Clinical features of COVID-19 in Pediatric Patients, long term effects

(COPP2-study)

(October2020)

PROTOCOL TITLE: ***'clinical features of COVID-19 in pediatric patients, long term effects'***.

Protocol ID	COPP-2
Short title	COVID-19 in pediatrics, follow-up.
EudraCT number	N/A
Version	7
Date	05-010-2020
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Inhoud

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie mensgebonden onderzoek.
Chest CT	Chest Computed Tomography (CT)
COPP	Clinical Features of COVID in Pediatric Patients (COPP Study).
COVID-19	Coronavirus Disease 2019
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
DMP	Data management plan
GC-MS	Gas chromatography–mass spectrometry
GDPR	General Data Protection Regulation; in Dutch: Algemene verordening Gegevensbescherming (AVG)
IC	Informed Consent
IMPD	Investigation Medical Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
PIMS-TS	Pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2.
RIVM	Rijksinstituut voor Volksgezondheid en Milieuhygiëne
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction.
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus type 2
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission is not regarded as the sponsor, but referred to as a subsidizing party.
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; In Dutch: Uitvoeringswet AVG.
WMO:	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch wetenschappelijk onderzoek met mensen.

SUMMARY

Rationale: The pandemic novel coronavirus (SARS-COV-2) causes the disease COVID-19, ranging from mild flu like symptoms to severe and potentially fatal acute respiratory distress. In the first case reports of adults who recovered from COVID-19, long term pulmonary sequela are reported. There are currently no long term follow-up data in children.
Objective: W**e** aim to describe the pulmonary characteristics at 6 to 12months following a COVID-19 diagnosis in children seeking care in either the outpatient or hospital setting in the Netherlands.
Study Design: Multi-center descriptive prospective cohort study.
Study population: Children aged 0-17 years who were diagnosed in the outpatient department or were hospitalized with COVID-19, and who were included in a previously approved pediatric study, named "clinical features of COVID-19 in pediatric patients" (also known as COPP). In this study, the clinical features, course of disease, response to treatment and risk factors for severe disease in hospitalized and outpatient pediatric patients with COVID-19 in the Netherlands, were described.
Main study parameters/endpoints: The primary endpoint will be long-term pulmonary morbidity (defined as frequency of pulmonary symptoms, any hospital readmission, emergency or outpatient visit for pulmonary symptoms, prescribed antibiotics for pulmonary infection since the diagnosis of COVID-19). Secondary endpoints include quality of life scores, exhaled breath profiles, pulmonary function tests, exercise tolerance, and CT abnormalities in a subgroup of patients.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: We do not expect individual patients to benefit from the study, other than early detection and, whenever possible, treatment of any (lung) abnormalities.

All patients above the age of 4 years old, will be subjected to pulmonary function tests. Pulmonary function tests are standard care in the follow-up of pediatric pulmonology patients, and are used as a screening test for pulmonary morbidity.

A subgroup of patients is subjected to a low dose radiation chest Computed Tomography (CT)-scan (dose depends on age and weight/ size of patient ranging between 0,3 – 0,8 mSV). These patients are either suffering from chronic respiratory symptoms and/or pulmonary function tests abnormalities. In these patients CT-scan is part of standard clinical care. (Scans are performed on a high end scanner (for example Siemens Force), with appropriate pediatric protocols).

The main burden of participating in this study, is visiting the hospital once, undergoing a physical examination, pulmonary function testing, exercise testing, and exhaled breath collection, and completing 3 questionnaires. The expected required time-investment of the children and their caregivers is approximately 2-4 hours, depending on the age and willingness of the child. In case a CT scan has to be performed on clinical grounds, the patient is asked to perform this at the study site to increase quality and optimize standardization. In the case of incidental findings, patients will be referred to their general pediatrician or pediatric pulmonologist. To reduce the burden of travelling, patients will travel to the participating study site, which is closest to their home.

Both the clinical disease-course and the capacity to recover is different in children from adults and we therefore cannot deduce long-term pulmonary sequelae from adults COVID studies.

1. INTRODUCTION AND RATIONALE

Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) is currently responsible for a severe pandemic. It was first reported in Wuhan, Hubei province in China in December 2019 (1). In the Netherlands, the first case was reported on February 27th, 2020 (RIVM).

The infection leads to the disease known as Corona Virus Disease 2019 (COVID-19). Clinical features in adults range from mild non-specific respiratory symptoms (e.g. sore throat, cough, fatigue, mucus, myalgia, headache) to a more severe illness (e.g. fever, pneumonia, acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure). In adults, an estimated 80% of infections follow a mild course, 13.8% of patients have severe complaints and 6.1% of patient suffer from very severe disease. In China, the case fatality rate was estimated 2.3%, but the true case fatality rate may be lower if there are more mildly symptomatic cases that are not detected (2-4).

The current data suggest that SARS-CoV-2 infection is less severe in children. The first data, summarized in a systematic review, show that children have accounted for 1-5% of diagnosed COVID-19 cases, have milder symptoms, and death rate is extremely low. Clinical signs are similar to adults, but appear to arise much less frequently (5). In the largest study to date, over 90% of 2.143 children with laboratory verified SARS-CoV-2 were asymptomatic or had mild to moderate disease, 5.2% had severe disease (dyspnea, central cyanosis, oxygen saturation < 92%), and 0.6% had critical disease, needing ICU admittance, because of respiratory failure, ARDS, shock, or multi-organ failure. Those with critical disease had underlying health conditions. Severe disease was mostly seen in children aged less than one year (5-7).

New data in this field are rapidly emerging and data from Spain and the United States of America were published after publication of this review. In Spain, 365 children were screened in 30 hospitals in the first 2 weeks of the pandemic and 11.2% tested positive for SARS-CoV-2 (8). Of those testing positive, the median age was 1 years old (range 0-15 years), 25 (60%) of these children were hospitalized, and 4 were admitted to a pediatric intensive care unit. While interpreting these figures, one should take into account the very restricted testing policy, where only patients with hospital presentations were tested. Initial clinical presentations were upper respiratory tract infection (34%), fever without a source (27%), viral like pneumonia (15%), bronchiolitis (12%), gastro-enteritis or vomiting (5%), bacterial-like pneumonia, (5%) and asthma flare-ups (2%). Two patients had a coinfection with influenza B.

