimal management of asymptomatic congenital pulmonary airway malformation (CPAM). For future studies, the CONNECT consortium (the COllaborative Neonatal Network for the first European CPAM Trial)—an international collaboration of specialised caregivers—has established consensus on a core outcome set of outcome parameters concerning respiratory insufficiency, surgical complications, mass effect and multifocal disease. These outcome parameters have been incorporated in the CONNECT trial, a randomised controlled trial which, in order to develop evidence-based practice, aims to compare conservative and surgical management of patients with an asymptomatic CPAM.

Methods and analysis Children are eligible for inclusion after the CPAM diagnosis has been confirmed on postnatal chest CT scan and they remain asymptomatic. On inclusion, children are randomised to receive either conservative or surgical management. Subsequently, children in both groups are enrolled into a standardised, 5-year follow-up programme with three visits, including a repeat chest CT scan at 2.5 years and a standardised exercise tolerance test at 5 years.

The primary outcome is exercise tolerance at age 5 years, measured according to the Bruce treadmill protocol. Secondary outcome measures are molecular genetic diagnostics, validated questionnaires—on parental anxiety, quality of life and healthcare consumption—, repeated imaging and pulmonary morbidity during follow-up, as well as surgical complications and histopathology. This trial aims to end the continuous debate surrounding the optimal management of asymptomatic CPAM.

Ethics and dissemination This study is being conducted in accordance with the Declaration of Helsinki. The Medical Ethics Review Board of Erasmus University Medical Centre Rotterdam, The Netherlands, has approved this protocol (MEC-2022–0441). Results will be disseminated through peer-reviewed scientific journals and conference presentations.

Trial registration number NCT05701514.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first prospective study comparing elective surgical resection to conservative management in asymptomatic congenital pulmonary airway malformation cases.
⇒ Data will be collected up to the age of 5 years, hereby providing valuable information on the mid to long term outcome in this patient group.
⇒ The rarity of the disease requires a European multicentre approach which comes with challenges in study coordination, patient recruitment and local legislation.

INTRODUCTION

Congenital pulmonary airway malformation (CPAM), formerly known as congenital cystic adenomatoid malformation, is the most common congenital lung abnormality (CLA), comprising approximately 30% of all CLA.[1] A CPAM is a congenital cystic lung lesion with an abnormal connection to the tracheobronchial tree and normal pulmonary vascularisation. Advances in prenatal ultrasound have led to increased incidence figures, suggesting that this abnormality is more common than originally thought.[2 3] Large population studies undertaken in Canada, Hong Kong and the UK estimate the current incidence around 4 in 10 000 births.[2 4–6] Despite the increasing incidence, much is still unknown about the aetiology,[7] best treatment options[8–12] and natural course of CPAM.[13]

When patients with CPAM present with symptoms, surgical resection is usually recommended.[14] However, a considerable proportion of patients with CPAM are asymptomatic at birth and remain so during childhood

(36–97%).[8 13 15–17] For these children, some clinicians recommend an elective surgical resection, while others argue for a conservative management for this originally benign, possibly regressive disease. Advocates for an active surgical approach put forward several arguments, such as the possibility of symptom development in initially asymptomatic patients. These symptoms can include recurrent infection, persistent cough or even acute respiratory insufficiency, in some cases requiring emergency surgery. The latter being associated with a worse outcome than is resection in an elective setting.[15 18] Nevertheless, elective surgical resection can also become cumbersome following the development of symptoms, possibly due to infectious alterations of the lung architecture.[15 19 20] Furthermore, early resection could possibly optimise compensatory postnatal lung growth, and thereby improve long-term lung function. No strong evidence supports this theory and surgical practice, with some clinical reports showing variable results.[21–25] Another argument for elective surgical resection is the possible association between CPAM and malignancy, that is, adenocarcinoma in situ (AIS) and pleuropulmonary blastoma (PPB).[26–29] While AIS is associated with a relatively favourable prognosis, PPB is an aggressive childhood tumour, that is, often indistinguishable from an 'ordinary' CPAM on radiological review.[9 26 30] Knowledge is lacking on the exact incidence of malignant degeneration in CPAM tissue and the pathways involved in this process, and thus further research is urgently needed.[31–33] However, particular caution is advised in cases where the lesion is diagnosed after birth, or in relatively rare cases of CPAM type 4—as these characteristics are associated with a higher risk of malignancy.[26 30 34 35] On the other hand, clinicians in favour of conservative management put forward several arguments against elective surgery for CPAM. For one, they underline the risks of surgery in neonatal and paediatric patients.[36 37] Additionally, most children who are asymptomatic at birth remain so during childhood, which implies that elective surgery of every patient could lead to overtreatment.[8 13 15 16] Finally, advocates of conservative management highlight that the risk of malignancy related to CLA is estimated to be very low in prenatally diagnosed cases, and that this risk is not reduced to zero after elective resection.[9 15 27 38]