In the US, 2572 children tested positive for SARS-CoV-2. Of these, signs and symptoms were known in 291 children: 56% showed fever, 54% cough, 13% shortness of breath, 23% myalgia, 7% a runny nose, 24% a sore throat, 28% headache, 11% nausea/vomiting, 6% abdominal pain, 13% diarrhea. Among 345 children with information on underlying conditions 23% had at least one underlying condition (of which: 50% asthma, 31% cardiovascular disease, 13% immunosuppression). Six patients were admitted to an ICU and, unfortunately, 3 of them died. Review of these cases is ongoing to confirm COVID-19 as the likely cause of death. 32% of SARS-CoV-19 infections occurred in children aged 15-17, 27% in

children 10-14 years, 15% in children aged 5-9 years, 11% in children aged 1-4 year and 15% in children < 1 year (9).

Liguoro published a recent systematic review including the previous articles in which 4780 children with SARS-CoV-2 infection were summarized, confirming the relatively mild disease. In this study 9.2% of children needed oxygen suppletion, and 2% was admitted on the pediatric intensive care unit and required mechanical evaluation. Mortality was 0.08% (10).

More recently, we became aware of a Kawasaki like disease related to SARS-CoV-2 infection. Whittaker describes in a retrospective study 58 children with this pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Their median age was 9 years old (5.7-14), with 33% girls. 26% had a positive PCR for SARS-CoV-2, and 87% had positive IgG. All children presented with fever and nonspecific symptoms, like vomiting (45%), abdominal pain (53%), diarrhea (52%), rash (52%) and conjunctival infection (45%). CRP and ferritin levels were high. 29% developed shock and required inotropic support and fluid resuscitation, of these 79% required mechanical ventilation. 13 of them met the criteria for Kawasaki disease (11).In the Netherlands, 50.147 patients have tested positive for SARS-CoV-19, of which 11.285 were admitted to the hospital, and 5.422 patients have died. Of these 50.147 positive patients, 1.056 (2.3%) were younger than 19 years old, and 91 were admitted to the hospital (RIVM data June 29th, 2020). A survey by the Dutch Pediatric Society showed 10 additional patients who were diagnosed with PIMS-TS (12).

Due to lack of sufficient testing material, for a long time we have had a restrictive SARS-CoV-2 testing policy in the Netherlands, so the number of Dutch inhabitants, including children, who were infected with SARS-CoV-2 is probably much higher. Since June 2020, testing is possible for all Dutch inhabitants. Although the incidence of severe or critical COVID-19 disease in children is low, some children do get very sick. Shekerdemian et al. published a case series of 48 patients from Canada and the US who were admitted in a period of three weeks in the pediatric ICU. 83% of them suffered from an underlying condition. 50% had one comorbidity, 17% two and 19% had 3 or more significant comorbidities. 40% was medically complex, defined as children with a long term dependence on technical support associated with developmental delay and/or genetic anomalies. At admission 69% were severely or critically ill, 23% experienced multi-organ failure. 81% required respiratory support that exceeded their baseline (oxygen 13%, HFNC 23%, CPAP 8%, mechanical ventilation or tracheostomy ventilation 38%). No children required renal replacement therapy. It is encouraging that in this cohort only 5% of cases were fatal, compared to adult cohorts in which 50-62% of cases are fatal. (13)A survey from the Dutch patient association for patients with chronic lung disease (Longfonds) shows that adult patients with a history of COVID-19 (91% was not admitted in the hospital) are still suffering from tiredness, shortness of breath, tightness of the chest, headache or muscle strain. (14) Although, these data have a high risk of bias, they give cause for concern. There are currently no data on the long-term pulmonary sequelae after diagnosis in children with COVID-19.

In (parents of) pediatric patients with COVID-19 we notice anxiety about long term sequelae. We are in contact with the treating physician of a lot of these patients, who report that parents are keen to exclude long term morbidity. A questionnaire about anxiety and stress in

(parents of) patients with COVID-19 is part of the COPP study providing information about this yet unexplored matter.

Since follow-up data on pulmonary characteristics in children previously diagnosed with SARS-CoV2 are currently lacking, we aim to describe potential long-term pulmonary sequelae at 6 months following COVID-19 diagnosis in pediatric patients who were diagnosed in Dutch hospitals. . As stated above, since COVID-19 in children in less severe than in adults, possible sequelae cannot be deduced from adult studies.

We aim to include all children with COVID-19 who were diagnosed in the outpatient department or were hospitalized, and who were included in the COPP study, in which their clinical features were described.

The COPP study is a large multicenter, observational, prospective cohort study in hospital-setting in the Netherlands, in which during 18 months data will be collected from pediatric patients with COVID-19. (15). Currently, 44 of the 72 pediatric departments in the Netherlands are participating and this number is still rising. From an international view this is an unique study in which national collaboration of all pediatric departments provides an excellent overview of the impact of COVID-19 in pediatric care. The COPP study aims to include all pediatric cases in hospitals in the Netherlands, and collaborates closely with the Dutch Pediatric Society and researchers from all seven University Medical Centers in the Netherlands. The COPP study aims to:
- describe the clinical features of the COVID-19 in hospitalized and outpatient pediatric patients in the Netherlands.
- describe the clinical course of the COVID-19 in hospitalized and outpatient pediatric patients.
- describe the response to treatment, including supportive care.
- determine risk factors for severe disease in children with COVID-19.
- characterize the host responses to infection with SARS-CoV-2 in COVID-19 in pediatric patients.
- describe interregional treatment variations of COVID-19 in Dutch hospitals.
- describe respiratory symptoms and quality of life 6 weeks after COVID-19 infection.COVID-19 is a new disease, therefore, in terms of choice of follow-up investigations, we have to rely on our experience with other viral pneumonia's or bronchiolitis patients and the established CT abnormalities in COVID-19 patients. Since SARS-CoV2 is one of the coronaviruses, we sought evidence for the long term effects in children who had suffered from severe coronaviruses in general. SARS-CoV-1 shows some similarities to SARS-CoV-2 and also runs a more benign course in children. Li et al described 47 patients (median age 13.6 years) who had a history of hospital admittance due to severe acute respiratory syndrome (SARS-CoV-1). All children were asymptomatic and had no physical abnormalities at 6 months follow-up. However, mild pulmonary abnormalities were detected on HRCT in 34% of these patients, including residual ground-glass opacification, air trapping, and a combination of these. There were no lung function abnormalities, but exercise testing showed exercise impairment in these patients, with a reduced peak oxygen consumption compared to controls. At 15 months of follow-up, these patients still showed lower absolute and mass related peak oxygen consumption, higher ventilatory equivalent for oxygen, lower oxygen pulse and a

lower oxygen uptake efficiency slope. Chest CT abnormalities at 15 months did not differ from the CT scan results at 6 months follow-up (16-18).

Of the 674 children with SARS-COV-19 infection in the study by Liguoro who had radiological examination, up to 49.1% showed abnormalities, even if asymptomatic (15% CT abnormalities). 73.9% underwent a chest CT scan, which was normal in 32.7% of cases, whereas typical groud-glass opacities, nonspecific unilateral and bilateral lesions were identified in 29.4, 26.6 and 23.2% of patients, respectively (10).

Cui et al investigated specifically CT abnormalities in children and included 2597 patients in a systematic review (many of these studies were also included in Liguoro's review). 7.6% were asymptomatic, 45.5% and 41.5% had mild or moderate disease, 4.4% had severe disease, and 0.9% were critical. From 409 patients chest CT results during time of admittance were known, 43.5% had normal CT scans, in the other patients ground-glass opacities, local patchy or bilateral shadows, interstitial lesions or "white lung change" were seen (19).

In a Chinese cohort with adult COVID-19 patients with a median age of 43 years, 53% showed complete radiological resolution at three weeks postdischarge. The predominant pattern of abnormality observed at discharge were ground-glass opacification (44%), fibrosis (30%), and thickening of the adjacent pleura (10.7%). In this study, all patients suffered from pneumonia, and no critical patients were included (20). Bernheim et al showed that in adult patients with severe COVID-19 CT abnormalities showed progression during the course of disease, with 28% of patients with bilateral lung involvement in the early phase of disease (0-2 days) and 88% at a late stage (6-12 days) of disease. In this study no long term follow-up data were available. There are no follow-up CT data in children with COVID-19. (21)

Summarized, ground-glass opacification, pulmonary fibrosis are the most common CT abnormalities in patients with COVID-19. 34% of children with a history of SARS-COV-1 show CT abnormalities at 6 months follow-up, despite lack of clinical symptoms.

HRCT and lung function tests are the investigations of choice for the detection and evaluation of air-space and airways diseases, especially if associated with small airways disease. Ground glass opacifications and fibrosis, found in adults with COVID-19, may lead to restrictive lung disease. However, in children, especially the younger group, a clinical diagnosis of bronchiolitis or bronchitis is also seen in relation to SARS-CoV-19 infection. Most children with other causes of viral bronchiolitis or pneumonia have a short course of disease, however, some suffer from post-infectious bronchiolitis obliterans, an obstructive lung disease.

In the current Dutch protocol for children with severe COVID-19 CT scans currently are not performed, since CT abnormalities in children are not specific for COVID-19 (22). In the Dutch proposal for the protocol concerning follow-up of adult COVID-19 patients CT scans are performed in case a patient shows abnormal pulmonary function tests or do have respiratory complaints.

In this study we use questionnaires about respiratory symptoms and quality of life, pulmonary function tests and exhaled breath profiles to determine pulmonary morbidity in

the follow-up of COVID-19 in children, if needed. We expect to be able to identify restrictive or obstructive pulmonary disease, and diminished diffusion capacity, leading to reduced exercise tolerance. HRCT in patients without current symptoms was found not ethical. Therefore, we will only perform CT scan in patients with current respiratory symptoms or pulmonary function test abnormalities, in which there is a clinical need for further evaluation.

2. OBJECTIVES

Primary objectives:

- To describe potential pulmonary sequelae, in particular symptoms, the need for hospital care, at 6 to 12-months following a COVID-19 diagnosis among pediatric patients receiving care in the hospital or outpatient setting in the Netherlands.
- To determine risk factors for pulmonary sequelae among COVID-19 hospitalized and outpatient pediatric patients in the Netherlands.

Secondary objectives

- To describe lung function in the follow-up of children with COVID-19.
- To describe exhaled breath profiles (SpiroNose/GC-MS) in children with a history of COVID-19
- To assess the quality of life in children with a history of COVID-19.
- To describe CT abnormalities in patients with chronic respiratory complaints and/or pulmonary function test abnormalities and a history of COVID-19.

3. STUDY DESIGN

Study design: This will be a multi-center, descriptive observational prospective cohort study.

Duration: Following an initial baseline registration as part of the COPP study, children and their caregivers will be requested to return for a follow-up visit at 6 to 12 months after diagnosis with COVID-19. We will enroll participants throughout a 1.5 year period.

Setting: Pediatric department. Currently, approximately two third of all pediatric departments in the Netherlands will include patients in the COPP study (date June 16th), however, this study has only just started. It aims to collaborate with all pediatric departments in the Netherlands. (16) All children will be asked to come to the hospital for their follow-up visit for the COPP 2 study, at 6 to 12 months after diagnosis with COVID-19.