The liveliness of the debate on the management of asymptomatic CPAM was clearly demonstrated by the simultaneous publication of two contradictory articles in Seminars in Paediatric Surgery in 2015, one of which argued in favour of an operative approach in patients with asymptomatic lung lesions while the other contended in favour of a conservative follow-up.[9 11] Moreover, three recent survey studies—conducted in Canada, the UK and among members of the European Paediatric Surgeons' Association, respectively—highlighted the heterogeneous opinions and favoured management strategies among paediatric surgeons.[12 39 40] In all studies, the majority (67–77%) of paediatric surgeons opted for elective surgical resection of asymptomatic CPAM. However, it is apparent from these surveys that there is no consensus on the optimal age for resection, the surgical technique or the length and structure of follow-up concerning patients with asymptomatic CPAM.

All aforementioned arguments are based on retrospective studies, expert opinion or empiricism, but substantial, prospective evidence is lacking, and no robust postnatal determinants have been identified that may predict outcome in patients with CPAM.[10 12 41 42]

Therefore, a three-round Delphi study was conducted among members of the CONNECT consortium, an international collaboration focused on the optimisation of CPAM care.[43 44] Fifty-five participants (33 surgeons and 22 non-surgical specialists) from 13 European countries completed a survey, which resulted in a set of seven outcome parameters that reached consensus (see below).

We hypothesise that stratification of patients with CPAM into a low-risk and high-risk group for the development of symptoms, infection and risk of malignant degeneration could lead to a personalised, case-by-case approach towards better management. The main goal of this trial is therefore to compare surgical and conservative management of patients with an asymptomatic CPAM in order to develop robust evidence-based practice.

METHODS AND ANALYSIS

The CONNECT trial is an international, multicentre, randomised controlled trial with a 1:1 allocation of patients with asymptomatic CPAM to either (a) elective surgical resection or (b) conservative management. We will include 176 patients in this study, which includes a follow-up period of 5 years irrespective of the randomisation arm. The participating centres are paediatric hospitals who routinely care for patients with CPAM and collaborate within the CONNECT consortium. This study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials guidelines (online supplemental file 1). The underlying protocol also follows the Consolidated Standards of Reporting Trials guidelines for non-pharmacological treatments.

Participants

The study population will consist of neonates with a prenatally detected CPAM who remain asymptomatic up to inclusion at the age of 3–9 months after confirmation of index diagnosis on chest CT imaging. Considering the low incidence of this congenital anomaly, a multicentre design has been chosen, involving large metropolitan paediatric-surgical centres in Europe.

To be eligible to participate in this study, a subject must meet all of the following criteria:

- Lesion detected during routine prenatal ultrasound screening.
- Delivery at term: gestational age ≥37 weeks.
- Birth weight > −2 SD or >P10.
- Asymptomatic at birth defined as no prolonged respiratory distress or oxygen support (<24 hours).

- Asymptomatic up to the moment of inclusion.
- Confirmation of CPAM on postnatal chest CT scan at 3–9 months of age, according to a structured report form.[45]
- Unilobar lesion as assessed on chest CT at 3–9 months of age.
- Signed informed consent form, please see online supplemental file 2 for the model information and consent form.

A potential subject who meets any of the following criteria will be excluded from participation:

- Bilobar lesion.
- Development of symptoms before randomisation, considered by treating physician as caused by CPAM with reasonable certainty.
- Complicated pregnancy defined as (pre-)eclampsia, pregnancy diabetes in mother, fetal hydrops or severe polyhydramnios on prenatal ultrasound.
- Syndrome associated anomalies on genetic analysis confirmed by genetic expert.
- Major associated malformations. Anomalies include cardiac malformations requiring surgical correction or follow-up by a paediatric cardiologist, congenital malformations requiring major surgical intervention and anomalies that may affect normal lung growth and development.
- Suspicion of malignancy on chest CT scan evaluation at the age of 3–9 months.
- Participation in another randomised controlled trial.

Sample size calculation

The sample size calculation is a power analysis for the difference in mean SD scores (SDS) of maximal exercise endurance between conservatively and patients with surgically treated asymptomatic CPAM. Our calculations are based on data from patients with CPAM in our surgical long-term follow-up cohort, which includes all patients with CPAM either born in or referred to the Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands from January 1999 onward. We found a mean Bruce SDS of −0.41 with an SD of 1.09 in the surgical group, that is, patients with CPAM that had undergone a surgical resection. A mean of 0.1 with an SD of 0.7 was found for the conservative group. To obtain 90% power with a two-sided significance level of 0.05 in a Mann-Whitney U (ie, without adjustment for confounding), 73 patients are needed in each study group. To make sure that the power remains sufficient after adjustment for relevant confounder variables, and to account for dropout and missing data, we increased the sample size by 20%. This calculation leads to a planned inclusion of 176 patients (88 patients per group). Inclusion of subjects will take place up to the moment this number of patients has visited the hospital for their follow-up visit at the age of 1 year. On average, a large metropolitan paediatric hospital treats approximately 10–20 patients with asymptomatic CPAM per year. Considering this, each participating centre is committed to include 8–12 patients each year.

Recruitment

Patients will be recruited from various hospitals, primarily within Europe. To date, 32 major hospitals across 16 nations have agreed to participate. During the inclusion period, it will remain possible for other centres to join the study. The collaboration between this large number of centres should make patient recruitment feasible despite the rarity of the disease.

Randomisation, blinding and treatment allocation

Randomisation will take place using blocked randomisation with stratification by centre with a 1:1 allocation. For randomisation, the tool incorporated in the CASTOR database system will be used (www.castoredc.com), automatically randomising study participants after inclusion and ensuring concealed allocation for future randomisation blocks. There will be no blinding in this study, as a sham operation is not viable. Radiological assessment can neither be blinded, as the follow-up chest CT will clearly show if a study subject has undergone resection of the lesion or not.

Investigational product

The study timeline is illustrated in figure 1. The investigational treatment is surgical resection of the CPAM lesion after confirmation of diagnosis on chest CT according to the structured report (online supplemental file 3). This resection will take place between 6 and 9 months of age. The type and extent of the surgical procedure is dependent on the lesion characteristics, local protocol and the surgeon's preference. Preferably, small lesions are treated with an anatomical segmentectomy, that is, sublobar resection. Larger lesions are generally treated with lobectomy. Non-anatomical wedge resection is not advised due to higher reported risks of postoperative air leakage and residual disease.[15] Surgical details will be documented according to a structured report (see online supplemental file 4). The resected specimen is processed and stored according to the study pathology protocol (online supplemental file 5). The local pathologist will analyse the material, and document the results according to the structured pathology report for CPAM (see online supplemental file 6), as published earlier.[31] If a participating centre is not capable of analysing the pathology material according to the protocol, the material is stored according to local protocol guidelines. Future funding will possibly enable central analysis of this material but is not part of the current trial protocol.