Description: Children aged 0-17 years who were diagnosed with COVID-19 will be recruited from the COPP database if they gave permission to be approached for follow-up studies. Study measurements include: questionnaires and physical examination for all children and exhaled breath (SpiroNose/GC-MS), growth measurements, pulmonary function, exercise testing, and Chest CT scans in a subgroup of patients.

COPP study: clinical features and clinical course of COVID-19 patients: multicenter, prospective descriptive cohort study.
Data during presentation/admittance for COVID-19:

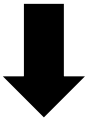
- Patient characteristics, clinical features at presentation, course of illness
- Laboratory parameters.

Data at 6 week follow-up:

- Pulmonary symptoms questionnaire
- quality of life (PROMIS and PedSQL)

Previously collected data from COPP study (16)

COPP study: Permission to approach for follow-up study? → inclusion in COPP2 study



COPP2 study: Long term follow-up of patients with COVID-19: multi center, prospective descriptive cohort study.

All ages: Data from COPP study	All ages: Pulmonary symptom questionnaire Quality of life questionnaire: - > 8y: PROMIS - >2y: PedSQL - >0-2y: TAPQL		> 2 y: exhaled breath analysis > 4y: spirometry and exhaled breath analysis > 8 y: spirometry, body plethysmography and exhaled breath analysis	> 6 y: Exercise testing.

All ages:
Chest CT scan when indicated for clinical care, as is the case in patients with:

- Chronic respiratory complaints and/or
- Pulmonary function test abnormalities.

COPP 2 study (this protocol)

4. STUDY POPULATION

4.1 Population (base)

Pediatric patients with COVID-19 who presented at the emergency or outpatient department and/or were hospitalized in a hospital in the Netherlands. Estimates from China, the United States, and the United Kingdom (websites RIVM, CDC, ref 6) suggest that only about 1.5-3.4% of clinically apparent SARS-CoV-2 infections occur in children. The RIVM Pienter study shows a seroprevalence of 2.5-5% in Dutch children aged 3-18 years old (23). Depending on the course of the COVID-19 pandemic, ongoing public health measures, a possible "second wave" during autumn and wintertime, and the availability of a vaccine, the number of pediatric cases of COVID-19 will rise. Therefore, we expect to be able to include a considerable number of pediatric patients over the course of 1.5 year (June 2020-December 2021), with a maximum of 120 patients.

4.2 Inclusion criteria

A child will be eligible for this study, if he/she was:

- Aged 0-17 years at COVID-19 diagnosis, AND
- Presented to an emergency or outpatient department of a Dutch hospital and/or admitted to hospital, AND
- Diagnosed with COVID-19 in his/her medical history, based on at least one positive real-time RT-PCR test on nasopharyngeal, oropharyngeal, sputum or fecal sample for SARS-CoV-2 OR fulfilled a clinical diagnosis of COVID-19, should testing of SARS-CoV-2 yield inconclusive results and/or if testing is no longer possible due to lack of reagents, AND
- Enrolled in the COPP study (Clinical features of COVID-19 in Pediatric Patients (23)), with specific consent to be approached for follow-up studies.

4.3 Exclusion criteria

A child will be excluded from the study, if:

- Consent from guardians and/or patient is not received, or
- Consent for COPP study data access is not received

4.4 Sample size calculation.

Not applicable. We will include all patients who were included in the COPP study in the course of 18 months, with a maximum of 120 patients.

As this is an observational cohort study a clear power calculation is not possible. Previous studies in SARS showed that 16/47 children (34%) who were treated in hospital in Hong Kong had abnormal chest CT's 6 months post-diagnosis (9-11). In addition, 11% of children who were able to perform spirometry (n=38) had lung function abnormalities. In the current COPP cohort a very wide spectrum of patients with SARS-CoV-19 is included, ranging from two day old neonates to 17-year old children, with different medical backgrounds and different presenting symptoms of COVID-19. Based on these observations, we plan to perform an

interim analysis after inclusion of 60 patients, of which at least 20 with need of oxygen for more than 24 hours or a diagnosis of corona associated inflammatory syndrome. If abnormalities in pulmonary function tests or exercise tests, attributable to COVID-19, are seen in less than 5% of patients, the study will be discontinued.

5. TREATMENT OF SUBJECTS

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint – long-term respiratory 'morbidity' or pulmonary sequelae, defined as:

- Frequency of respiratory symptoms, hospital readmission, emergency department or GP visits for respiratory symptoms, antibiotic courses for pulmonary infections or start of inhaled corticosteroids and/or b2-mimetics after admission for COVID-19 since diagnosis of COVID-19;

8.1.2 Secondary study parameters/endpoints (if applicable)

- Frequency of pulmonary symptoms in the month prior to the follow-up study visit.
- Quality of life (including sleep, fatigue)
- Growth
- Pulmonary function abnormalities
- Exercise tolerance
- Exhaled breath profiles (SpiroNose/GC-MS)
- Frequency of Chest CT abnormalities in patients with chronic pulmonary complaints and/or pulmonary function abnormalities.

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

1. Patients will be included following a SARS-CoV-2 positive test result (or fulfilling a clinical diagnosis of COVID-19) and/or clinical signs of COVID-19 in their medical history, enrollment in the COPP study, combined with informed consent (IC) for contacting patient and/or guardians for a follow-up study, and after obtaining IC from guardians and/or patients.

2. Clinical data at the time of (in-hospital) treatment of COVID-19 are noted in the database of the COPP study. (see appendix I). These will be combined with follow-up data from the COPP2 study, consisting of the following:

Questionnaires about pulmonary complaints:
A questionnaire regarding pulmonary symptoms will be used to assess complaints 6 months after diagnosis, this contains questions about hospital readmissions, emergency department, or GP visits with a respiratory cause, antibiotics received for respiratory infection, prescription of inhaled corticosteroids and/or b2-mimetics, frequency of dyspnea, coughing, wheezing, exercise intolerance, limitations in physical activity or social activities, sleep problems and general health questions. This questionnaire will also be used in the COPP study at a 6-week follow-up visit, but will be slightly adapted. (see F1 documents).