Retrieved blood from the study participants, which is taken when an intravenous needle is placed for the administration of intravenous contrast for the chest CT, will be stored in a plastic EDTA vacutainer blood collector tube. Similarly, blood of both parents (10 mL) will be drawn and stored in a plastic EDTA vacutainer blood collector tube. These samples will be sent for DNA isolation and genetic analysis to the local departments of clinical genetics, where DNA will be stored. Preferably whole genome sequencing will be performed, but in case

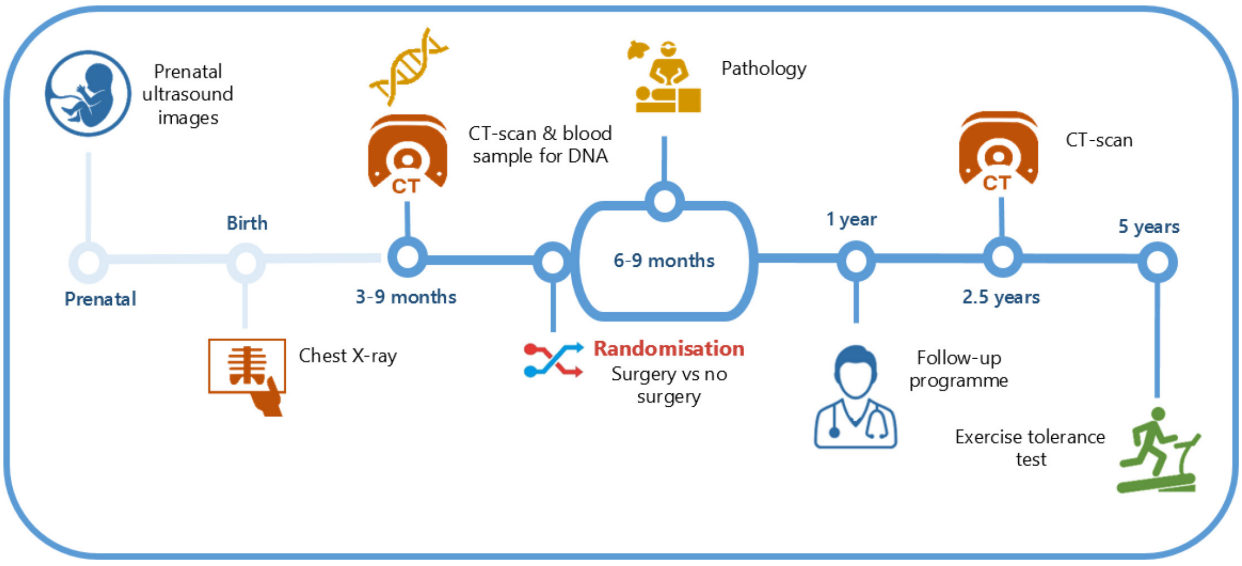

Figure 1 Timeline of the CONNECT trial.

this is not possible trio single nucleotide polymorphism array/whole exome sequencing will also be adequate. If a participating centre is not capable of these procedures, the material is stored according to local protocol guidelines. Future funding will possibly enable central analysis, but this is not part of the current protocol momentarily.

Patient timeline

Parents expecting a child with an antenatal diagnosed CPAM will be counselled and informed about the study prenatally. At the age of 6 months, each child will undergo a chest CT scan with intravenous contrast to confirm the diagnosis, as part of the standard of care. This chest CT will be evaluated according to a structured report (see online supplemental file 3).[45] If the chest CT confirms the CPAM diagnosis and the child remains asymptomatic, the child is eligible for inclusion. After having obtained informed consent from parents or caregivers, randomisation to the surgical arm or the non-surgical arm will take place. At this point, the prenatal ultrasound images will be retrospectively evaluated according to a structured report (see online supplemental file 7).[46] In case of randomisation to the surgical arm, resected specimen will be sent to the local pathology department for analysis and the pathological results will be discussed with parents during the hospital admission or the postoperative visit at the outpatient clinic some 2–6 weeks after surgery.

Genetic testing will be offered as part of routine diagnostic procedures if local legislation permits. If parental consent is obtained, blood will be drawn from the study subject when an intravenous needle is placed for the administration of the intravenous contrast—ideally just before the diagnostic chest CT.

The follow-up programme lasts 5 years, is uniform for all patients and consists of three assessments at the ages of 1 year, 2.5 years and 5 years (with a margin of 2 months towards the patient's age for each assessment). This follow-up structure is standard of care in most of the participating centres. Patients assigned to the surgical arm will visit the hospital one additional time, 2–6 weeks after surgery, for surgical scar inspection, postoperative reports/symptoms and evaluation of the pathology report. At the second visit (at 2.5 years) a follow-up chest CT will be performed, and during the last visit at 5 years participants will perform a standardised exercise test (see outcome parameters), supervised by a certified paediatric physical therapist.[47 48] Furthermore, parents will be asked to complete several questionnaires, addressing anxiety, quality of life and healthcare use.

The duration of the follow-up was set to 5 years to ensure enough time to observe potential differences in clinical outcome between the two study groups (ie, post-surgical complications, the development of pulmonary symptoms, lesion development on repeated imaging). Another consideration was that the age of 5 years is the youngest age at which standardised endurance tests have been validated.

Outcome parameters

A Delphi survey was conducted within the CONNECT consortium, a collaboration with specialised caregivers across 13 countries, which led to a core outcome set for determining the optimal management of patients with asymptomatic CPAM consisting of seven outcome parameters: respiratory insufficiency, surgical complications, mass effect/mediastinal shift (at three time points) and multifocal disease (at two time points).[43 44] All these outcome parameters have been incorporated in this study protocol, as shown below. Though these outcome parameters are relevant for the measurement of outcome(s) in this patient group, none of them are fully suitable as the primary outcome measure for the comparison between those patients that are managed conservatively and those that will undergo elective surgical resection. Considering that both patient groups show a relatively favourable outcome, a functional outcome is desirable to

detect any possible difference(s) in lung function during follow-up.[13 15] Therefore, the primary outcome measure of this trial is exercise tolerance, measured with the Bruce treadmill test protocol.[47 49 50] During this standardised test, children will be encouraged by a trained paediatric physiotherapist to keep walking on a treadmill as long as possible during consecutive rounds of increased speed and inclination. The total time will be recorded and is then converted to an age-matched SDS.[47]

Secondary outcome parameters are

Pulmonary morbidity

- Pulmonary morbidity during follow-up: occurrence of lower respiratory tract infections (with either a proven infection at the lesion site, the start of antibiotics, diagnosis of viral bronchitis/bronchiolitis), persistent cough, dyspnoea, wheezing (defined as ≥3 episodes per year), respiratory insufficiency (requiring supplemental oxygen, ventilation and/or surgical resection).
- Frequency of surgical intervention due to pulmonary morbidity during follow-up period. The primary physician will decide if symptoms are of sufficient severity to indicate surgery.

Surgery-related

- Surgical details, reported according to a structured report form (online supplemental file 4).
- Pathological characteristics of resected material (macroscopic, microscopic, immunohistochemistry and molecular diagnostics) as assessed by the local pathologist of participating centre according to the structured report form (online supplemental file 6).[31]

Imaging

- CPAM characteristics on prenatal ultrasound images, reported according to structured report (see online supplemental file 7).[46] If multiple ultrasounds were undertaken, those images closest to the gestational age of 30 weeks will be used for analysis.
- CPAM characteristics on chest CT scans at 3–9 months of age, reported according to structured report form (online supplemental file 3).[45]
- CPAM development/postsurgical appearance on repeated chest CT imaging, reported according to a structured report form (online supplemental file 3).[45]
- CPAM development/postsurgical appearance on chest CT imaging—scored according to the congenital lung abnormality quantification (CLAQ) method.[51]

Questionnaires

- Parental anxiety, assessed preoperatively and at all follow-up visits, by means of the Visual Analogue Scale for Anxiety (VAS-A).[52 53]
- Quality of life, assessed at all follow-up visits, by means of the Infant Toddler Quality of Life Questionnaire (ITQOL).[54]
- Healthcare resource consumption, assessed at all follow-up visits, by means of the Institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire (iMCQ).[55]
- Child Health Utility Index (CHU9D) assessed at the last study visit at 5 years of age.[56]

Other

- Abnormal anthropometric measurements during follow-up, measured with the help of local SDS computation.
- Cost-effectiveness of both management strategies and comparison between them.

Statistical analysis

The primary outcome parameter, the exercise tolerance of subjects as measured by the Bruce treadmill test protocol, is measured in seconds, which is then converted to an SDS based on age and gender using Dutch normative values.[47] The Mann-Whitney U test will be applied to assess the difference between the two study arms.