Physical examination and length/weight.
All children will undergo physical examination, including evaluation of ear - nose – throat infections, pulmonary and cardiac abnormalities during chest examination, vital signs and measurement of length and weight.

Quality of life questionnaires:
We will use the PedSQL questionnaire in all children aged 2-18 years old (proxy report for children < 8 years old), the TAPQOL questionnaire for children 0-2 years old (proxy report), and the PROMIS questionnaire (self-report) in patients older than 8 years of age. Combined, these questionnaire will take approximately 10 minutes to complete.

The PedsQL and TAPQOL questionnaires measure Health Related Quality of Life and allow a comparison between HRQOL at 6 weeks and 6 to 12 months after diagnosis in all children. The PedsQL and TAPQOL are well translated, validated questionnaires and Dutch norm scores are available.

To measure overall health and specific domains of functioning (anxiety, depression, peer relationships, sleep problems and anger), we will use the PROMIS items in children older than 8 years of age. During the present pandemic, norm data for these items are currently being collected. Including these PROMIS item banks provides the opportunity to compare outcomes of children with a history of COVID-19 to their healthy counterparts with the same restrictions. Comparison of the quality of life scores at 6 weeks and 6 to 12 months after diagnosis is possible.

Pulmonary function testing
<u>Spirometry</u>
Spirometry will be performed in children older than 4 years of age at time of the study visit to measure:

- FVC: maximal volume of air exhaled with maximally forced expiratory effort from a position of maximal inspiration;
- FEV1: volume of air expressed in liters exhaled during the first second of performance of the FVC;
- bronchodilator reversibility: improvement in the percentage of the predicted normal value FEV1 after administration of 400 mcg of salbutamol.

Spirometry measurements will be performed according to the ATS/ERS 2005 guideline (24). Predicted normal values will be calculated according to GLI (Global Lung Initiative) standards. FVC and FEV1 will be assessed using standardized spirometry equipment, with mouthpieces suitable for the pediatric population. Airflow reversibility will include a pre-salbutamol spirometry, followed by administration of salbutamol by oral inhalation (100 mcg x 4 puffs). Spirometry will be performed 20-30 min post-salbutamol. The reversibility test will be considered positive if patients show improvement of FEV1 ≥ 12% after administration of salbutamol. Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate (three curves to be provided), and the best result selected according to the guidelines. The best of three efforts will be defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria with a maximum of five maneuvers. On the day of the study visit, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking (if applicable) should be discouraged throughout the visit day and will not be permitted in the 30-minute period prior to spirometry. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odors (e.g. perfumes). If treated with bronchodilators, a wash-out of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry, respectively.

<u>Body plethysmography</u>
In children older than 8 years of age, plethysmography will be conducted to measure the total lung capacity (TLC), residual Volume (RV) and to determine the specific airway conductance (sGaw) at time of the study visit.

Body plethysmography contains a series of gentle breaths at a frequency between 0.5 and 1.0 Hz to calculate lung volumes. Lung volumes will be displayed as predicted percentage of RV (RV%pred) and TLC (TLC%pred) and RV/TLC.

Pulmonary function tests will be conducted by highly trained professionals with experience performing these tests in pediatric patients. They will ensure that the tests are performed with the correct technique, manually deselect efforts which do not meet minimum standards.

Spirometry and body plethysmography results will be reviewed by two independent pediatric pulmonologists to determine whether abnormalities are present.

Exercise tolerance testing:
Standardized cardiopulmonary exercise testing by cycle ergometry will be performed using the Cooper protocol from the age of 6 years old. (25)

The integrated response of different physiological systems (the cardiovascular, pulmonary, neuromuscular, musculoskeletal, and metabolic systems) will be objectively evaluated at rest, during progressive exercise up to maximal exertion, and during recovery.

Chest Computed Tomography (CT) thorax:
The previous investigations may lead to a clinical indication to perform a chest CT scan. Results of these CT scans can lead to an increased understanding of the pathophysiology of pulmonary sequelae in pediatric patients with COVID-19.

In order to optimize standardization of these CT results, we invite patients to perform the chest CT scan, when indicated, at the hospital where the study visit has taken place.

A Chest CT will only be performed as part of standard clinical care, following standards from both international and national societies (the European Respiratory Society and the Dutch Pediatric Pulmonology Society). In the following cases the investigator will contact the treating physician of the patient to discuss the indication to perform a chest CT scan.

- Chronic respiratory complaints consisting of:
    - chronic wet cough, not caused by any pre-existing chronic disease
    - two episodes of pneumonia in the 12 months before the study visit. (not all children with COVID-19 have suffered from pneumonia). In children with 2 or more periods of pneumonia in one year chest CT is standard clinical care in the search for underlying disease.
    - In children < 6 years old and unable to perform exercise testing, we will ask for exercise intolerance observed by parents. In severe exercise intolerance, a chest CT scan evaluates bronchiectasis, post-infectious bronchiolitis obliterans, pulmonary fibrosis, pulmonary ground glass abnormalities.
- Pulmonary function test abnormalities, not primarily caused by any pre-existing chronic disease. When pulmonary function tests are previously performed, we ask for consent to review previous tests and compare pulmonary function testing results before and after complaints of COVID-19.
    - Not reversible airway obstruction: FEV1 < 80% or FEV1/FVC < 70% post bronchodilatation.
    - Body plethysmography showing pulmonary restriction or airtrapping: TLC < 80%. RV/TLC >30%.
    - Exercise capacity <80% of normal for age and gender, defined as a VO2 max lower than 80% of normal.

Afterwards we will contact the patient for permission to perform the chest CT scan at the study center. Chest CT's will be performed on a dedicated pediatric scanner, according to the pediatric HRCT protocol. This CT will be performed when the patient is without clinical symptoms of pneumonia.