Secondary study parameters

All participants

- Height and weight measurements will be converted to gender and age matched SDS, which will then be compared between the treatment groups using the independent sample t-test. Furthermore, the distance to target height, converted to an SDS, will be compared using the independent samples t-test or the Mann-Whitney test, depending on normal distribution of the values.
- Hospital admittance during follow-up will be compared between the treatment groups using the χ^2 test.
- The frequency of pulmonary symptoms, as measured at every follow-up visit, will be compared between the treatment groups using the χ^2 test. Furthermore, the time to the development of symptoms will be compared using a Cox proportional hazards model with correction for the clinically relevant covariates including lesion size on CT scan imaging, baseline characteristics, anthropometric measurements.
- The radiological appearance of the CPAM on CT imaging will be scored according to the previously published CLAQ-method, and compared between the treatment groups using the Mann-Whitney U test.[51]
- Anxiety, measured by means of the VAS-A, will be compared between treatment groups using the independent samples t-test.
- Quality of life will be measured during follow-up using the ITQOL and the CHU9D. In both cases the results will be compared between the treatment groups using the independent samples t-test.

Conservative treatment group

- The need for pulmonary surgical intervention during follow-up will be measured, and the time to surgery will be displayed using a Cox proportional hazards model.

- The radiological appearance of the CPAM on CT imaging will be scored using the CLAQ-method,[51] and the difference in percentage of abnormal lung tissue will be measured between the first and the second chest CT. This difference will be tested for significance using the Wilcoxon signed-rank test. The association between percentage of abnormal lung tissue on the first chest CT scan and the development of pulmonary symptoms during follow-up will be calculated using a logistic regression.

Surgical treatment group

- The correlation between the percentage abnormal lung tissue (measured using the CLAQ method), as measured on the first chest CT and the frequency of postsurgical complications will be calculated using logistic regression.
- The complication rate within 30 days after surgery will be displayed using a frequency table. Complication rates will be compared between conventional lobectomy and lung-sparing surgical interventions using the χ^2 test.
- The pathological analysis will be documented, that is, the type of CPAM, lesion characteristics, the frequency of mucinous proliferation, oncogenic mutations and proven malignancy.

Cost-effectiveness analysis

The cost consequences and cost-effectiveness of surgical versus conservative management of CPAM will be analysed through a trial-based economic evaluation. The analysis will adopt a societal perspective, using the techniques of cost-effectiveness analysis and cost-utility analysis. Established methodologies for economic evaluations in healthcare will be used.[57–59] Briefly, this evaluation may be described as follows.

The analysis will cover both medical and non-medical costs. Medical costs (ie, costs within the healthcare sector) include all the costs of hospital days, surgeries, medications, diagnostic imaging, laboratory tests and intercollegial consultations. The cost analysis will include costs of treating postoperative complications and will extend beyond the initial hospital admission, including readmissions, medications, visits to the outpatient department, etc. Data on healthcare resource consumption will be extracted from both the electronic information systems of the participating centres and the iMTA iMCQ, administered to the parents of patients at all scheduled follow-up visits.[55] These data will then be combined with unit costs (calculated using economic cost prices or standard prices) to generate patient-level costs.

Non-medical costs will comprise out-of-pocket costs incurred by the patients' parents. Since no appreciable differences are expected between the study groups in this respect, costs of informal caregiving and possible productivity losses in the parents will be ignored in this study.

As regards the effects of the intervention, the economic evaluation will look at maximal endurance time and quality-adjusted life-years (QALYs), which is a measure of health outcome that combines quality of life with length of life. The calculation of QALYs will be based on survival data and on responses to the CHU9D questionnaire.[56 60 61] The CHU9D is a generic, preference-based health-related quality of life instrument designed exclusively for application with children. It consists of nine items that assess the child's functioning across domains of worry, sadness, pain, tiredness, annoyance, schoolwork/homework, sleep, problems with daily routine and ability to join in activities. The CHU9D will be administered at 5 years follow-up, using the CHU9D proxy version, completed by the parent.

Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in costs between the groups by the difference in effects, unless one treatment strategy dominates the other (ie, has lower costs and greater effects). The ICERs will be expressed as incremental costs per extra minute of endurance gained and incremental costs per QALY gained. The time horizon of the analysis will match the follow-up period for the underlying clinical trial (ie, until the age of 5). Future costs and effects will be discounted to their present value at recommended rates. Analysis of uncertainty is illustrated through cost-effectiveness planes (via bootstrapping). Where relevant, sensitivity analysis will be performed to assess the robustness of the analysis to certain assumptions. Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards guidelines.[62]

Patient and public involvement

Patient and public were not formally involved in the development of this research protocol, but will be informed on trial results through patient societies and social media.

Adverse events and auditing

Adverse events will be handled according to the guidelines of the Institutional Review Board (IRB) of the Erasmus Medical Centre. All adverse events will be registered during the study. Serious adverse events will be reported to the sponsor immediately and registered appropriately within 24 hours. All participating sites will be audited once a year by an independent monitor and a written monitor report will be submitted to the sponsor afterwards.

Benefits and risk assessment

The risk associated with participation in this study is considered to be intermediate. Participants randomised to a surgical intervention will undergo resection of the lesion between 6 and 9 months of age. Pulmonary resection in young children is considered an effective treatment for congenital lung malformations.[15 63 64] Literature shows in-hospital mortality to be close to zero and total complications to occur in 16–18%, seldom resulting in long-term morbidity.[36] A conservative policy in the case of asymptomatic patients is considered potentially safe: literature states that between 3% and 60% of patients

that are asymptomatic in the neonatal period will develop symptoms during the first years of childhood, although follow-up duration between studies varies widely.[8 13 15 16 65] Conservative policy is currently the standard of care for patients with asymptomatic CPAM in the Erasmus MC Sophia Children's Hospital, but multiple surveys taken across the world have shown that the treatment of this patient group differs per centre and country and that international consensus is lacking.[12 39 40] In summary, the treatments of both arms in this trial are common and internationally accepted.

The burden associated with participation in this study is considered to be relatively low.

DATA MANAGEMENT

Data will be handled confidentially and anonymously using the Castor online database system for data collection (Castor EDC, USA), thus complying with ICH E6 Good Clinical Practice. The data from (1) the prenatal images, (2) the imaging during the trial inclusion, (3) the surgical details in case of surgery and (4) pathological details following surgical resection, will be documented according to structured report forms as can be found in online supplemental file 3,4,6 and 7. The questionnaires will be conducted through the Castor system and distributed by email. The localprincipal investigator has access to the study subject data, which will be coded using a subject identification code list. The local PI safeguards the key to these codes. Apart from this, access to the personal patient data is only possible for monitoring purposes, audits or for evaluation by the IRB and the Healthcare Inspectorate. All data and human material will be kept for 20 years. The handling of personal data will comply with the General Data Protection Regulation (GDPR, https://gdpr.eu/). All pathology specimens and withdrawn blood will be stored locally in each participating centre according to the relevant study protocols.

Ethics and dissemination

This study protocol was approved by the IRB of the Erasmus Medical Centre for implementation of this trial in both the Erasmus Medical Centre Sophia Children's Hospital Rotterdam and the Radboud University Medical Centre Nijmegen (MEC-2022–0441/NL81003.078.22). The protocol will shortly be submitted for ethical approval in other contributing centres, which have expressed interest in participation through earlier collaboration within the CONNECT consortium.[43 44] In addition, the trial protocol is registered with ClinicalTrials.gov.[66]

In case of any modifications of the protocol, an official amendment will be submitted to the IRB. Approved changes will be communicated to all relevant parties according to the rules of the IRB.

A committee of external experts has been assembled, in the form of a Data Safety Management Board (DSMB). This committee consists of a paediatric surgeon, a paediatric pulmonologist, a statistician and paediatric physiotherapist, all of whom are independent of the sponsor. The DSMB will meet once on the start of the trial, and once a year after this or more often when this is indicated. The primary duty of the DSMB is the monitoring of the safety of study subjects and the accompanying data.

The results of this trial will be published in an international peer-reviewed scientific journal as soon as possible after the end of the follow-up period of the last included patient. Furthermore, we aim to present the results at several major international conferences.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Supporting information—including the statistical analysis plan, informed consent form and clinical study report—will be publicly accessible within reasonable time after the results of the trial have been published.

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