The Chest CT protocol consists of a CT without IV contrast, performed during the inspiratory phase. When children can follow instructions, an expiratory phase will be added. In children who are unable to follow instructions, a free breathing scan will be performed.

Anesthesia is not needed to perform the CT scan; young children will be held by a vacuum mattress, which holds them still, while being comfortable. The scan takes about 1 minute to perform, with preparation and explanation approximately 10 minutes in total time. Chest CTs will be scored by two independent radiologists, blinded to the outcome of the patient (see appendix II)

In the event of incidental findings, patients will be referred to their general pediatrician or pediatric pulmonologist.

In case a chest CT scan is already performed as part of clinical care, patients and/or parents approval will be asked for consent to share these CT images with the investigator.

In case a chest CT is performed during the initial admittance, we ask for approval to review these images.

Exhaled breath analysis:
The analysis of volatile organic compounds (VOC's) in exhaled breath (breathomics) is an attractive non-invasive technique that can be used to assess pulmonary phenotypes, which might be implemented in clinical care. Studies of our own research group, as well as that of others, have shown that the collection of exhaled breath is acceptable and feasible in children from the age of 2 years (26). VOC analysis captures gaseous molecules from exhaled air. The two main approaches to study VOCs are 1) gas chromatography – mass spectrometry (GC-MS) and 2) electronic nose (eNose using a SpiroNose) technology. GC-MS enables identification of individual VOC's and consists of 2 parts; gas chromatography, which can separate compounds in a complex gas mixture, and mass spectrometry, to identify the different individual compounds present in the sample. On the other hand, eNose technologies identify complex mixtures of VOC's based on pattern recognition algorithms. The technique consists of cross-reactive nonspecific sensor arrays that are exposed to the VOC's and generate a so-called "breathprint"of the VOC profile. (27,28).

Previous studies have shown that VOC measurements are associated with clinical outcomes such as sputum eosinophilia and sputum neutrophilia in adult patients with chronic respiratory diseases, and can predict loss of asthma control as well as steroid responsiveness in asthma (29-32). However, very limited data is available in children. There are no data available in COVID-19 patients. More research is needed to validate VOC analyses for clinical use in these children and to assess the diagnostic value of a point of care eNose test for the screening for long term pulmonary abnormalities in COVID-19 patients.

In its current form, the SpiroNose is a spirometry coupled electronic nose based on metal-oxide semiconductor (MOS) sensors with high between-sensor reproducibility. The SpiroNose consists of eight sensor arrays of metal oxide sensors (Breathomix, The Netherlands). Seven sensors are divided over two arrays, which are both present in duplicate. This total of four arrays is also present as reference of the VOC's in ambient air. Patients will perform 5 tidal breaths, then, after a single deep inspiratory vital capacity maneuver and a 5 second breath hold, the patient exhales a vital capacity volume into the measurement setup. The exhaled air is directly measured by the SpiroNose, which is connected to an Ethernet cable for immediate secure data transmission to the online server. This technique has been applied to

children older than 6 years without issues. The obtained breathprints will be securely stored in an online server; the BreathBase. Data can be downloaded for further processing and analysis with offline pattern recognition software.

The collection of exhaled breath for the GCMS analysis is very simple and does not bring any kind of burden to the child. The child will be asked to breath tidally through a mouthpiece into a breath sampling system, as described previously (23). Children breathe tidally through a facemask connected to a non-rebreathing valve system, while watching cartoons. On the expiratory port of the valve, a 3-L polycarbonate bag (Tedlar® bag; SKC Ltd, Blandford Forum, UK) is connected to collect exhaled breath. After the bag is filled, it will be emptied across a stainless steel, two-bed sorption tube, filled with Carbograph 1 TD/Carbopack™ X (Markes International, Llantrisant, UK) for rapid adsorption and stabilisation of volatile compounds. The tubes are airtight capped and stored at room temperature until analysis. VOCs will be released from the tube using thermal desorption (Unity desorption unit; Markes International). Next, the sample will be injected into the gas chromatography (GC) capillary (Trace GC; ThermoFischer Scientific, Austin, TX, USA). In the GC capillary, VOCs are separated and subsequently detected and identified using time-of-flight (TOF) mass spectrometry (MS) (Tempus Plus; ThermoFischer Scientific). The remaining part of the breath will be used for other VOC sensing techniques like the SIFT-MS and the CNT chip sensor. The duration of the breath collection procedure is approximately 5-10 minutes. In case of resistance of the child, the measurements will be terminated. The collection and analysis of VOCs in the exhaled breath follows an standard SOP created and validated in our research group. (appendix III)

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1. Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Subjects will not be replaced after withdrawal

8.6 Follow-up of subjects withdrawn from treatment.

Not applicable

8.7 Premature termination of the study

Not applicable

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The investigator will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1.Adverse events (AEs)

9.3 Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. Adverse events are not expected to occur in the COPP2 study because it is a low risk observational study and therefore, there will be no need for adverse events to be reported. Annual safety report

Not applicable

9.4 Follow-up of adverse events

Not applicable

9.5 Data safety monitoring board (DSMB)/safety committee

Not applicable

10. STATISTICAL ANALYSIS

IBM SPSS Statistics software (SPSS Statistics for Window: IBM, Armonk, NY) will be used.

10.1 Primary study parameters

Numerical data will be summarized using descriptive statistics: mean and standard deviations for normally distributed data, median and quartiles for non-normally distributed data. Group comparisons of independent samples will be done using the Student's t-test for normally distributed data and the Mann-Whitney-U test for non-normally distributed data. Dependent data will be compared using the paired student t-test and the Wilcoxon signed rank matched pair analysis. Risk factors for chest-CT abnormalities and lung function abnormalities will be analyzed by multivariate logistic regression analysis. A log-binomial model will be used to identify patient and clinical characteristics (such as age, sex, medical history, severity of

disease at time of diagnosis of COVID-19 (maximum respiratory support), pharmacological treatment, Chest CT or x-ray abnormalities and laboratory abnormalities) that are associated with an increased risk of having pulmonary sequelae at 6 to 12-months following a COVID-19 diagnosis in children.

10.2 Secondary study parameters

Secondary endpoints will also be summarized using descriptive statistics as mentioned above. Lung function indices, quality of life scores, and exercise capacity will be compared with standard reference sets obtained from normal controls.

10.3 Other study parameters

Not applicable

10.4 Interim analysis

After 60 patients are included, including at least 20 patients who were admitted and were treated with oxygen for > 24 hours, or were diagnosed with inflammatory syndrome, preliminary results will be evaluated. If abnormalities in pulmonary function tests or exercise tests, attributable to COVID-19, are seen in less than 5% of patients, the study will be discontinued

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This prospective cohort study is subject to the Medical Research Involving Human Subjects Act (WMO). This study will be conducted according to the principles of the Declaration of Helsinki (version 2013, 19-10-2013, (www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO), the General Data Protection Regulation (AVG), the Dutch Act on implementation of the General Data Protection Regulation (uitvoeringswet AVG) and other guidelines, regulations and acts. We will comply with the principles enshrined in the Council of Europe Convention on human rights and biomedicine – known as the Bioethics Convention Oviedo). Its main purpose is to protect individuals against exploitation.

11.2 Recruitment and consent

The recruitment and informed consent procedures will be done by researchers of the COPP2 study. Parents and/or children were asked consent during their participation in the COPP study to be approached for a follow-up study. The parents and children will be informed by email about this study by the investigators of the COPP study. In the event that the participation rate is less than 70%, the COPP investigators contact the parents and children directly, through the local investigator in all hospitals participating in the COPP study (23). They will receive their subject identification number from the COPP study, which they will give to the investigators of the COPP2 study, to ensure matching of the data from the COPP study and COPP 2 study. The investigators will provide the patient and parents with the appropriate patient information forms. They will be given at least 1 week to consider their decision and are free to reconsider their decision at any moment during the study. A research assistant will contact the participants and parents who are willing to participate, to schedule

a study visit. Before start of the study visit written consent is obtained from both parents/caregivers.

Due to the current COVID-19 pandemic and the related precaution rules, it is in most part of the hospitals no longer allowed for both parents/caregivers to be present at a medical appointment at the outpatient clinic. For this situation there will be an exceptional procedure for the signature of the patient informed consent (PIF). The parent/caregiver who will not be present at the study visit will sign the PIF at home and this signed version will be taken to the hospital at the occasion of the study visit. The study investigator will make it clear for both parents/caregivers that they can contact the study investigator per telephone or email to ask for clarification at any time before signing the PIF.

Informed consent for the usage of the data of the COPP study is explicitly asked for.

11.3 Objection by minors or incapacitated subjects (if applicable)

The research will be conducted according to the Code of Conduct for Medical Research by the Federation of Dutch Medical Scientific Societies (Federa) and the code of conduct relating to expressions of objection by minors participating in medical research by the Netherlands Association for paediatric research.
https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/codes-of-conduct/code-of-conduct-for-medical-research

Code of conduct

1. Individual children respond differently to diagnostic and treatment procedures and to participation in medical research. Various factors help to determine the nature of the response: the way the child is prepared for what is going to happen, the parent-child relationship, the doctor-patient relationship, the child-friendliness of the environment in which the procedure takes place and so on. One child will not be unduly disturbed by having an injection (even if he or she winces or makes some other display of pain), while another will find the experience distressing. Although responses vary considerably from child to child, there is a general correlation between the degree of 'invasiveness' of a procedure and the strength of the response. In some cases, fear regarding participation or a particular procedure will prompt a child to object. Patient and understanding explanation and reassurance will generally be sufficient to enable the research or the procedure to proceed without problems. Where a newborn child or infant is concerned, it is much harder to ascertain whether objection has been expressed. As a general rule, however, it is reasonable to suggest that a child may be deemed to object if its behaviour clearly differs in nature or degree from that normally displayed by the child when confronted with situations not encountered in everyday life. In this context, situations not encountered in everyday life may be considered to include diagnostic or therapeutic procedures.

2. Before seeking consent for a child's participation in medical research, an investigator must fully inform the child's custodial parent(s) or guardian about what is proposed. Information should be provided orally and in writing. The nature of the procedures involved in the research should be discussed with the parents and their views sought on the child's likely response. The possibility of the child objecting to participation and the type of behaviour that should be regarded as an expression of objection should also be discussed. The investigator should also explain what is to happen in the event of the child objecting. The consent

obtained from the parents should include agreement to the proposed procedure for dealing with expressions of objection by the child.

3 The consent statement signed by parents should stipulate that, if the child should object to participation in the research, consent for its further participation will be invalidated.

4 If prior to the research there is doubt as to whether a child should participate, consideration may be given to involving the patient in the research for an agreed pilot period.

5 While the research is in progress, the behaviour of the child should be continually assessed at the research location to determine whether the child's behaviour is within the bounds normally associated with the child when confronted with situations not encountered in everyday life. If a child's behaviour is not within these bounds, he or she should be deemed to have expressed an objection in the sense of the WMO.

6 The parents, the investigator(s) and possibly a behavioural scientist should be involved in assessment of a child subject's behaviour. Assessment of a child subject's behaviour should not be a one-off exercise, but should continue through all phases of the research.

7 The parents of a child subject should be able to withdraw their consent at any point during the research. If a child subject expresses an objection, the child's participation should be discontinued.

8 In all medical research involving child subjects, the burden associated with participation should be minimised; where non-therapeutic research is concerned, the law stipulates that it must be negligible. Medical studies often involve the combination of research procedures with diagnostic procedures necessary in connection with the subject's treatment. Where research involves an invasive procedure, such as a finger prick or venepuncture, this should if possible be combined with a procedure necessary for diagnostic or treatment purposes, such as blood sampling. If possible, a needle or line that has already been inserted should be utilised, so that the number of 'jabs' is kept to the minimum. The burden can also be reduced by the use of plasters with local anesthetic. The various steps to be taken with a view to minimising the burden should be detailed in the research protocol and in the information given to the parents and subjects.

9 The following should be noted in the research file or the medical (status) report, as appropriate:
a the outcome of any trial participation;
b the consent of the custodial parent(s) or guardian, including the procedure to be followed in the event of a possible expression of objection;
c an account of the subject's participation in the research, stating whether objection was expressed;
d an assessment as to whether the subject's behaviour constitutes objection, as referred to above;
e the names of the people responsible for assessing the subject's behaviour, as described above;
f an assessment as to whether the subject's behaviour in the course of the study constitutes

objection;
g the steps taken to minimise the burden associated with participation.

10 The protocol for a medical research project in which minors are to be used as subjects should state that the NVK's code of conduct for dealing with subjects' expressions of objection in the course of the research will be adhered to.

11 This code of conduct will be evaluated in consultation with the research community two years after its initial publication and amended as necessary.

This code of conduct was approved by the Board of the Netherlands Association for Paediatric Medicine (NVK) on 21 May 2001 and published in NVK Newsletter no. 3, June 2001.

11.4 Benefits and risks assessment, group relatedness.

Subjects do not benefit personally from study participation, although possible long term sequelae can be detected early and proper treatment if necessary can be initiated. This non-therapeutic research with minors will have negligible risks and some burden. The burden is low.

Participants will be asked to visit the participating site hospital once.

They will undergo physical examination, 3 questionnaires will have to be filled in (quality of life, pulmonary symptoms), and depending on age they will also undergo pulmonary function testing, exercise testing and exhaled breath analysis. A subgroup of patients will undergo chest CT-scan as part of standard care, and will be asked to travel to the study site for the CT scan to optimize standardization.

Since we do not yet know the outcome in these patients we cannot predict possible benefits for patients to be included in this study. If patients do show abnormalities, these will be detected. The burden is mostly due to pulmonary testing.

All patients above the age of 4 years old, will be subjected to pulmonary function tests. Pulmonary function tests are standard care in the follow-up of pediatric pulmonology patients, and are used as a screening test for pulmonary morbidity. The pulmonary function test has a DISCO score of 1.46 (33). The DISCO score is developed to aid researchers and ethics committees to evaluate discomfort in children during research procedures and uses a 5 point Likert scale (ref 34) from not burdensome (1) to extremely burdensome (5). The research protocol and PIF's have been commented by both the JAR (jongeren advies raad, AmsterdamUMC hospital) and the Dutch pediatric patient foundation, called "stichting kind en ziekenhuis", which both approved the first version of the protocol and considered the pulmonary function tests as not burdensome.

This study includes only minors. Since COVID-19 in children is less severe than in adults, the long term effects cannot be deduced from future adult studies. In adults, severe sequalae of COVID-19 are seen. In the future, the results of this study may lead to a better understanding for the need of follow-up of pediatric COVID-19 patients.

The family doctor or the general pediatrician of the child will be informed about participation in this study. In the event that incidental findings are discovered, patients will be referred to their general pediatrician or pediatric pulmonologist for further follow-up and necessary treatment.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor was granted dispensation by the METC for the statutory obligation to provide insurance for damage to research subjects, because participating in this study is without risks.

11.6 Incentives (if applicable)

Patients and parents will receive compensation in travel costs based on travelled kilometers or costs of public transport. Participants will receive a small present for participation.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Extracted data are or will be coded, used and stored by the research team of the COPP study (Buddingh, Mooij, van Asmuth) and data of the COPP2 study will be added by the research team of the COPP2 study (Hashimoto, Brackel, Terheggen). Patient data will be coded with a study number. The key to the code will be safeguarded by the research team. Documentation belonging to the trial will be archived for 15 years in the “Investigator File”. Persons who will be involved in the research will be listed in the Signature List with the corresponding tasks. Data will be collected in Castor EDC. This is a AmsterdamUMC approved data storage program. The majority of the data registered at the CASTOR database will be done as direct entry during the study visit, this will comprehend the demographic data, physical examination, general clinical information and pulmonary symptoms. The source information for the lung function, exercise test and chest CT will be available primarily at the EPD from the patient and afterwards entered at the castor study database.

Questionnaires for assessments of quality of life will be filled-in directly by the patient (parents/caregivers) at a website developed for the COPP2 study using the KLIK platform. The KLIK questionnaires will be stored on VPS (KVM) server managed by hosting company Sensson. Daily backups are made to a backup server using backup software R1Soft. These backups are encrypted with a strong password. Biomedia (part of the KLIK expert team) is responsible for the storage and backup of the data. Biomedias is ISO and NEN certified.

The company Breathomix and possible associated partners will have access to the data related and necessary for the breath analysis (Spironose). The data sent to Breathomix will be coded and will not include any personal information that could lead to the identification of study participants. Breathomix will keep the data for unlimited time.

12.2 Monitoring and Quality Assurance

For this study a monitoring plan has been made according to the good clinical practice (GCP) guidelines. (see appendix K6 monitoring plan). An independent monitor will perform regular monitoring starting after the inclusion of the first subject and subsequently twice a year during the trial. After the study is finished, the monitor will conduct a final monitoring. The monitor's tasks during the visits are described in detail in the monitoring plan. The specific monitor plan will be discussed in detail with the CRU (see appendix B2 AMC appendix bijlage 2.0 Aanvraag Centrale CRU monitoring COPP2 study).

12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the data of inclusion of the first subject, number of subjects included and number of subjects that have completed the study, serious adverse events/serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report within the results of the study, including any publications/abstracts of the study, toe the accredited METC.

12.6 Public disclosure and publication policy

Upon closure of the study, data will be reported in a scientific journal. Data published in articles (scientific or non-scientific) will not be traceable to the actual patients.

13. STRUCTURED RISK ANALYSIS

Not applicable.

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